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Troubles psychiatriques en période périnatale : facteurs environnementaux et génétiques

Sarah Tebeka

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UNIVERSITE DE PARIS
ECOLE DOCTORALE CERVEAU, COGNITION, COMPORTEMENT -
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THESE D'UNIVERSITE

TROUBLES PSYCHIATRIQUES EN PERIODE PERINATALE :
FACTEURS ENVIRONNEMENTAUX ET GENETIQUES

SARAH TEBEKA, née le 10.11.87

THESE SOUTENUE LE 16 MARS 2021

DISCIPLINE : NEUROSCIENCES

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Table des matières

Table des matières

Remerciements	4
Résumé.....	6
Introduction.....	8
I. Dépression de la grossesse au post-partum	8
I.A. Épidémiologie	8
I.B. Sémiologie	10
I.C. Outils diagnostics.....	12
I.D. Facteurs de risque	12
I.E. Complications et conséquences	27
II. Trouble bipolaire en périnatalité.....	30
II.A. Épidémiologie	30
II.B. Sémiologie	31
II.C. Facteurs de risque	33
II.D. Complications et conséquences	34
Matériel et méthodes.....	37
I. Cohorte IGEDEPP	37
I.A. Participants.....	37
I.B. Évaluations.....	37
I.C. Aspect réglementaires.....	43
II. Cohorte FACE-BD.....	44
II.A. Participants	44
II.B. Évaluations	44
II.C. Aspects règlementaires	46
III. Cohortes de la NESARC (vagues 1 et 2)	46
III.A. Participants	46
III.B. Évaluations	47
III.C. Aspects règlementaires	49
Résultats.....	50
I. Dépression du post-partum, prévalence et incidence	50
Article 1 : Prevalence of mental disorders and stressful life events during pregnancy : the IGEDEPP cohort	50

II.	Dépression du post-partum, facteurs environnementaux.....	55
II.A.	Article 2 : Developmental trajectories of pregnant and postpartum depression in an epidemiologic survey.....	55
II.B.	Article 3 : Correlates of early and late postpartum depression: results from the IGEDEPP cohort	59
II.C.	Article 4 : Childhood trauma and perinatal depression : data from the IGEDEPP cohort	64
III.	Dépression du post-partum : un GWAS	68
IV.	Trouble bipolaire et périnatalité	73
IV.A.	Article 5 : Is parity status associated with bipolar disorder clinical features, severity or evolution?.....	73
	Et correspondance : Parity and bipolar disorder : new analyses	73
IV.B.	Article 6 : Clinical characteristics of bipolar disorders with postpartum depressive onset	78
	Discussion	82
I.	Résultats principaux	82
II.	Forces et limites	90
III.	Perspectives.....	92
III.A.	Améliorer les connaissances sur la dépression périnatale.....	92
III.B.	Améliorer le dépistage de la dépression périnatale.....	94
	Conclusion	98
	Références.....	99
	Annexes	130

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Résumé

La période périnatale est une période à risque de pathologies mentales, et en particulier des troubles de l'humeur, uni- ou bipolaire. Ainsi, la dépression périnatale reste sous-diagnostiquée malgré des conséquences sévères pour les femmes et leurs enfants.

Notre travail a consisté à mieux comprendre cette pathologie, ses déterminants mais également l'impact des grossesses sur l'évolution des troubles de l'humeur, à l'aide de 3 cohortes, françaises et américaine.

Prévalence et incidence de la dépression périnatale

Nous avons retrouvé une prévalence de la dépression périnatale à 10,8 % en population américaine. En population française, la prévalence de la dépression post-partum à début précoce était de 8,3 % et de 12,9 % pour la dépression du post-partum à début tardif, résultant en une incidence cumulée annuelle de la dépression du post-partum de 18,1 %. Ces données sont cohérentes avec les données de la littérature.

Déterminants biographiques, cliniques, et génétiques de la dépression périnatale

En population américaine, le meilleur prédicteur de la dépression périnatale est une histoire personnelle de trouble psychiatrique, et en particulier un antécédent de dépression. Un antécédent personnel d'abus sexuel dans l'enfance et des antécédents familiaux de dépression étaient également associés à la dépression périnatale. Les événements stressants de la vie au cours de l'année écoulée, y compris le deuil et les violences conjugales, sont également des déterminants de la dépression périnatale.

En population française, nous avons confirmé et affiner ces résultats. Ainsi, si la dépression du post-partum à début précoce et celle à début tardif partagent certains facteurs de risque communs, comme des antécédents personnels de trouble dépressif ou des événements de vie stressants pendant la grossesse, on peut distinguer début précoce et tardif par des corrélats socio-économiques, des événements de vie et des troubles psychiatriques associés. De même, le poids des antécédents familiaux semble plus important pour la dépression du post-partum à début tardif, ce que corroborent nos données génétiques ou une région du chromosome 20 comportant 10 marqueurs est spécifiquement associé à ce phénotype.

Impact des grossesses sur l'évolution du trouble bipolaire

Nous nous sommes ensuite intéressés au trouble bipolaire, d'une part à l'impact du nombre de grossesses sur l'évolution du trouble, d'autre part en caractérisant un sous-groupe de femmes ayant débuté le trouble par une dépression du post-partum. Ainsi, en population américaine, la parité au-delà d'un enfant était associée au trouble bipolaire de type I et à davantage d'épisodes hypomaniaque au cours du suivi. Cependant, il n'y a pas d'association avec le nombre d'épisodes thymiques passés, le taux d'hospitalisation ou le risque suicidaire. Par ailleurs, en population française, les femmes débutant un trouble bipolaire par une dépression du post-partum avaient une évolution plus favorable de la maladie, en particulier moins de tentative de suicide et moins d'épisodes dépressifs au cours de la vie. Cela peut refléter que ces femmes représentent un sous-groupe phénotypiquement homogène, avec des caractéristiques spécifiques. Ces travaux suggèrent que la parité ou le début dans le post-partum sont des marqueurs de bon pronostic d'évolution du trouble bipolaire.

L'ensemble de ces résultats témoignent de la fréquence des troubles de l'humeur en période périnatale. Une bonne compréhension, avec en particulier la caractérisation de sous-groupes au phénotype plus homogènes et des déterminants mieux maîtrisés, apparaissent comme des pistes permettant l'amélioration du dépistage et de la prise en charge des femmes.

Introduction

Depuis l'Antiquité, les auteurs évoquent la grossesse et le post-partum comme une période de grande vulnérabilité au regard des pathologies psychiatriques – et plus particulièrement des troubles de l'humeur. Hippocrate décrivait déjà dans son traité *les maladies des femmes*, « la fièvre du lait » et « la folie des parturientes » (Hippocrate 1839). Au XIX^e siècle, ces troubles ont été étudiés par Esquirol dans *Des maladies mentales : considérées sous les rapports médical, hygiénique et médico-légal*, où il décrit la « folie des accouchées » (1818), puis approfondis par Marcé dans *Traité de la folie des femmes enceintes, des nouvelles accouchées et des nourrices* (1858) (The International Marce Society 2015; Esquirol 1838; Marcé 1858).

La période périnatale comprend la grossesse et le post-partum (Gelaye et al. 2016). Le post-partum n'a pas de définition univoque. Ainsi, les critères diagnostiques internationaux retiennent un début des troubles au cours de la grossesse et avant la quatrième (pour le DSM-5) ou six semaines (pour la CIM-11) après l'accouchement (American Psychiatric Association 2013; World Health Organization 2018). Si certains auteurs considèrent les 3 ou les 6 premiers mois post-partum, une définition plus large du post-partum, allant jusqu'à un an après l'accouchement, est la plus couramment utilisée (Paulson et Bazemore 2010). Cette définition est également retenue par la société internationale Marcé de la santé mentale périnatale et l'Organisation Mondiale de la Santé (The International Marce Society 2015).

Au cours de cette période, le risque tient tant à une décompensation d'un trouble psychiatrique préexistant qu'à une entrée dans un trouble psychiatrique, qu'il soit aigu ou persistant (Jones et al. 2014; L. M. Howard, Molyneaux, et al. 2014). Les troubles de l'humeur sont parmi les plus fréquentes des pathologies périnatales. Dans cette première partie, nous présenterons l'épidémiologie, la symptomatologie et les facteurs associés à la dépression et au trouble bipolaire en période périnatale.

I. Dépression de la grossesse au post-partum

I.A. Épidémiologie

La dépression est un trouble psychiatrique fréquent qui touche plus de 15% de la population au moins une fois au cours de la vie (Kessler et al. 2003). La prévalence de la dépression est

près de deux fois plus importante chez les femmes que chez les hommes (Kessler et al. 2003; Soares et al. 2003). Cette vulnérabilité des femmes pour les troubles de l'humeur est constatée dès la puberté (Bertschy, De Ziegler, et Bianchi-Demicheli 2005; Salk, Hyde, et Abramson 2017). Chez les femmes, la période périnatale est la plus à risque : la prévalence de la dépression périnatale est classiquement estimée entre 10 et 20 % des accouchées (Ko et al. 2012; Heron et al. 2004; Shorey et al. 2018; Schmied et al. 2013). Norhayati et al. ont retrouvé dans une revue de la littérature une prévalence de la dépression post-partum dans les pays développés variant de 5,5 à 34,4 % sur les quatre premières semaines post-partum, de 2,6 à 35,0 % entre la quatrième et la huitième semaine, et de 6,0 à 29,0 % sur les 12 mois suivants. Cette prévalence serait sensiblement plus élevée dans les pays en voie de développement, allant de 12,9 à 50,7 % pour les quatre premières semaines, et de 21,0 à 33,2 % dans la première année post-partum (Norhayati et al. 2015). Ces grandes variations s'expliquent par l'hétérogénéité des études en termes de populations, de périodes d'évaluations et d'outils de diagnostic (Norhayati et al. 2015; Woody et al. 2017).

On retrouve classiquement deux pics de survenue dans le post-partum (Kothari et al. 2016; Wikman et al. 2019). Ainsi, on peut distinguer la dépression du post-partum à début précoce, c'est-à-dire débutant avant la fin des deux premiers mois, de la dépression du post-partum à début tardif, celle s'installant entre deux mois et un an après la naissance (Norhayati et al. 2015; PACT Consortium 2015; The International Marce Society 2015; Gjerdingen et al. 2011). Historiquement, le post-partum a fait l'objet d'une attention plus importante que la période anténatale (Gavin et al. 2005; Woody et al. 2017; Leahy-Warren et McCarthy 2007). Pourtant, le début des symptômes de dépression du post-partum a lieu au cours de la grossesse dans un tiers des cas (Wisner et al. 2013). Il est donc indispensable de s'intéresser à la période périnatale dans sa globalité, considérant la grossesse et le post-partum dans un continuum. Deux revues systématiques de la littérature ont montré une prévalence globale de la dépression périnatale de 11,9 à 16 % (Woody et al. 2017; Underwood et al. 2016). La revue de Woody et al. a mis en évidence des facteurs influençant jusqu'à 31 % la variabilité de la prévalence rapportée entre les différentes études. Les deux principaux facteurs étaient le type d'évaluation proposée, rappelant que certaines échelles de symptômes risquaient de surévaluer le diagnostic de la dépression, et le pays d'évaluation, la dépression périnatale étant plus fréquente dans les pays pauvres (Woody et al. 2017).

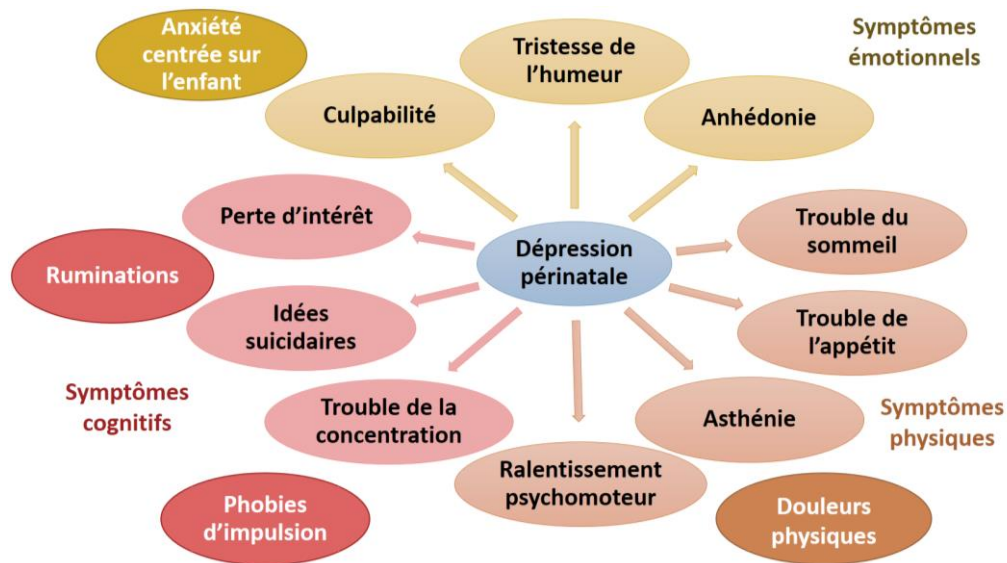
Peu d'études ont en revanche estimé l'incidence de la dépression périnatale. Ainsi, Gavin et al. ont trouvé une incidence de la dépression à 7,5 % au cours de la grossesse et 6,5 % dans le post-partum (Gavin et al. 2005). Dans leur méta-régression, Woody et al. trouvaient une incidence de dépression au cours de la grossesse à 13,0 %, et les estimations retrouvées dans leur revue de littérature allaient d'une incidence de la dépression du post-partum de 5 à 25 % (Woody et al. 2017). Ces données reposent sur des échantillons de petites tailles et non représentatifs (Woody et al. 2017).

Nos travaux essayeront d'apporter d'autres éléments concernant la prévalence et l'incidence de la dépression périnatale.

I.B. Sémiologie

Les critères diagnostiques de la dépression périnatale sont ceux de l'épisode dépressif caractérisé, comme définis par le DSM-5 ou la CIM-11 (cf. figure 1). Elle associe notamment une tristesse de l'humeur, des idées de dévalorisation, une perte du plaisir et un ralentissement psychomoteur qui persistent au moins 15 jours consécutifs. Les patientes sont volontiers asthéniques, et leurs fonctions instinctuelles – sommeil, alimentation, libido – altérées. On retrouve dans les descriptions cliniques classiques quelques caractéristiques spécifiques à la dépression périnatale, telles qu'une anxiété centrée sur le bébé, une culpabilité marquée et une aggravation vespérale des symptômes. Les patientes peuvent décrire des phobies d'impulsion, c'est-à-dire des pensées intrusives reposant sur la crainte d'un passage à l'acte dangereux, classiquement sur l'enfant, venant majorer le sentiment de culpabilité. Des plaintes somatiques – céphalées, asthénie, douleurs – peuvent également être mises au premier plan par les patientes (Jardri, Maron, Delion, et al. 2010; Moriyama et al. 2019). En période périnatale, les femmes peuvent également présenter davantage d'agitation et d'anxiété associée aux symptômes dépressifs et moins d'idées suicidaires, en comparaison aux femmes présentant des dépressions hors du contexte périnatale (I. H. Bernstein et al. 2008; Hendrick et al. 2000). Ainsi, la dépression périnatale est une maladie hétérogène en terme de sémiologie (PACT Consortium 2015; Putnam et al. 2017).

Figure 1 : Signes et symptômes de la dépression périnatale



La sévérité de la dépression tient à l'intensité des symptômes et peut aller jusqu'à un épisode mélancolique. De plus, il existe un continuum dépressif : ainsi la tristesse, sans épisode dépressif caractérisé, est associée à un risque plus important de développer un trouble psychiatrique au décours, et en particulier une dépression (Tebeka et al. 2018; Tebeka, Geoffroy, et al. 2020). En cas d'épisode dépressif avec caractéristiques mélancoliques, la culpabilité est exacerbée ; le tableau est dominé par la perte d'énergie vitale, une souffrance intense, une mésestime de soi et les idées d'incurabilité. L'indifférence éprouvée pour son entourage, en particulier pour le nouveau-né est centrale. Parfois, des idées délirantes congruentes à l'humeur peut s'installer. Les thématiques délirantes concernent la culpabilité ou l'indignité de la mère à s'occuper de son enfant.

Les symptômes dépressifs peuvent parfois être confondu avec des symptômes liés à la grossesse ou au post-partum, tels quel l'asthénie, les troubles du sommeil, les modifications du poids (Ford, Lee, et al. 2017; Boyd et al. 2011). Ainsi, la dépression périnatale est sous-diagnostiquée et insuffisamment prise en charge. Moins de la moitié de ces patientes seraient dépistées (Boath, Bradley, et Henshaw 2005; Vesga-López et al. 2008). Il existe d'autres raisons à ce sous-diagnostic. En particulier, les femmes peuvent avoir du mal à reconnaître leur symptômes dépressifs pendant ou après la grossesse : du fait du chevauchement entre symptômes dépressifs et symptômes de grossesse, mais également d'une culpabilité importante et de la peur d'être stigmatisées (Bilszta et al. 2010; Button et al. 2017).

I.C. Outils diagnostics

Il existe différentes méthodes pour diagnostiquer la dépression périnatale : des entretiens structurés, comme le Composite International Diagnostic Interview (CIDI) (Robins et al. 1988) ou le Mini International Neuropsychiatric Interview (MINI) (Lecrubier et al. 1997), des entretiens semi-structurés comme le Structured Clinical Interview for DSM (SCID) (First 2015), ou la Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al. 1994), ou des auto-questionnaires tels que l'Edinburgh Postnatal Depression Scale (EPDS) (Cox, Holden, et Sagovsky 1987; Chaudron et al. 2010). Les entretiens structurés administrés par des enquêteurs, non-cliniciens, peuvent induire une surestimation de la dépression (Levis et al. 2018; 2019).

Les auto-questionnaires sont faciles à utiliser et bien acceptés. L'EPDS est l'outil le plus validé et le plus largement utilisé pour la dépression périnatale dans le monde (Hewitt et al. 2010). Il s'agit d'un auto-questionnaire de 10 items, validé en français, pour dépister la dépression en au cours de la grossesse et du post-partum (Harris et al. 1989; Chaudron et al. 2010; Kozinszky et Dudas 2015; Jardri et al. 2006). Cependant, il s'agit d'un auto-questionnaire validé uniquement pour le dépistage de la dépression périnatale, et non pour le diagnostic. Différents scores ont été validés selon les différents pays, ou selon qu'ils concernent la période d'évaluation ante ou postnatale (Hewitt et al. 2010; Norhayati et al. 2015; Smith-Nielsen et al. 2018).

I.D. Facteurs de risque

I.D.1 Socio démographiques

Certaines études rapportent des facteurs de risque sociodémographiques tels que l'âge, le statut marital ou le niveau socio-économique (Beck 1996; 2001; Sharma et al. 2008; Lanes, Kuk, et Tamim 2011; Le Strat, Dubertret, et Le Foll 2011; Räisänen et al. 2013; Muraca et Joseph 2014; Maina et al. 2014; Sit et al. 2015; Biaggi et al. 2016; Dadi et al. 2020; van der Waerden et al. 2014). Concernant l'âge maternel, on retrouve une courbe en U : les femmes de moins de 20 ans et de plus de 40 ans sont à risque de dépression périnatale (Guintivano, Manuck, et Meltzer-Brody 2018; Viguera et al. 2011; Lara et al. 2015; Sidebottom et al. 2014). Un bas niveau socio-économique (Dolbier et al. 2013; Sidebottom et al. 2014; Guintivano, Manuck, et Meltzer-Brody 2018) et un bas niveau d'éducation (Savarimuthu et al. 2010; Lara et al. 2015; Wisner et al. 2013; Choi et al. 2012; van der Waerden et al. 2014) sont également

associés au risque de dépression périnatale. Un faible revenu personnel ou familial, ainsi que le statut vis-à-vis de l'emploi sont également classiquement associés à un risque élevé de dépression périnatale (Choi et al. 2012; Lara et al. 2015; Guintivano, Manuck, et Meltzer-Brody 2018; van der Waerden et al. 2014).

Le fait d'être célibataire, ou de manquer de soutien de la part du conjoint ou de l'entourage sont également des facteurs associés de risque de dépression périnatale (Gaillard et al. 2014; Khanlari et al. 2019; Nakamura et al. 2020; Boekhorst et al. 2019).

Enfin, le fait d'être sans domicile fixe, de ne pas maîtriser la langue du pays d'accueil sont également associés au risque de dépression périnatale (Roze et al. 2018). Concernant le statut migratoire, les données sont contrastées selon les pays (Anderson et al. 2017). Ainsi, il semble que les femmes migrantes de première génération, mais pas de deuxième génération, représentent un groupe à risque de dépression au cours de la grossesse et dans le post-partum (El-Khoury et al. 2018). Un faible soutien social, une appartenance à une ethnie minoritaire, un niveau socio-économique bas, un manque de maîtrise de la langue du pays d'accueil et du statut de réfugié ou de demandeur d'asile, ainsi qu'un antécédent de dépression exposent les femmes à un risque accru de troubles mentaux périnataux (Anderson et al. 2017; Fellmeth, Fazel, et Plugge 2017).

I.D.2 Évènements de vie

I.D.2.a Dans l'enfance

En population générale, les traumatismes infantiles sont associés à un risque multiplié par deux de dépression (Chapman et al. 2004; Benarous et al. 2014). Parmi les individus souffrant de dépression, ceux avec traumatismes infantiles ont un âge de début du trouble plus précoce, une pathologie plus sévère et résistante (Sala et al. 2014; Garno et al. 2005; Post et al. 2015; Janiri et al. 2014; Marwaha et al. 2015; Upthegrove et al. 2015; Scott et al. 2012; Teicher et Samson 2013; Aas et al. 2016). En ce qui concerne la dépression périnatale, les données sont contradictoires (Leeners et al. 2014; Rich-Edwards et al. 2011; Lara et al. 2015; Edwards et al. 2008; Choi et Sikkema 2016; De Venter et al. 2015). Nous nous intéresserons plus spécifiquement à cette question dans ce travail.

I.D.2.b Au cours de la vie

Les abus physiques, psychologiques ou sexuels, qu'ils aient lieu avant ou au cours de la grossesse, semblent augmenter le risque de dépression périnatale chez les femmes (Turkcapar et al. 2015; Ahmed, Alalaf, et Al-Tawil 2012; Savarimuthu et al. 2010; Sidebottom et al. 2014). Parmi ces abus, les violences conjugales sont particulièrement associées au risque de dépression périnatale (Halim et al. 2018; Navarrete, Nieto, et Lara 2021; Dennis, Heaman, et Vigod 2012; Gaillard et al. 2014; Cerulli et al. 2011; Woolhouse et al. 2012). Ainsi une étude récente retrouve chez les femmes ayant subi des violences conjugales, un risque de dépression multiplié par 3,5 au cours de la grossesse, et par 18 durant le post-partum (Navarrete, Nieto, et Lara 2021).

Ainsi, les évènements de vie stressant sont parmi les principaux facteurs associés à la dépression périnatale. On retrouve une relation de type effet-dose de ces facteurs sur la dépression périnatale (Guintivano, Manuck, et Meltzer-Brody 2018; Dennis, Heaman, et Vigod 2012). Nos travaux tenteront d'améliorer nos connaissances sur l'impact des différents évènements de vie stressant, dans l'enfance ou au cours de la grossesse, sur la dépression périnatale.

I.D.3 Santé physique

Plusieurs facteurs de risque cardiovasculaires et maladies chroniques ont été associées à la dépression périnatale, tels que le diabète, l'hypertension artérielle, et l'obésité (Molyneaux et al. 2014; Pavlik et Rosculet 2020; Prairie et al. 2012; Dalfrà et al. 2012) et l'épilepsie (Bjørk et al. 2015). D'une manière plus générale, une mauvaise santé physique ou une maladie chronique sont associées à un risque accru de dépression périnatale (Cheng, Walker, et Chu 2013; Gaillard et al. 2014; Brown et al. 2019).

De façon plus spécifique, certaines caractéristiques obstétricales sont également associées à un risque accru de dépression du post-partum, y compris après ajustement sur les facteurs sociodémographiques et psychiatriques (Verdoux et al. 2002; Guintivano, Manuck, et Meltzer-Brody 2018; Hompoth et al. 2020). Ainsi, une grossesse non désirée, une césarienne en urgence ou des complications de la grossesse (en particulier le diabète gestationnel ou la pré-éclampsie), sont également associées à la dépression périnatale (Gaillard et al. 2014; Räisänen et al. 2013; Strapasson, Ferreira, et Ramos 2018; Mak et al. 2018; Biaggi et al. 2016; Sundaram, Harman, et Cook 2014; Rigó et al. 2015; Wilson et al. 2020). L'association avec la prématurité

est bidirectionnelle : d'une part, les femmes souffrant de dépression, qui plus est si elles sont non traitées au cours de la grossesse, présentent un risque significativement plus élevé d'accoucher prématurément par rapport aux femmes sans dépression, et ce d'autant plus si la dépression est sévère (Jarde et al. 2016; Hermon et al. 2019) ; d'autre part, l'accouchement prématuré est associé à un risque dépression du post-partum (Ihongbe et Masho 2017; Helle et al. 2015; Vigod et al. 2010).

I.D.4 Santé mentale

I.D.4.a En périnatalité

I.D.4.a.i Continuum dépressif

Comme nous l'avons mentionné précédemment, il existe un continuum entre la dépression au cours de la grossesse et la dépression du post-partum (Gaillard et al. 2014; Batmaz et al. 2015; Woolhouse et al. 2012; Turkcapar et al. 2015). Selon une étude portant sur 1105 femmes, 44 % des dépressions du post-partum débutaient au cours de la grossesse (Heron et al., 2004). Après ajustement sur les principaux facteurs de risque, la dépression au cours de la grossesse restait associée à un risque 140 fois plus important de dépression du post-partum dans les 6 premières semaines, et constitue ainsi le facteur de risque le plus important (OR = 139,35 ; IC 95 % = 120,40-161,68) (Räsänen et al. 2013). Une méta-analyse de Robertson et al. (2004) incluant plus de 3000 femmes, confirme l'importance de ce facteur de risque (d de Cohen = 0,75).

I.D.4.a.ii Anxiété au cours de la grossesse

L'anxiété au cours de la grossesse a été également associée à la dépression du post-partum (McGrath, Records, et Rice 2008; Kirpinar, Gözüm, et Pasinlioğlu 2010; Guintivano et al. 2018; Eastwood et al. 2017; Ogbo et al. 2018). Même après ajustement sur la dépression au cours de la grossesse, l'anxiété restait associée au risque de développer une dépression du post-partum à 8 semaines et 8 mois (OR=3,22 ; $p < 0,001$) (Heron et al., 2004) ; avec une taille d'effet important (d de Cohen = 0,68) évaluée sur plus de 1000 femmes par la méta-analyse de Robertson et al. (2004).

I.D.4.b. Sur la vie entière

I.D.4.b.i Dépression

Un antécédent de dépression confère une augmentation significative du risque de dépression périnatale, avec un risque multiplié par 2 à 4-6 semaines post-partum et par plus de 3 à 6 mois post-partum (Rich-Edwards et al. 2006; Räisänen et al. 2013; Pataky et Ehlert 2020; Dennis et al. 2018). La méta-analyse de Robertson et al. (2004) retrouvait une taille d'effet importante (d de Cohen =0,58) mesurée sur 3700 femmes.

De façon plus spécifique, un antécédent personnel de dépression périnatale est un facteur de risque important de nouvel épisode dépressif au cours des grossesses ultérieures (Dennis et al. 2018; Turkcapar et al. 2015; Limlomwongse et Liabsuetrakul 2006; Bloch et al. 2005), pouvant aller jusqu'à 40 % (Wisner et al. 2004).

I.D.4.b.ii Trouble bipolaire

La période périnatale, et en particulier le post-partum, est à risque important de décompensation thymique chez les femmes souffrant d'un trouble bipolaire (Sharma et Pope 2012).

Devant une patiente souffrant d'une dépression du post-partum, il faut rechercher des arguments en faveur d'un trouble bipolaire, en particulier un antécédent personnel ou familial d'épisode maniaque ou hypomaniaque. En effet, il existe de nombreuses erreurs diagnostiques, avec des troubles bipolaires sous-diagnostiqués – le trouble bipolaire débutant plus souvent par une dépression que par un épisode (hypo)maniaque (Cremaschi et al. 2017; Tundo et al. 2015) ; et pouvant débiter dans le post-partum (Jones et al., 2014). Ainsi, après un premier épisode dépressif, les études ont trouvé qu'il faut en moyenne 9 ans pour corriger le diagnostic en trouble bipolaire (Fritz et al. 2017), avec un changement en trouble bipolaire de type I chez 1 % des patients par an et en trouble bipolaire de type II chez environ 0,5 % de patients par an (Angst et al. 2005). De façon plus spécifique, une étude retrouvait que plus de 50 % des patientes diagnostiquées « dépression du post-partum » ont été réévaluées comme ayant un trouble bipolaire (Sharma et al. 2008). Un premier épisode dépressif dans le post-partum est connu pour être plus susceptible d'évoluer vers un trouble bipolaire qu'un premier épisode dépressif en dehors du post-partum ; en particulier, une première dépression au cours du premier mois après l'accouchement était associée à un risque deux à quatre fois plus élevé

de changement vers un diagnostic de trouble bipolaire qu'une première dépression en dehors du post-partum (Liu et al. 2017; Munk-Olsen et al. 2012).

Nous détaillerons l'impact de la période périnatale sur le trouble bipolaire par la suite (cf. Partie II, p.30).

I.D.4.b.iii Syndrome prémenstruel

Plusieurs études transversales retrouvaient une association significative entre un antécédent de syndrome prémenstruel ou de trouble dysphorique prémenstruel et la dépression du post-partum (Kara et al. 2008; Buttner et al. 2013). Les résultats d'études prospectives suggéraient que le syndrome prémenstruel était un facteur de risque important pour la dépression du post-partum à 6-8 semaines post-partum (Limlomwongse et Liabsuetrakul 2006; Bloch et al. 2005; Dennis et Ross 2006; Pataky et Ehlert 2020).

Ce lien vient appuyer l'hypothèse hormonale de la physiopathologie de la dépression du post-partum. En effet, les modifications hormonales physiologiques liées à la grossesse et au post-partum font partie des représentations classiques de la physiopathologie de la dépression, mais sont également sous-tendues par une abondante littérature scientifique (Bloch, Daly, et Rubinow 2003; Glynn, Davis, et Sandman 2013; Glynn et Sandman 2014; Sylvén et al. 2013; Le Donne, Settineri, et Benvenga 2012; Keshavarzi et al. 2011; Schiller, Meltzer-Brody, et Rubinow 2015). De plus, il a été décrit que certaines femmes sont plus vulnérables aux fluctuations hormonales et vont présenter un syndrome dysphorique prémenstruel, des épisodes thymique en période périnatale et des dépressions pendant la péri-ménopause (Graziottin et Serafini 2009; E. W. Freeman 2010; Schiller, Meltzer-Brody, et Rubinow 2015).

I.D.4.b.iv Troubles anxieux

Sur une grande cohorte en population générale, l'existence d'un trouble anxieux au cours de la vie était associée à la dépression périnatale ($OR_{\text{ajusté}} = 22,64$; IC 95 % = 2,94-174,21; $p < 0,01$) (Le Strat, Dubertret, et Le Foll 2011). Une autre étude prospective répliquait ces résultats en ajustant sur les principaux facteurs de confusion ($OR = 1,09$; IC 95 % = 1,05-1,13; $p < 0,001$) (Kirpinar, Gözüm, et Pasinlioğlu 2010). En particulier, le trouble panique était associé à la dépression du post-partum, qu'il se soit manifesté au cours de la vie ($RR = 2,47$; IC 95 % = 1,11-5,49) ou au cours de la grossesse ($RR = 4,25$; IC 95 % = 1,48-12,19) (Rambelli et al. 2010).

I.D.4.b.v Consommations d'alcool

Une large étude menée en population générale ne parvenait pas à mettre en évidence d'association significative entre les troubles liés à l'usage d'une substance, d'alcool ou de tabac et la dépression du post-partum (Le Strat, Dubertret, et Le Foll 2011). Cependant, cette étude retrouvait une association entre l'usage d'alcool et la dépression périnatale : les femmes présentant une dépression périnatale avaient une consommation d'alcool plus importante que les femmes sans dépression en période périnatale mais également que les femmes présentant une dépression en dehors du contexte périnatal (Le Strat, Dubertret, et Le Foll 2011). A noter que ces consommations d'alcool sont également associées aux consommations d'alcool avant la grossesse (Ethen et al. 2009; Skagerström et al. 2013; McCormack et al. 2017), à l'usage du tabac, aux conflits importants avec le partenaire ou à des antécédents traumatiques d'abus sexuels ou d'exposition à des violences (Skagerström et al. 2013; O'Keeffe et al. 2015; Lamy et al. 2019).

Si la dépression périnatale est retrouvée associée aux consommations d'alcool, celles-ci représentent indépendamment un problème de santé publique important. Une récente méta-analyse retrouvait une prévalence de l'usage de l'alcool au cours de la grossesse à 9,8 % (IC 95 % 8,9 – 11,1) (Popova et al. 2018). Or, l'alcool est un agent tératogène majeur. Les conséquences sur la santé de la consommation d'alcool pendant la grossesse peuvent être graves pour le fœtus, du fait d'un risque accru de fausses couches spontanées, de prématurité, de petit poids de naissance ou de trouble du spectre de l'alcoolisation fœtale (TSAF) (Sokol, Delaney-Black, et Nordstrom 2003; Popova et al. 2011; Hoyme et al. 2016). On retrouve également des troubles cognitifs chez les enfants ayant été exposés à l'alcool in utero (Easey et al. 2019; L. M. Howard et Khalifeh 2020; Mamluk et al. 2020). Les études ne retrouvent pas un seuil d'exposition à risque. Dans ce contexte, l'ensemble des recommandations nationales et internationales préconisent l'abstinence totale en alcool pour les femmes enceintes (FDA 2005; Thibaut et al. 2019). L'American College of Obstetricians and Gynecologists recommande également un dépistage systématique de la consommation d'alcool chaque année chez les femmes en âge de procréer ainsi que pendant le premier trimestre de la grossesse pour toutes les femmes enceintes (Obstetric and Gynecologic Implications - ACOG 2011).

Compte tenu de l'ensemble de ces recommandations, nous avons cherché à évaluer l'évolution de ces consommations d'alcool chez les femmes en âge de procréer et chez les

femmes en contexte périnatale. Ainsi, à partir de deux échantillons indépendants, représentatifs de la population américaine, la NESARC (The National Epidemiologic Survey on Alcohol and Related Conditions) et la NESARC-III, nous avons mesuré les consommations d'alcool ainsi que les consommations massives (plus de 4 verres en une occasion) entre 2001-2002 et 2012-2013 chez les femmes en âge de procréer et chez les femmes enceintes ou durant le post-partum (Tebeka, De Premorel Higgons, et al. 2020).

Notre échantillon était composé de 24 536 femmes en âge de procréer, dont 2 846 femmes enceintes et post-partum. La prévalence de la consommation d'alcool sur 12 mois a augmenté de 2001-2002 à 2012-2013, tant chez les femmes en âge de procréer (66,14 % à 75,48 % ; $OR_{ajusté} = 1,62$, IC à 95 % = 1,46-1,80) que chez les femmes enceintes et dans le post-partum (57,81 %) à 66,19 %; $OR_{ajusté} = 1,56$, IC à 95 % = 1,25 à 1,94). La prévalence des consommations massives sur 12 mois a également augmenté de 2001-2002 à 2012-2013, tant chez les femmes en âge de procréer (22,57 % à 36,34 %; $OR_{ajusté} = 1,97$, IC à 95 % = 1,79-2,16) que chez les femmes enceintes et post-partum (17,85 % à 28,21 %; $OR_{ajusté} = 1,84$, IC à 95 % = 1,47-2,30) (Tebeka, De Premorel Higgons, et al. 2020) (cf. article en annexe 1, p. 130). Ainsi, malgré les préconisations et l'évolution des connaissances, les consommations en périodes périnatales continuent d'augmenter au cours des 10 dernières années.

I.D.4.c. Antécédents familiaux

On retrouve également un risque accru de dépression périnatale en cas d'antécédents psychiatriques familiaux, et cela pour toutes pathologies psychiatriques confondues (Corwin et al. 2010; Ahmed, Alalaf, et Al-Tawil 2012; Bauer et al. 2018; Robertson et al. 2004).

Ainsi, une femme dont la sœur souffrait de dépression unipolaire avait 42 % de risque de dépression du post-partum, contre 15 % en absence d'antécédent familial (Forty et al. 2006). Une autre étude prospective canadienne retrouvait un risque multiplié par 7 de dépression du post-partum en cas d'antécédents de dépression périnatale chez un apparenté au premier degré (Dennis et Ross 2006).

I.D.5 Génétique

Les antécédents familiaux de dépression représentent un facteur de risque important pour la dépression du post-partum, ce qui suggère un rôle de facteurs génétiques. Ainsi, des études d'agrégation familiale confirmaient un risque de dépression du post-partum multiplié par 2 à

3 lorsqu'un apparenté au premier degré avait souffert de dépression du post-partum (Murphy-Eberenz et al. 2006; Payne et al. 2008). Une étude estimait l'héritabilité de la dépression du post-partum autour de 50 % ; c'est-à-dire que la variation phénotypique de ce trouble est liée pour moitié à des facteurs génétiques (Viktorin et al. 2016). De façon intéressante, un tiers de cette variance génétique n'était pas partagée avec celle de la dépression en population générale, suggérant que les étiologies génétiques ne se chevauchent que partiellement pour la dépression périnatale et la dépression non périnatale (Viktorin et al. 2016). Deux études basées sur les scores de risque polygénique, c'est-à-dire considérant les variations de l'ensemble du génome pour fournir des estimations de risque pour la dépression, retrouvaient également un chevauchement génétique entre la dépression du post-partum et d'autres troubles de l'humeur (Byrne et al. 2014; Bauer et al. 2019).

La majorité des études génétiques sur dépression périnatale utilisent une approche de type « gènes-candidats », ce qui signifie que seule une liste de gènes définie a priori impliqués dans la pathologie est explorée. Cette approche présente l'avantage de restreindre l'analyse aux loci qui sont le plus probablement impliqués, et permet ainsi d'augmenter la puissance statistique en diminuant de manière importante le nombre de tests statistiques réalisés par rapport à une analyse pangénomique. Cette approche a néanmoins comme limite les connaissances physiopathologiques que nous avons du trouble. Les gènes candidats de la dépression du post-partum sont tout particulièrement ceux qui codent pour des transporteurs, des neurotransmetteurs ou des molécules impliquées dans les modifications neuro-hormonales du post-partum (Elwood et al. 2019; Couto et al. 2015; McEvoy et al. 2017; Figueiredo et al. 2015). En revanche, une telle approche ne permet pas de mettre en évidence des variants génétiques associées à la maladie si ceux-ci sont situés en dehors des gènes candidats.

I.D.5.a. Gènes candidats

I.D.5.a.i Modulateurs de la neurotransmission sérotoninergique

Les modifications de la neurotransmission sérotoninergique jouent un rôle majeur dans la physiopathologie de la dépression en population générale. Les gènes modulant la signalisation cette voie sont donc des candidats intéressants pour expliquer la dépression du post-partum.

Gènes TPH1 et TPH2

Certains polymorphismes des gènes codant pour la tryptophane hydroxylase (*TPH1* et *TPH2*), impliqué dans la synthèse de la sérotonine, étaient significativement associés au risque de dépression périnatale (Sun et al. 2004; Fasching et al. 2012; Lin et al. 2009). Ainsi, un SNP (single nucleotide polymorphism) du gène codant pour la TPH1 était associé à la dépression au cours de la grossesse (Sun et al. 2004), mais pas à la dépression du post-partum précoce (Khabour et al. 2013). De même, des polymorphismes de TPH2 étaient associés à la dépression du post-partum précoce et tardive (Fasching et al. 2012; Lin et al. 2009), mais pas au cours de la grossesse (Khabour et al. 2013).

Gène 5HTT

Plusieurs études montraient que certains polymorphismes fonctionnels du gène 5-HTT (5HTTLPR, STin2 VNTR), responsables d'une forte expression du transporteur de la sérotonine, donc d'une augmentation de la sérotonine dans l'espace synaptique, étaient associés au risque de dépression du post-partum précoce (Sanjuan et al. 2008; Doornbos et al. 2009; Binder et al. 2010), association par ailleurs non retrouvée dans le post-partum tardif (Sanjuan et al. 2008).

Des études d'interaction gène-environnement ont également cherché à mettre en évidence l'impact conjoint de polymorphismes du gène 5-HTT et des événements de vie dans le risque de développer une dépression du post-partum. On retrouvait ainsi une interaction entre le 5HTTLPR et le niveau d'éducation ou un événement de vie durant la grossesse ou encore une insatisfaction dans le couple sur le risque de dépression du post-partum (Mitchell et al. 2011; Mehta et al. 2012; Pinheiro et al. 2013; Zhang et al. 2014).

Gènes COMT et MAOA

Certains polymorphismes des gènes de la monoamine oxydase A (MAOA) et de la catéchol-O-méthyltransférase (COMT) - deux enzymes associées à la dégradation de la sérotonine, la dopamine et la noradrénaline - étaient également associés avec la dépression du post-partum précoce, mais pas avec la dépression du post-partum tardif (Doornbos et al. 2009; Comasco et al. 2011; A. Alvim-Soares et al. 2013; Costas et al. 2010; Ivorra et al. 2010).

I.D.5.a.ii Les perturbations de l'axe hypothalamo-hypophysaire

Gène *CRHR1*

Plusieurs polymorphismes du *CRHR1*, gène codant pour le récepteur de type 1 au CRH (corticotropin-releasing hormone), étaient significativement associés à la dépression du post-partum précoce (Engineer et al. 2013). Là encore, l'association n'était pas retrouvée avec la dépression du post-partum précoce par d'autres équipes (Tan et al. 2015; Schneider et al. 2014).

Gène *BDNF*

L'expression du BDNF (Brain-derived neurotrophic factor) – impliquée dans la neuroplasticité cérébrale (Duman 2002) – est impliquée dans la régulation de l'axe hypothalamo-hypophysaire (Scaccianoce et al. 2003). Or, les taux BDNF sont nettement diminués, à la fois avant et après l'accouchement chez les femmes développant une dépression du post-partum ($p < 0,03$) (Gazal et al. 2012; Lommatzsch et al. 2006). Comasco et al. (2011) ont trouvé une association entre le polymorphisme rs6265 du gène *BDNF* (Val66Met) et la dépression du post-partum à 6 semaines ($p = 0,004$), contrairement à Figueira et al. (2010). Une étude d'interaction gène-environnement observait un risque multiplié par 3 chez les femmes porteuses de l'allèle Met lorsqu'elles accouchaient en automne/hiver (IC 95% = 1,0–12,0) ; les auteurs mettant en avant une association entre le BDNF et le système circadien, lui-même déjà impacté par les mois d'automne/hiver à moindre luminosité (Comasco et al. 2011).

I.D.5.a.iii L'implication des hormones stéroïdiennes

Gène *HMCN1*

Le gène *HMCN1* (Hemicentin 1) code pour une protéine contenant quatre sites de liaison aux récepteurs œstrogéniques ; or les œstrogènes modulent à la fois la sécrétion du BDNF (Scharfman et Maclusky 2005; Franklin et Perrot-Sinal 2006) et l'axe hypothalamo-hypophysaire (de par un rétrocontrôle négatif sur les sécrétions de LH et d'FSH) (Handa et al. 1994). Une étude génome entier a permis pour la première fois de mettre en évidence une forte association entre la dépression du post-partum et le gène *HMCN1* ($p < 0,001$) (Mahon et al. 2009). Ce résultat a été répliqué depuis (A. M. Alvim-Soares et al. 2014).

Gène ESR1

Pinsonneault et al. (2013) ont montré que certains polymorphismes du gène ESR1 codant pour le récepteur œstrogénique alpha étaient associés à la dépression du post-partum tardif ($p = 0,007$). Il a également mis en évidence une possible interaction gène-gène avec le gène du transporteur de la sérotonine (*SERTLPR*) ($p=0,007$) – qui pourrait expliquer le rôle d'ESR1 dans la dépression du post-partum par la modulation de la signalisation sérotoninergique.

El-Ibiary et al. (2013) ont mis en évidence une association entre certains SNP du gène ESR1 et la dépression du post-partum tardif. D'autres études n'ont pas retrouvé cette différence (Costas et al. 2010; Tan et al. 2018).

I.D.5.a.iv L'ocytocine

Enfin, les recherches concernant le rôle de l'ocytocine et de la régulation de son expression génétique sont également intéressantes. L'ocytocine a un rôle particulier dans le post-partum (Feldman et al. 2007; Niwayama et al. 2017). Ce neuropeptide augmente pendant la grossesse, et diminue dans le post-partum. De nombreuses études ont trouvé un lien entre les taux d'ocytocine et l'attachement maternel : une faible concentration plasmatique ou salivaire d'ocytocine pendant la période périnatale était associée à un attachement de moindre qualité (Gordon et al. 2010; Seltzer, Ziegler, et Pollak 2010; Stuebe, Grewen, et Meltzer-Brody 2013; Feldman et al. 2010). À l'inverse, un faible taux d'ocytocine semble prédire la dépression post-partum (Skrundz et al. 2011; Stuebe, Grewen, et Meltzer-Brody 2013; Lara-Cinisomo et al. 2019). De plus, les symptômes dépressifs pendant la grossesse étaient corrélés à de faibles taux plasmatiques d'ocytocine pendant la période post-partum (Eapen et al. 2014; Moura, Canavarro, et Figueiredo-Braga 2016).

L'ocytocine exerce son effet sur la cellule par interaction avec le gène du récepteur de l'ocytocine (*OXTR*), un récepteur couplé à la protéine G (Gimpl et Fahrenholz 2001). Certains polymorphismes du gène *OXTR* sont associés également à la dépression en population générale (Riem et al. 2011; McQuaid et al. 2013; S. M. Thompson et al. 2014) et dans le post-partum (Bell et al. 2015; Asherin et al. 2020). Les études d'association génétique retrouvent également un lien entre certains variants du gène *OXT*, codant pour l'ocytocine, et la dépression du post-partum à début tardif (Jonas et al. 2013; Mileva-Seitz et al. 2013).

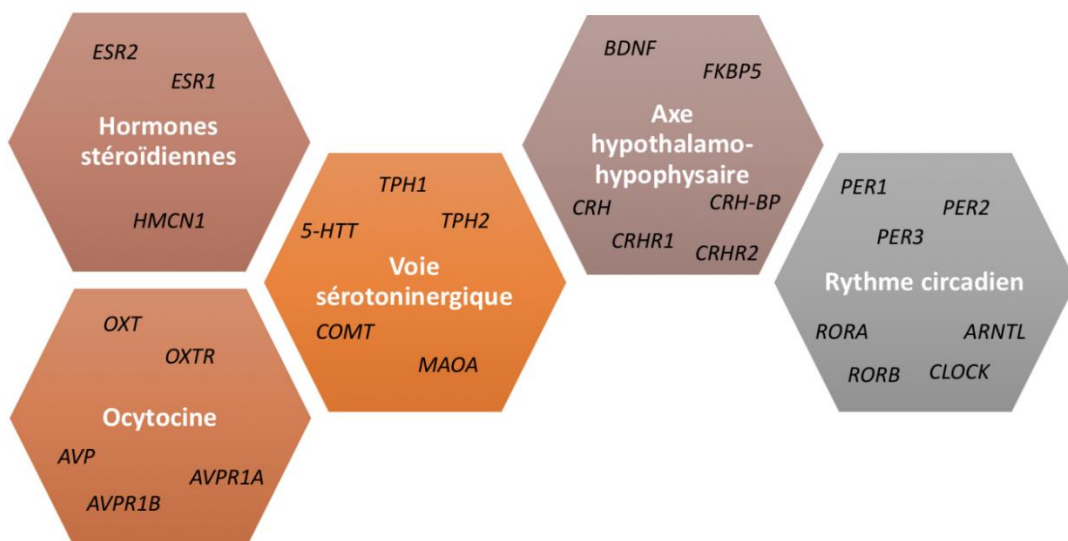
L'arginine-vasopressine (AVP) est un autre neuropeptide dont l'action est opposée à celle de l'ocytocine. Elle est également impliquée dans la physiopathologie de la dépression par une action synergique avec le CRH pour activer la sécrétion d'ACTH (Surget et Belzung 2008). L'AVP agit par l'intermédiaire de deux récepteurs : AVPR1a et AVPR1b. Une hyperstimulation de cet axe est associée à la dépression (Gelman et al. 2015).

I.D.5.a.v Les rythmes circadiens, et gène de l'horloge

La période périnatale est classiquement marquée par des troubles du sommeil (Bei, Coo, et Trinder 2015; Bhati et Richards 2015). Les rythmes circadiens influencent l'humeur en post-partum (Gallaher et al. 2018; Lawson et al. 2015). Les gènes de l'horloge jouent un rôle central dans le maintien des rythmes circadiens ; les polymorphismes de ces gènes sont associés aux troubles de l'humeur (Dørheim et al. 2009). Un cycle veille-sommeil perturbé a été associé à une dépression post-partum indépendamment d'autres facteurs de risque (Goyal, Gay, et Lee 2007; Dallaspezia et Benedetti 2009).

Un polymorphisme du gène *PER3* a été associé à l'apparition de la dépression du post-partum dans le trouble bipolaire (S. Dallaspezia et al. 2011). En revanche, les polymorphismes du gène *PER2* n'étaient pas associés à la dépression du post-partum précoce (Comasco et al. 2011).

Figure 2 : Synthèse des gènes candidats associés à la dépression périnatale



I.D.5.b. Épigénétique

L'épigénétique, c'est-à-dire les changements dans l'expression du gène sans modification de la séquence d'ADN, est également susceptible de jouer un rôle dans l'étiologie de la dépression du post-partum (Mill et al. 2008; Carnevali et Buoli 2021; Payne et al. 2020).

Par exemple, les modifications de méthylation sur deux gènes (*TTC9B* et *HP1BP3*) au cours de la grossesse semblent prédire le risque de dépression du post-partum avec une précision de 96 %, indépendamment du statut sur la dépression anténatale (Guintivano et al. 2014). Ce travail a été répliqué dans deux cohortes, retrouvant une fiabilité du modèle à 81 % (Osborne et al. 2016).

Une autre étude retrouvait que les symptômes dépressifs avant et pendant le post-partum étaient associés à une méthylation du gène *OXTR* significativement plus élevée au sein de l'exon 3. L'expression du gène *OXTR* pourrait être supprimée lorsque la dépression est caractérisée par une durée plus longue (King et al. 2017). Un autre travail mettait en évidence une méthylation de l'ADN du gène *OXTR* dans le sang de cordon était associée négativement aux symptômes dépressifs (Unternaehrer et al. 2016).

Enfin, les femmes enceintes déprimées ont montré une hyperméthylation de *CLOCK* et une hypométhylation de *CRY1*, *PER1* et *PER2*, 4 gènes impliqués dans les rythmes circadiens (Buoli et al. 2019).

I.D.5.c. Étude d'association pangénomique, GWAS

Nous avons parcouru les gènes candidats de la dépression périnatale. Cependant, jusque-là, les études reposent sur de petits effectifs de femmes, et ne sont que rarement répliquées. De plus, la variation génétique liée à l'origine des femmes est peu ou pas considérée, créant un biais de stratification, une hétérogénéité génétique rendant les résultats difficilement interprétables. Plus précisément, l'origine ethnique des participants est associée à des variations importantes dans les fréquences alléliques de nombreux variants. Dans le cas où certaines origines ethniques seraient associées au risque de dépression, cette origine peut jouer le rôle de facteur de confusion et biaiser les résultats des études d'association. Ce mécanisme se nomme stratification de population. Enfin, la dépression périnatale, comme les

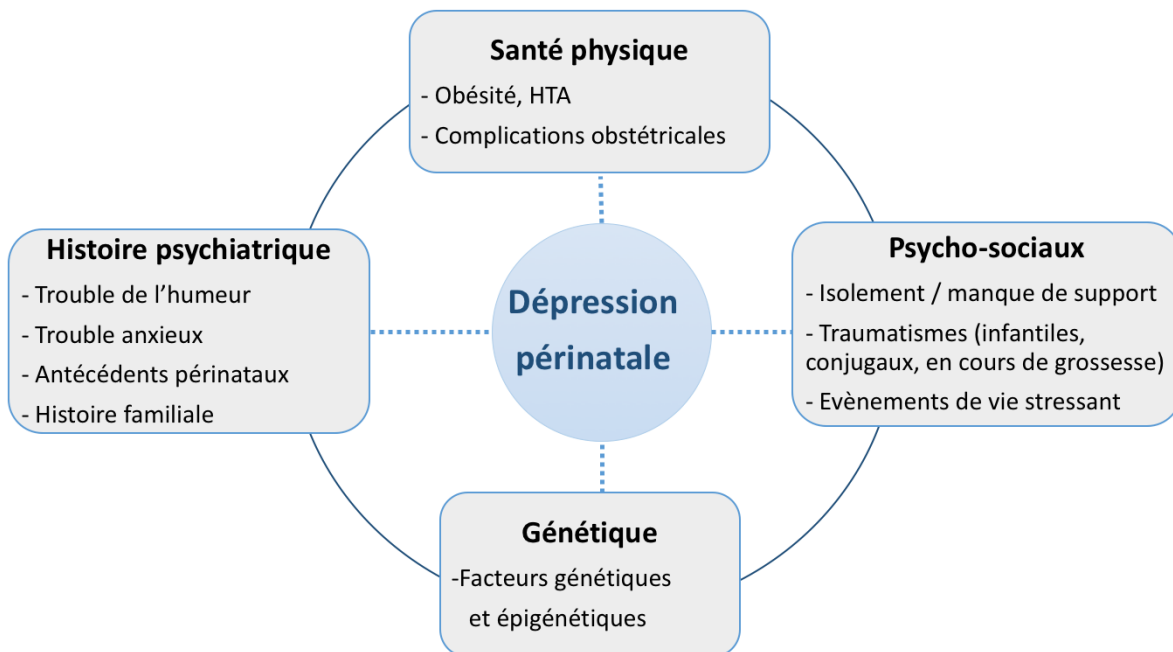
autres troubles mentaux, est une maladie complexe : plusieurs gènes peuvent intervenir, de façon synergique, avec un effet relativement mineur exercé par chaque gène (Fan et al. 2020). L'approche gène-candidat est insuffisante dans la mesure où elle ne repose que sur des hypothèses physiopathologiques et ne considère pas les voies métaboliques dans leur ensemble.

Une approche génome entier, sans hypothèse initiale, permet d'une part de confirmer ou non l'implication des gènes candidats et d'autre part, de caractériser des voies biologiques non connues.

Plusieurs études d'association pangénomique (GWAS) ont été réalisées sur la dépression en population générale. Récemment, le *Psychiatric Genomics Consortium* (PGC) a publié les résultats d'un GWAS sur le trouble dépressif caractérisé, basée sur 135 458 cas et 344 901 témoins, retrouvant 44 loci indépendants significativement associés à la dépression sur l'ensemble du génome (Wray et al. 2018). Par la suite, une méta-analyse a été réalisée portant sur 246 363 cas et 561 190 témoins provenant des trois plus grandes études d'association pangénomique de la dépression. Elle a permis d'identifier 102 variants indépendants et 15 ensembles de gènes associés à la dépression, y compris les gènes et les voies génétiques associés à la structure synaptique et à la neurotransmission. Une analyse d'enrichissement a fourni des preuves supplémentaires de l'importance des régions cérébrales préfrontales. Dans un échantillon de réplique indépendant de 414 055 cas et 892 299 témoins, 87 des 102 variantes associées ont été répliquées (D. M. Howard et al. 2019). En revanche, il n'existe à ce jour aucun GWAS portant spécifiquement sur la dépression du post-partum, un phénotype particulier des troubles de l'humeur.

En conclusion, les facteurs associés à la dépression périnatale sont nombreux. Il s'agit d'une maladie complexe, multifactorielle. Les facteurs de risque retrouvés sont synthétisés dans la figure 3.

Figure 3 : Principaux facteurs associés à la dépression périnatale



I.E. Complications et conséquences

I.E.1. Pour la mère

Toutes les études montrent que la dépression périnatale a un impact négatif sur la mère comme sur les enfants (Fonseca et al. 2020).

La durée de l'épisode dépend de la précocité du diagnostic et de la prise en charge, mais on estime qu'environ 30 % des femmes restent symptomatiques un an après l'accouchement (Goodman 2004; L. M. Howard, Molyneaux, et al. 2014). Les symptômes dépressifs, parfois stables dans le temps, s'aggravent le plus souvent – avec des conséquences sur le fonctionnement psycho-social général des patientes, de leur enfant, de leur couple et plus généralement de leur famille (Roberts et al. 2006; Fonseca et al. 2020; Slomian et al. 2019).

Une étude danoise récente portant sur 15 852 femmes souffrant d'un trouble psychiatrique du post-partum léger à modéré et 4 266 femmes souffrant d'un trouble psychiatrique du post-

partum sévère, retrouvait un risque plus élevé de développer une pathologie médicale non psychiatrique ultérieurement par rapport aux femmes du même âge (Johannsen et al. 2020). La mortalité due à la fois à des causes naturelles et non naturelles était plus également plus élevée chez les femmes souffrant d'un trouble psychiatrique du post-partum, qu'il soit léger à modéré ou sévère (Johannsen et al. 2020).

Des idées suicidaires ainsi que des passages à l'acte peuvent émailler l'épisode dépressif – et ce d'autant plus que le tableau est sévère (Orsolini et al. 2016). Une étude retrouve une fréquence des idées d'automutilation de « quelques fois » à « souvent » chez 5,4 % des femmes déprimées dans le post-partum – ces pensées étant associées à l'importance des troubles du sommeil et de l'anxiété (Sit et al. 2015). Le suicide abouti correspond à la septième cause de décès maternel dans les 6 mois suivant l'accouchement (1,27 par 100 000 de décès maternels), soit plus de 4 % des décès maternels (Metz et al. 2016) ; et dans 21 % des cas les mères souffraient de dépression périnatale (Cantwell et al. 2011). Les conduites suicidaires sont majorées par l'absence de prise en charge (Cantwell et al. 2011).

A distance de la période périnatale, le risque de récurrence dépressive est évalué à 40 % au cours de la vie (Wisner et al. 2004; L. M. Howard et Khalifeh 2020) et approche de 50 % pour les grossesses suivantes (Goodman 2004). Plus généralement, la dépression du post-partum peut signer l'entrée dans une pathologie psychiatrique chronique telle qu'un trouble dépressif récurrent (ou trouble unipolaire), un trouble bipolaire, ou plus rarement, une schizophrénie.

I.E.2. Pour l'enfant

Concernant le bébé, la qualité des premiers échanges avec la mère est déterminante pour le devenir psychique de l'enfant. Ainsi, l'irritabilité, l'asthénie ou encore la culpabilité de la mère peuvent altérer la qualité des interactions précoces (Netsi et al. 2018; Slomian et al. 2019) et l'attachement de l'enfant (Śliwerski et al. 2020). L'enfant peut manifester des troubles de l'alimentation ou du sommeil et présenter un risque accru de troubles du développement cognitif, psychomoteur, émotionnel et social (Grace, Evindar, et Stewart 2003; Slomian et al. 2019; Stein et al. 2014). Les enfants dont la mère présentait des symptômes dépressifs persistants de la grossesse au post-partum, qu'ils soient intermédiaires ou élevés, présentaient des niveaux les plus élevés de difficultés émotionnelles et comportementales à l'âge de 5 ans (van der Waerden et al. 2015). De plus, les enfants dont la mère présentait des

niveaux élevés persistants de symptômes dépressifs avaient un mauvais développement cognitif altéré, marqué par des scores de QI moindre à 5 ans, en particulier chez les garçons, par rapport aux enfants dont les mères n'avaient jamais été déprimées (van der Waerden et al. 2017). Ces enfants sont également plus à risque de troubles psychiatriques pendant l'enfance, l'adolescence et à l'âge adulte (Murray et al. 2011; Kingston, Tough, et Whitfield 2012).

II. Trouble bipolaire en périnatalité

II.A. Épidémiologie

Les troubles bipolaires sont des troubles de l'humeur sévères, touchant 1 à 3 % de la population générale (Merikangas et al. 2011). Le trouble bipolaire débute classiquement chez les jeunes adultes avant l'âge de 25 ans et affecte également les hommes et les femmes (Ferrari et al. 2016). Le trouble bipolaire est l'une des principales causes d'incapacité et de décès prématuré chez les femmes en âge de procréer (The World Health Organization 2001; Ferrari et al. 2016; Global Burden of Disease Study 2013 Collaborators 2015).

La période périnatale est associée à un risque plus élevé de premier épisode ou de récurrence du trouble bipolaire (Sharma et Pope 2012; Jones et al. 2014; Parial 2015; Pope, Sharma, et Mazmanian 2014). Ainsi, près d'un quart des femmes souffrant de trouble bipolaire vont présenter un épisode thymique au cours de la grossesse, principalement dépressif ; ce qui est prédictif d'une décompensation dans le post-partum (Viguera et al. 2011; 2007; Stevens et al. 2019; Salim, Sharma, et Anderson 2018). Au cours du post-partum, plus de la moitié des femmes souffrant de trouble bipolaire vont présenter un épisode thymique (Viguera et al. 2011; Maina et al. 2014), ce risque augmente à 75 % chez les souffrant de trouble bipolaire non traitées au cours de leur grossesse (Viguera et al. 2011; Maina et al. 2014). En cas de décompensation, les dépressions sont les plus fréquentes (autour de 80% des épisodes thymiques du post-partum chez les patientes souffrant d'un trouble bipolaire) (Maina et al. 2014). Des épisodes hypomaniaques, maniaques ou mixtes peuvent également survenir pendant la période post-partum (Viguera et al. 2011; Doyle et al. 2012; Maina et al. 2014; Koukopoulos et al. 2020). Ils débutent plus précocement dans le post-partum que les épisodes dépressifs du post-partum (Di Florio et al. 2013). Ainsi, les épisodes maniaques apparaissent classiquement dans les trois premières semaines du post-partum, alors que l'apparition des épisodes dépressifs est plus largement distribuée dans la période post-partum (Laursen et Munk-Olsen 2010; Di Florio et al. 2013; Munk-Olsen et al. 2009). Les épisodes maniaques sont plus à risque de présenter des caractéristiques psychotiques que les épisodes dépressifs en période périnatale (Di Florio et al. 2013; Maina et al. 2014).

II.B. Sémiologie

II.B.1. Le trouble bipolaire en population générale

Le trouble bipolaire est caractérisé par une alternance d'épisodes dépressifs, d'épisodes (hypo)maniaques et de périodes d'euthymie (Grande et al. 2016).

Les épisodes (hypo)maniaques sont caractérisés par une humeur exaltée, expansive ou irritable de façon persistante (American Psychiatric Association 2013; Grande et al. 2016). Classiquement, les patients présentent une agitation psychomotrice. Les symptômes fréquemment associés sont une augmentation de l'estime de soi, des idées de grandeur, des troubles du sommeil sans fatigue associée, une distractibilité et un discours diffluent, ou encore une irritabilité. Il peut y avoir également une désinhibition comportementale, sexuelle, ou des achats pathologiques. Un épisode hypomaniaque est par définition moins intense. On parle d'épisode hypomaniaque si les symptômes cités sont présents de façon quasi constante, tous les jours, pendant au moins 4 jours. Un épisode maniaque est défini par la présence quasi permanente des symptômes décrit pendant au moins une semaine. Si la symptomatologie associe des éléments délirants, et/ou nécessite une hospitalisation, on parlera également d'épisode maniaque.

Le DSM5 distingue principalement deux entités cliniques (American Psychiatric Association 2013; Grande et al. 2016) :

- le trouble bipolaire de type I : défini par la présence d'un épisode maniaque au cours de la vie
- le trouble bipolaire de type II : défini par la présence d'au moins un épisode hypomaniaque et au moins un épisode dépressif au cours de la vie.

II.B.2. Le trouble bipolaire en périnatalité

Les épisodes thymiques du trouble bipolaire en période périnatale sont susceptibles d'être plus longs, résistants au traitement et associés à davantage de comorbidités addictives et comportements suicidaires que les épisodes survenant hors de cette période (Battle, Weinstock, et Howard 2014; Khan et Sharma 2015). Les femmes souffrant de trouble bipolaire sont plus susceptibles d'être hospitalisées dans le post-partum qu'en dehors de cette période ; et nécessitent également davantage d'hospitalisations que les femmes souffrant d'une autre maladie psychiatrique durant le post-partum (Munk-Olsen et al. 2009). Ainsi, une femme souffrant de trouble bipolaire sur quatre va nécessiter une hospitalisation en psychiatrie au

cours de la première année post-partum ; et ces hospitalisations sont plus longues qu'en dehors du contexte périnatale (Langan Martin et al. 2016; Shlomi-Polachek et al. 2017; Munk-Olsen et al. 2009).

Plus spécifiquement, les épisodes hypomaniaques sont largement sous-diagnostiqués (Sharma, Viguera, et al. 2020). Ils peuvent être confondus avec la dysphorie classique, non pathologique, du post-partum immédiat (Heron et al. 2009; Sharma, Burt, et Ritchie 2009). Une récente revue de littérature retrouvait que 9,6 à 49,1% des femmes en post-partum présentaient des symptômes hypomaniaques ; avec un risque plus important pour ces femmes de développer une dépression du post-partum par la suite (Sharma, Singh, et al. 2020). Les symptômes d'hypomanie ou de manie concernaient 12 à 30% des femmes orientées vers des établissements spécialisés en psychiatrie périnatale (Sharma, Singh, et al. 2020).

La manie survient classiquement dans les premiers jours post-partum. Le tableau clinique est dominé par une irritabilité, une agitation, une anxiété importante. Les symptômes maniaques classiques, tels qu'une logorrhée, une exaltation, une désinhibition et des idées de grandeur, sont moins fréquents dans les épisodes du post-partum qu'en dehors. En revanche, les caractéristiques mixtes y sont plus fréquentes, avec en particulier davantage de culpabilité, de tristesse, d'asthénie, et de moments de perplexité (Gordon-Smith et al. 2020; Ganjekar, Desai, et Chandra 2013).

Les caractéristiques psychotiques semblent également fréquentes dans le post-partum (Gordon-Smith et al. 2020; Ganjekar, Desai, et Chandra 2013).

II.B.3. La psychose puerpérale

La psychose puerpérale est un trouble rare : son incidence est estimée à 1-2 pour 1000 accouchements (Kendell, Chalmers, et Platz 1987). Son début est précoce, classiquement dans les premières semaines suivant l'accouchement et la durée moyenne est de 40 jours (Sit, Rothschild, et Wisner 2006). Cependant, il n'existe actuellement pas de consensus sur le délai d'apparition des symptômes après l'accouchement permettant de classer l'épisode dans le post-partum. Selon les auteurs, il peut aller des trois premières semaines aux six premiers mois après l'accouchement.

Le tableau clinique est volontiers polymorphe (Kamperman et al. 2017). On retrouve une irritabilité marquée, ainsi qu'une dysphorie. Les manifestations délirantes, comme des hallucinations, un déni de maternité, des idées de filiation mystique, ou encore une conviction

de substitution de l'enfant sont souvent prédominantes. Les thèmes de persécution (menaces, empoisonnements) sont fréquents. L'anxiété, des éléments confusionnels, une angoisse extrême et une insomnie complètent classiquement la clinique (Sit, Rothschild, et Wisner 2006). Le pronostic est marqué par le risque d'infanticide qui concerne 4 % des femmes présentant une psychose puerpérale (Spinelli 2004), et le risque suicidaire (Oates 2003).

La psychose puerpérale fait débat dans les classifications nosologiques. Les classifications internationales, la CIM-11 et le DSM-5, ne reconnaissent pas la psychose puerpérale comme une entité à part entière (American Psychiatric Association 2013; World Health Organization 2018). Depuis 2016, elle fait partie des maladies rares répertoriées par « Orphanet » (« Orphanet : Psychose puerpérale » 2016).

Bien qu'environ 50 % des femmes souffrant de psychose post-partum n'aient pas connu d'épisode psychiatrique antérieur, il existe un lien clair avec le trouble bipolaire, en particulier le trouble bipolaire I (Jones 2020). En effet, 20 % des patientes souffrant de trouble bipolaire vont présenter un tableau de psychose puerpérale au décours de leur accouchement (Jones et al. 2001; Robertson et al. 2005; Di Florio et al. 2013). Les femmes ayant des antécédents de psychose puerpérale ont un risque de près de 50 % de récurrence après un accouchement ultérieur (Di Florio et al. 2018). De plus la psychose puerpérale évolue dans plus de 60 % des cas vers un trouble bipolaire (Chaudron et Pies 2003; Robertson et al. 2005; Bergink, Rasgon, et Wisner 2016; Munk-Olsen et al. 2012).

II.C. Facteurs de risque

Le trouble bipolaire de type I est plus pourvoyeur de décompensation en période périnatale, et en particulier en post-partum, que les troubles bipolaires de type II (Maina et al. 2014).

Le facteur le plus prédictif d'une nouvelle décompensation périnatale chez femmes souffrant d'un trouble bipolaire est le fait d'avoir un antécédent de dépression périnatale : ainsi 55 % des patientes qui ont présenté un épisode à la première grossesse récidivent au cours de la suivante (Di Florio et al. 2018; Akdeniz et al. 2003; Wesseloo et al. 2016). Dans ce cas, dans plus de 85 % des cas, le nouvel épisode périnatal aura la même polarité que le premier (Maina et al. 2014).

L'absence de traitement thymorégulateur au cours de la grossesse est également un facteur de risque important de décompensation du trouble bipolaire en période périnatale, avec un risque multiplié par 3 comparé aux femmes souffrant de trouble bipolaire traitées (Wesseloo

et al. 2016). Ainsi, une revue systématique retrouvait une réduction de 66 % du risque de récurrence du trouble bipolaire chez les femmes ayant un traitement au cours de la grossesse, comparées à celles non traitées (Stevens et al. 2019).

De plus, la présence de symptômes thymique au cours de la grossesse, qu'ils soient dépressifs et/ou maniaques, est associé à un risque dix fois plus élevé de symptômes thymiques en post-partum (Marsh et Viguera 2012).

Enfin, un trouble dysphorique prémenstruel est également un facteur de risque de dépression durant le post-partum chez les femmes présentant un trouble bipolaire ; en particulier chez les femmes souffrant d'un trouble bipolaire de type II (Payne et al. 2007; Fornaro et Perugi 2010).

II.D. Complications et conséquences

II.D.1. Pour la mère

Les femmes souffrant de trouble bipolaire présentent un risque accru de suicide et davantage de comorbidités addictives par rapport aux femmes dans la population générale (Masters et al. 2019; Battle, Weinstock, et Howard 2014; Khan et Sharma 2015; Maina et al. 2014). Ainsi, près de 12 % des femmes souffrant d'un trouble bipolaire vont présenter un geste suicidaire (Maina et al. 2014).

Les épisodes thymiques au cours de la période périnatale sont un facteur de risque de récurrence lors de grossesses ultérieures (Pope, Sharma, et Mazmanian 2014; M. P. Freeman et al. 2002). Cependant, les conséquences sur l'évolution du trouble bipolaire sont mal connues. Nous étudierons cette question au cours de ce travail.

II.D.2. Pour la grossesse et l'enfant

On retrouve des complications obstétricales associées au trouble bipolaire, y compris chez des patientes euthymiques. Les patientes souffrant d'un trouble bipolaire présentent davantage d'hypertension gravidique, d'hémorragie de la délivrance et de retard de croissance intra-utérin (Rusner, Berg, et Begley 2016; Kingston, Tough, et Whitfield 2012; Johnson et al. 2014). Les épisodes de décompensations thymiques périnataux, et en particulier durant le post-partum, peuvent également avoir un impact négatif sur les interactions précoces entre la mère et l'enfant (Anke et al. 2019). Ainsi, les enfants dont les mères souffrent de trouble bipolaire

sont à risque de trouble du développement cognitif et émotionnel (Kingston, Tough, et Whitfield 2012; Johnson et al. 2014).

En conclusion, les troubles de l'humeur en période périnatale, et en particulier la dépression, sont donc des pathologies fréquentes, dont les conséquences à court et long terme, tant pour la mère que pour l'enfant, sont majeures, ce qui en font un problème de santé publique (Katherine L. Wisner, Chambers, et Sit 2006; Muñoz 2019). Il s'agit de maladies complexes dont les déterminants sont multiples : biologiques, psychiatriques et sociodémographiques.

Un antécédent de trouble unipolaire (au cours de la grossesse ou antérieur à celle-ci) ou de trouble bipolaire est le facteur de risque le plus important de dépression périnatale (Räsänen et al. 2013; Robertson et al. 2004; Biaggi et al. 2016; Guintivano, Manuck, et Meltzer-Brody 2018). Les autres troubles psychiatriques – addiction, troubles anxieux, trouble de la personnalité – peuvent être interprétés comme une vulnérabilité sous-jacente ou une comorbidité préexistante au trouble de l'humeur. Les événements de vie stressants, qu'il s'agisse de traumatisme infantile ou de conflits conjugaux, qu'ils soient en lien ou non avec la grossesse, sont également des facteurs associés à la dépression périnatale.

Hypothèses de travail

La dépression périnatale peut être distinguée par son début d'apparition. En effet, nous avons vu que dans un tiers des cas, elle débute au cours de la grossesse, puis qu'il existe un premier pic dans les premières semaines post-partum mais que le risque perdure au cours de la première année après l'accouchement.

Notre travail a pour but d'évaluer les dépressions périnatales et d'identifier les facteurs de risques liés aux événements de vie, aux facteurs environnementaux et génétiques.

De plus, l'impact des grossesses sur l'évolution des troubles de l'humeur reste mal connu. Notre but sera de l'analyser, en particulier pour les femmes souffrant de trouble bipolaire.

Objectifs et stratégies

Dans ce travail, nous allons d'abord chercher à évaluer la prévalence et l'incidence de la dépression périnatale en population française et américaine, en précisant celles-ci en fonction de la date d'apparition du trouble.

Par la suite, nous évaluerons les événements de vie et facteurs environnementaux associés à la dépression périnatale. Là encore, nous tenterons de mettre en évidence les différences

entre la dépression du post-partum à début précoce et à début tardif à travers des corrélats sociodémographiques, d'évènements de vie traumatique de l'enfance, de facteurs environnementaux liés ou non à la grossesse et enfin de facteurs génétiques.

Enfin, nous questionnerons l'impact des grossesses sur l'évolution du trouble bipolaire. Puis nous testerons le sous-groupe des femmes débutant un trouble bipolaire par une dépression du post-partum afin d'évaluer si elle constitue un phénotype particulier.

L'ensemble de ces travaux a pour but de mieux caractériser les troubles de l'humeur chez les femmes en période périnatale, en décrivant en mieux leurs corrélats et leurs conséquences, afin de prévenir et accompagner de façon spécifique et cibler ces patientes.

Matériel et méthodes

Afin de répondre à l'ensemble de nos hypothèses, nous avons utilisé trois cohortes de femmes, de grandes tailles, portant sur la dépression périnatale ou sur les troubles de l'humeur en général mais renseignant la période périnatale.

I. Cohorte IGEDEPP

I.A. Participants

Il s'agit d'une étude observationnelle longitudinale, appelée « Interaction gène-environnement dans la dépression du post-partum » (IGEDEPP), et ayant suivi 3310 femmes caucasiennes âgées de plus de 18 ans, qui ont accouché entre novembre 2011 et juin 2016. Les participantes ont été incluses entre le deuxième et le cinquième jour après l'accouchement, dans 8 services de gynécologie obstétrique de l'Assistance Publique des Hôpitaux de Paris (AP-HP) : Beaujon, Bichat, Louis Mourier, Necker, Béchère, Pitié-Salpêtrière, Port-Royal et Trousseau. Les critères d'exclusion étaient un accouchement avant 32 semaines d'aménorrhée, avoir un diagnostic de retard mental ou de schizophrénie selon le DSM-IV-TR et ne pas parler et comprendre le français.

Le taux d'acceptation a été de 61,2 %.

I.B. Évaluations

Les femmes incluses bénéficiaient de trois entretiens par un clinicien formé (psychologue ou psychiatre) : d'un entretien en face à face à la maternité dans les jours suivant l'accouchement, et 2 par téléphone à huit semaines puis à un an du post-partum.

J'ai pu, au cours de mon année de master 2, participer à l'inclusion des femmes à la maternité de Port Royal ; ainsi que réaliser les entretiens téléphoniques de suivi à 8 semaines et un an. L'ensemble des évaluations est résumé dans le **tableau 1**.

Tableau 1 : Évaluations comprises dans IGEDÉPP : temps initial, à 8 semaines puis un an post-partum

	Baseline	At 8 weeks	At one year
Evaluation socio-démographiques	X		
Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al. 1994)	X	X ^a	X ^b
Family Informant Schedule and Criteria (FISC) (Andreasen et al. 1977)	X		
Edinburgh Postpartum Depression Scale (EPDS) (Cox, Holden, et Sagovsky 1987; Guedeney et Fermanian 1998)	X	X	X
Hospital Anxiety and Depression Scale (HAD) (Zigmond et Snaith 1983)	X	X	X
Maternity blues Questionnaire (Kennerley et Gath 1989)	X		
Childhood Trauma Questionnaire (CTQ) (D. P. Bernstein et al. 2003; Paquette et al. 2004)	X		
Scaling of life events (Paykel scale) (Paykel 1997)	X	X	X
Évènements obstétricaux	X	X	X
Brief COPE (Carver 1997; Muller et Spitz 2003)	X		
CES-d (Radloff 1977)	X		

^a évaluation de la dépression uniquement.

^b évaluation de la dépression et de la manie.

Abréviations : CES-D : Center for Epidemiologic Studies Depression Scale; COPE : Coping Orientation to Problems Experienced.

I.B.1. Sociodémographiques

De façon systématique, les données sociodémographiques ont été recueillies au cours de la première évaluation : l'âge, le sexe, le niveau d'étude, la situation professionnelle actuelle, la situation familiale actuelle et le mode de vie.

I.B.2. Histoire psychiatrique

I.B.2.a. Histoire psychiatrique personnelle

I.B.2.a.i Antécédent au cours de la vie

L'histoire psychiatrique a été évaluée à l'aide de la DIGS (Diagnostic Interview for Genetic Studies), un entretien semi-structuré basé sur les critères internationaux du DSM (Nurnberger et al. 1994). Cette évaluation permet d'évaluer les troubles de l'humeur, trouble anxieux, trouble du comportement alimentaire ainsi que les troubles liés à l'usage de substance (entre autre : tabac, alcool et cannabis).

L'ensemble des psychologues cliniciens a été formé à cet entretien semi-structuré.

I.B.2.a.ii Évaluation de la dépression périnatale

Toutes les femmes ont été évaluées pour la dépression périnatale selon les critères du DSM-5 pour le trouble dépressif caractérisé (American Psychiatric Association 2013). La dépression a été évaluée à trois temps, en utilisant la DIGS : à l'inclusion pour le diagnostic de dépression actuelle (correspondant à la dépression en fin de grossesse), à 8 semaines post-partum pour le diagnostic de dépression du post-partum à début précoce et à un an post-partum pour la dépression du post-partum à début tardif. La dépression du post-partum à début tardif était définie par la présence d'un épisode dépressif caractérisé apparaissant entre deux mois et un an post-partum. Ainsi, la dépression du post-partum à début tardif a été évaluée rétrospectivement un an après l'accouchement et pouvait persister au moment de l'évaluation ou non. La dépression du post-partum à début précoce et celle à début tardif sont exclusives.

Toutes les femmes ont également été dépistées pour la dépression périnatale à chacun des trois moments par l'Échelle de dépression post-partum d'Édimbourg (EPDS) (Cox, Holden, et Sagovsky 1987; Guedeney et Fermanian 1998), l'auto-questionnaire le plus largement utilisé pour la dépression périnatale, et par deux échelles utilisées en population générale pour la

dépression : l'échelle Hospital Anxiety and Depression Scale (HAD) (Zigmond et Snaith 1983), un hétéro-questionnaire, et l'échelle du Center for Epidemiologic Studies Depression (CES-d) qui est un auto-questionnaire (Radloff 1977). Bien que toutes les femmes aient complété l'EPDS à chacun des trois temps d'évaluation, le diagnostic de dépression périnatale est basé uniquement sur l'évaluation clinique de l'entrevue DIGS selon les critères du DSM-5 pour l'épisode dépressif caractérisé.

Pour compléter cette évaluation thymique, nous avons utilisé la version française du questionnaire « maternity blues », un auto-questionnaire en 28 items permettant d'évaluer l'intensité du blues post-partum des jours 2 à 5 post-partum (Glangeaud-Freudenthal et al. 1995).

I.B.2.b. Histoire psychiatrique familiale

Les antécédents familiaux au premier degré (parents, frères et sœurs) de troubles psychiatriques ont été obtenus à l'aide du Family Informant Schedule and Criteria (FISC) évaluant les troubles de l'humeur, les troubles anxieux, la schizophrénie, les troubles liés à la consommation d'alcool et de substances (Andreasen et al. 1977). Les participants rapportant au moins un parent au premier degré avec un trouble psychiatrique ont été considérés comme ayant des antécédents familiaux du trouble donné.

I.B.3. Histoire obstétricale

Les caractéristiques obstétricales ont été collectées à la maternité par un hétéro-questionnaire évaluant les sujets suivants : un antécédents de grossesse, le recours aux techniques de procréation assistée (PMA), l'existence d'une grossesse multiple, l'existence d'une maladie chronique sous-jacente, la prise de médicaments ou une consultation d'urgence ou une hospitalisation pendant la grossesse et la raison de l'hospitalisation (hypertension, menace d'accouchement prématuré, diabète gestationnel, événement thromboembolique).

Les données sur l'accouchement comprenaient : le début du travail (spontané ou provoqué), le mode d'accouchement (vaginal ou césarienne, avant ou pendant le travail), l'utilisation de l'analgésie obstétricale et le traumatisme périnéal (aucun, épisiotomie ou traumatisme périnéal si déchirure périnéale ≥ 2 degrés). La prématurité (< 37 semaines de gestation), le

faible poids à la naissance (< 2500 g), la présence d'hémorragie post-partum, l'utilisation de l'unité de soins intensifs pour le bébé ou la mère et des informations sur l'allaitement étaient également collectées.

Lors de l'évaluation post-partum à 8 semaines, des informations sur les événements post-partum suivants ont été collectées : l'hospitalisation du bébé ou de la mère, la douleur, l'incontinence, l'activité sexuelle et l'allaitement.

À un an, nous avons évalué les mêmes événements post-partum, y compris l'hospitalisation du bébé ou de la mère, l'allaitement et une nouvelle grossesse.

Nous avons interrogé les femmes sur l'impact de tous les événements obstétricaux : les événements obstétricaux stressants sont ceux qui ont un impact négatif « marqué à sévère ».

I.B.4. Évènements de vie

Les traumatismes infantiles ont été étudiés à l'aide d'un auto-questionnaire, le Childhood Trauma Questionnaire (CTQ), composé de 28 questions englobant 5 types différents de traumatismes infantiles : abus émotionnels, physiques ou sexuels, et négligence émotionnelle ou physique et abus (D. P. Bernstein et al. 2003). Les scores seuils ont été définis par Paquette et al. pour déterminer la présence d'abus et ou négligence : > 10 pour les sous-scores de d'abus physique et de sexuelle, > 13 pour les sous-scores de négligence physique et > 15 pour les sous-scores d'abus psychologique et de négligence émotionnelle (Paquette et al. 2004).

Pour identifier les événements de vie stressants survenant pendant la grossesse et le post-partum, nous avons utilisé l'échelle de Paykel, un questionnaire à 64 items mesurant l'impact subjectif de chaque événement ainsi que l'ampleur du changement de vie lié à l'événement (Paykel 1997). Ces éléments sont organisés en catégories (travail, éducation, richesse, santé, deuil, déménagement, relations amoureuses, problèmes juridiques, famille, conjugal et autres). Les événements de vie stressants ont été définis comme des événements évalués par les participants comme ayant un impact négatif « marqué » à « grave ». En d'autres termes, les événements stressants étaient définis par l'expérience subjective de l'événement et non la gravité objective de l'événement de la vie lui-même. Des échelles de Paykel ont été administrées à 3 moments : à la maternité pour l'évaluation des événements stressants de la vie pendant la grossesse, par téléphone à 8 semaines et 1 an post-partum pour l'évaluation

des événements stressants pendant les semaines le post-partum précoce (avant 8 semaines) et tardif (entre 8 semaines et un an) respectivement.

Pour compléter l'évaluation des événements stressants de la vie, le BRIEF COPE a été utilisé pour évaluer des stratégies d'adaptation inappropriées face à des situations stressantes (Carver 1997; Muller et Spitz 2003).

I.B.5. Génétique

III.B.5.a. Constitution de la DNAtèque

Lors de la visite d'inclusion, une participation à l'étude génétique était proposée aux participantes. Après information et signature d'un consentement, un prélèvement génétique était réalisé à la maternité, par prélèvement sanguin (3 tubes K3 EDTA plastique de 10 ml). Les prélèvements étaient acheminés à la banque d'ADN et de cellules du Cricm (Centre de recherche de l'Institut du cerveau et de la moelle épinière ; UPMC/Inserm UMR_S975 CNRS UMR 7225) sur le site de la Pitié-Salpêtrière.

La banque d'ADN et de cellules (directeur : Pr Alexis Brice) est une plate-forme CRB – Centre de Ressources Biologiques- qui assurera la réception et l'anonymisation des prélèvements, l'extraction de l'ADN, le stockage des ADN extraits générés et la distribution d'aliquots aux utilisateurs chargés des analyses génétiques.

L'ADN est extrait manuellement par une méthode utilisant le phénol, à partir du sang. La concentration et la pureté de l'ADN sont mesurées au spectrophotomètre et la concentration est ajustée à 200 ng/μl. Les ADNs extraits sont stockés dans des congélateurs à -80°C.

III.B.5.b. Stratégie d'exploration génétique

Le génotypage a été réalisé au Centre National de Recherche en Génomique Humaine. Les participantes ont été génotypés à l'aide de la puce Global Infinium Array (Illumina). Cette puce permet de génotyper simultanément plus de 680 000 marqueurs génétiques. Parmi ces variants, 339 000 sont décrits dans les bases génétiques et 16 545 ont un effet biologique connu. Une étude d'association génome entier (GWAS), afin de cribler l'ensemble du génome sans a priori quant à l'implication d'une voie biologique spécifique, a été réalisée.

Les paramètres de contrôle de qualité pour conserver les SNP ont été ceux décrit par l'étude de Turner (Turner et al. 2011). Ainsi, nous avons conservé les SNPs dont la fréquence de l'allèle mineur (MAF) était supérieure à 0,05 chez les contrôles de notre étude, afin de préserver la

puissance statistique. Les variants présentant un écart à l'équilibre d'Hardy-Weinberg trop important ($p < 1 \times 10^{-8}$) ou une proportion de génotypes manquants trop importante ($> 2\%$) ont été exclus.

Puis une deuxième étape du contrôle qualité a concerné les échantillons. Ont été exclus de l'analyse les échantillons pour lesquels la proportion de génotypes manquants était supérieure à 5% et ceux dont le taux d'hétérozygotie s'écartait de plus de 3 déviations standards de la moyenne observée. Nous avons également exclu les échantillons qui n'étaient pas de sexe féminin et gardé un seul échantillon lorsque des apparentés ont été détectés.

Nous avons ensuite procédé à une étape d'imputation à partir des haplotypes issus de la base 1000 génomes. Seuls les variants avec une fréquence raisonnable ($MAF > 5\%$) et une bonne qualité d'imputation ($INFO > 0,8$) ont été retenus pour l'analyse. L'imputation a été réalisée avec les logiciels Shapeit (pour l'étape de pré-phasage des échantillons) et Impute2 (pour l'étape d'imputation).

A l'aide du logiciel Plink, et selon un modèle additif, nous avons estimé différents modèles logistiques avec plusieurs phénotypes de dépression post-partum (dépression du post-partum à début précoce d'une part, et dépression à début tardif d'autre part) comparée à des contrôles n'ayant pas eu de dépression au cours de la vie et de la période périnatale jusqu'à un an post-partum. Nous avons effectué des analyses d'association pour chaque SNP candidat afin de mieux comprendre l'implication des SNP avec chacun des deux phénotypes. La significativité de chaque SNP a été déterminée par un test de rapport de vraisemblance.

Pour chaque variant, la variable explicative était le nombre d'allèle mineur (analyse de type dosage). Le seuil de significativité utilisé n'est pas 0,05 mais bien inférieur pour éviter les erreurs de type I étant donné le grand nombre de marqueurs indépendant à étudier. Le seuil de la valeur de p est de 5×10^{-8} (Dudbridge et Gusnanto 2008).

I.C. Aspect réglementaires

Concernant les aspects réglementaires, l'étude a été validée par un comité d'éthique (Comité de Protection des Personnes Ile de France I, numéro 14769) et autorisé par la Commission Nationale de l'Informatique et des Libertés (CNIL), en accord avec les bonnes pratiques des études expérimentales. Le protocole de recherche (ClinicalTrials.gov, identifiant : NCT01648816) comprenait l'information des participantes et le recueil d'un consentement écrit.

II. Cohorte FACE-BD

II.A. Participants

Le réseau de centres experts dédiés au trouble bipolaire est un système de santé innovant en France, mis en place en 2007. Jusqu'à présent, les soins psychiatriques en France reposaient essentiellement sur les secteurs. En raison de la complexité du diagnostic et de la prise en charge des troubles bipolaires, le réseau des centres experts a été créé pour apporter un soutien aux cliniciens dans la prise en charge des patients souffrant de trouble bipolaire et, en parallèle, pour générer des recherches cliniquement pertinentes. Ce réseau est financé par le ministère français de la Recherche et soutenu par le ministère français de la Santé.

La cohorte FACE-BD (FondaMental Academic Centers of Expertise for Bipolar Disorders) est la base de données correspondant de centres experts bipolaires (Henry et al. 2011). C'est une étude prospective multicentrique, dont nous n'utiliserons que le premier temps d'évaluation. Les participants sont des patients consultants en ambulatoire, au sein du réseau national de 12 centres d'experts (Besançon, Bordeaux, Clermont-Ferrand, Colombes, Créteil, Grenoble, Marseille, Monaco, Montpellier, Nancy, Paris, Versailles), mis en place par la Fondation FondaMental (www.fondation-fondamental.org).

Les participants sont adressés par leur psychiatre ou médecin généraliste pour une aide au diagnostic ou à la prise en charge des patients atteints de trouble bipolaire.

Il n'y a pas de critères d'exclusion : ainsi tous les patients qui répondent aux critères de diagnostic pour tout sous-type de trouble bipolaire (I, II ou non spécifié [NOS]) peuvent être évalués.

II.B. Évaluations

Tous les participants ont eu une évaluation clinique, approfondie et standardisée par des cliniciens formés. Toutes les évaluations ont déjà été décrites en détail (Henry et al. 2011).

II.B.1. Données sociodémographiques

Les caractéristiques sociodémographiques ont été systématiquement enregistrées : âge à l'inclusion, le niveau d'éducation, le statut vis-à-vis de l'emploi et le statut matrimonial. Le nombre d'enfants étaient également indiqués.

II.B.2. Histoire psychiatrique

Le diagnostic de trouble bipolaire était déterminé à l'aide d'un entretien semi-structuré : la SCID (Structured Clinical Interview for DSM (SCID)), basé sur les critères internationaux du DSM-IV-TR (First 2015). Étaient également évaluées les principales caractéristiques du trouble bipolaire : l'âge à l'apparition, l'âge au premier traitement, la durée de la maladie non traitée, la durée de la maladie, le type de trouble bipolaire (I, II ou NOS), le nombre d'épisodes thymiques au cours de la vie (dépressifs, (hypo) maniaques ou mixtes, selon les critères du DSM-IV-R) et d'hospitalisations, le nombre d'épisodes à caractéristiques psychotiques et l'existence de cycle rapide. Concernant le premier épisode, sa polarité et sa survenue ou non dans le post-partum (soit dans les 6 mois suivant l'accouchement) était indiquées.

Nous avons également évalué le nombre de tentatives de suicide, les comorbidités psychiatriques (troubles anxieux, troubles du comportement alimentaire), les troubles liés à l'usage de substances (tabagisme actuel, abus d'alcool, abus de cannabis et autres abus : sédatifs, stimulants, opioïdes, cocaïne et hallucinogène), les troubles du sommeil (Pittsburgh Sleep Quality Index, PSQI) (Buysse et al. 1989), mais également l'obésité (indice de masse corporelle, IMC > 25) et les anomalies de la protéine C réactive (CRP) (> 3).

Les antécédents familiaux de troubles de l'humeur ont également été systématiquement collectés.

L'état thymique au moment de l'évaluation a été évalué à l'aide de l'échelle d'évaluation de la MADRS pour la dépression (Montgomery Asberg Depression Rating Scale) (Montgomery et Åsberg 1979) et de l'échelle d'évaluation de la manie YMRS (Young Mania Rating Scale) (Young et al. 1978).

Le traumatisme infantile a été évalué à l'aide du CTQ (Childhood Trauma Questionnaire) (D. P. Bernstein et al. 2003; Paquette et al. 2004).

Le fonctionnement global a été évalué à l'aide de la FAST (Functioning Assessment Short Test), y compris l'autonomie du fonctionnement professionnel, le fonctionnement cognitif, les problèmes financiers, les relations interpersonnelles et les loisirs (Rosa et al. 2007). Un score total élevé indique un mauvais fonctionnement.

Les traitements médicaux ont été collectés par auto-évaluation, suivant 5 classes pharmacologiques (antipsychotiques de première et deuxième génération, antidépresseurs, lithium, stabilisateurs de l'humeur et anxiolytiques), le nombre de médicaments psychotropes

et l'observance du traitement selon l'échelle d'évaluation MARS (Medication Adherence Rating Scale) (K. Thompson, Kulkarni, et Sergejew 2000; Misdrahi et al. 2004).

II.C. Aspects réglementaires

Le protocole d'évaluation, comprenant une lettre d'information pour les patients, a été approuvé par le comité de protection des personnes (CPP-Ile de France IX, 18 janvier 2010), conformément aux lois françaises sur les études non interventionnelles.

Une application Web, e-bipolar© a été développée pour collecter des données à des fins de surveillance clinique et de recherche. L'accès au système est soigneusement réglementé et l'agrément a été obtenu auprès de l'organisme de contrôle de la sécurité des bases de données informatisées (Commission nationale de l'informatique et des libertés, demande DR-2011-069).

III. Cohortes de la NESARC (vagues 1 et 2)

III.A. Participants

Nos données sont issues de la NESARC (The National Epidemiologic Survey on Alcohol and Related Conditions) un échantillon représentatif de la population non institutionnalisée des États-Unis. Il s'agit d'une cohorte prospective : les sujets ont été évalués deux fois : une première entre 2001 et 2002 (vague 1), puis une seconde entre 2004 et 2005 (vague 2). La vague 1 ciblait une population civile, de plus de 18 ans – avec un taux de réponse globale de 81 %, correspondant à 43 093 participants. La vague 2, conduite environ 3 ans après (moyenne entre les deux entretiens : 36,6 mois) – correspondant à 34 653 ayant complétés les deux vagues d'entretiens, soit un taux de réponse global de 70.2 % (Grant et al. 2003).

Les interviews en face-à-face ont été menées par des membres du U.S. Census Bureau spécifiquement formés. L'enquête a utilisé un plan d'échantillonnage à plusieurs degrés avec un sur-échantillonnage pour les individus hispaniques et noirs.

III.B. Évaluations

III.A.1. Sociodémographiques

L'âge, le niveau d'éducation, le revenu personnel au cours d'une année, le statut vis à vis de l'assurance, le statut matrimonial, l'urbanicité, et la région de résidence étaient recueillis à la vague 1.

L'indice de masse corporel (IMC) était calculé à partir du poids et de la taille déclarés à la vague 1 (surpoids ou obésité lorsque l'IMC \geq 25).

La question « avez-vous été enceinte au cours des 12 derniers mois ? » permettait de définir un groupe de femmes enceintes et dans le post-partum (<1 an).

Le nombre d'enfants était également recensé à la vague 1.

III.B.2. Histoire psychiatrique

III.B.2.a. Troubles psychiatriques et addictologiques personnels

Les diagnostics psychiatriques ont été mesurés à l'aide de l'AUDADIS-IV, une évaluation structurée, fiable et largement validée (Chatterji et al. 1997).

La dépression était étudiée à la fois sur la vie et au cours des 12 derniers mois.

Le trouble bipolaire de type I était défini comme au moins une manie au cours de la vie. Le trouble bipolaire de type II était défini comme une hypomanie à vie en l'absence de manie au cours de la vie. Les caractéristiques du trouble bipolaire recherchées étaient : l'âge au premier épisode, le nombre d'épisode dépressif, le nombre d'épisode maniaque, les hospitalisations pour manie ou dépression. L'évaluation prospective au cours de la vague 2 répertoriait l'incidence sur trois ans d'au moins un épisode dépressif, manie et hypomanie et les hospitalisations pour un épisode thymique à l'aide de l'AUDADIS-IV.

Par ailleurs, les troubles liés à l'usage de substances (y compris l'abus ou la dépendance à l'alcool, au cannabis, aux sédatifs, aux tranquillisants, aux opiacés, aux stimulants, aux hallucinogènes, au crack / cocaïne, aux inhalants / solvants, à l'héroïne et à d'autres drogues), les troubles anxieux (y compris le trouble panique, la phobie spécifique, la phobie sociale et le trouble d'anxiété généralisée) et les troubles de la personnalité (paranoïde, schizoïde, histrionique, antisocial, évitant, dépendant et obsessionnel-compulsif) étaient également évalués via l'AUDADIS-IV.

Le suicide était évalué si les répondants approuvaient une période d'humeur dépressive et / ou d'anhédonie pendant au moins 2 semaines. On a demandé aux participants s'ils avaient

déjà « tenté de se suicider » ou « envisagé de se suicider ». Les participants y répondant positivement ont été considérés comme ayant des antécédents de « tentative de suicide » ou « d'idées suicidaires », respectivement. Cette évaluation était répétée au cours de la vague 2 également.

III.B.2.b. Troubles psychiatriques familiaux

Un module spécifique de l'AUDADIS a été utilisé pour obtenir les antécédents familiaux de dépression évalués lors de la vague 1. Nous nous sommes intéressés aux antécédents familiaux au premier degré (soit les parents et la fratrie).

III.B.3. Évènements de vie

III.B.3.a. De l'enfance et l'adolescence

Un antécédent d'abus sexuel ou de violences physiques au cours de l'enfance était détectée au cours de vague 2 par les questions « Avez-vous été victime de violences sexuelles, de viol ou de rapports sexuels non désirés ? », « Avez-vous été agressé, battu, blessé avant l'âge de 18 ans ? » respectivement.

L'estime de soi était évaluée à la vague 1 par la question « Pensez-vous que vous n'êtes pas aussi bon, aussi intelligent, aussi attirant que la plupart des gens ? ».

Cinq questions permettaient de définir le soutien familial avant 18 ans – évaluant si quelqu'un dans sa famille lui voulait de la réussite, croyait en lui, l'aidait à se sentir important, ou si sa famille était une source de soutien ou encore qu'elle était unie. Dans cette étude, un manque de soutien familial au cours de l'adolescence était retenu si moins de 4 réponses sur les 5 étaient favorables.

III.B.3.b. Au cours des 12 derniers mois

L'ensemble des évènements de vie stressants était évalué sur la période des 12 mois précédent la deuxième interview en utilisant les 12 questions du Social Readjustment Rating Scale – telles que la perte d'un proche, ou la perte d'un emploi (Holmes and Rahe, 1967). Le deuil était évalué de façon spécifique.

La relation avec le conjoint était évaluée par le statut marital et en particulier une rupture récente ou des violences physiques ou sexuelles de la part du conjoint. De plus, la présence d'un trouble lié à l'usage d'alcool du conjoint était précisée.

Par ailleurs, les facteurs obstétricaux – parité et grossesse compliquée – reposaient chacun sur une question posée au cours de la vague 1 (nombre d'enfant et existence de complications lors de la dernière grossesse ou à l'accouchement).

Enfin, le diagnostic d'une pathologie physique (diabète, hypertension artérielle, dyslipidémie ou VIH) au cours des 12 derniers mois nécessitait une réponse positive à deux questions (« Avez- vous eu ... ? » puis « Un médecin a-t-il confirmé le diagnostic ? »)

La question « En général, diriez-vous que votre santé est excellente, bonne, passable ou mauvaise ? » permettait d'évaluer l'état de santé général perçu par le participant à la vague 2 – distinguant deux catégories dans notre étude (mauvais = « passable » ou « mauvais »).

III.C. Aspects règlementaires

Le protocole de recherche, y compris les procédures de consentement éclairé, a reçu l'approbation des instances éthiques américaines (l'US Census Bureau et le Bureau de la gestion et du budget pour NESARC).

Résultats

I. Dépression du post-partum, prévalence et incidence

Article 1 : Prevalence and incidence of postpartum depression and environmental factors: the IGEDEPP cohort

ARTICLE 1



Prevalence of mental disorders and stressful life events during pregnancy: the IGEDEPP cohort

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Ce premier travail permet de décrire la cohorte IGEDEPP (Interaction Gene Environnement dans la Dépression du Post-Partum), et d'évaluer dans cet échantillon la prévalence et l'incidence de la dépression du post-partum selon que son début soit précoce ou tardif (cf. méthodologie p. 37).

Dans les 8 maternités, 3310 femmes ont été incluses. Parmi elles, 3015 (91,1 %) ont été évaluées à 8 semaines post-partum et 2351 (71,0 %) femmes ont été suivies à 1 an post-partum.

Les participantes perdues de vue étaient significativement plus jeunes ($p < 0,05$) et moins instruites ($p < 0,05$). Les autres caractéristiques sociodémographiques et cliniques psychiatriques n'étaient pas significativement différentes selon que les participantes étaient perdues de vue ou non, y compris les antécédents d'épisode dépressif caractérisé.

Dans l'échantillon, la prévalence de la dépression du post-partum à début précoce était de 8,3 % (IC à 95 % 7,3 - 9,3) et de la dépression du post-partum à début tardif de 12,9 % (IC à 95 % 11,5 - 14,2), résultant en une incidence cumulée de la dépression du post-partum sur 8 semaines de 8,5 % (IC à 95 % 7,4- 9,6) et une incidence cumulée sur un an de 18,1 % (IC à 95 % : 17,1 à 19,2). Parmi les femmes présentant une dépression à début précoce, 68 restait déprimé en post-partum tardif (mais n'étaient pas considérés comme ayant une dépression du post-partum à début tardif).

La majorité des femmes de notre population avaient entre 26 et 34 ans (62,7 %), avec un âge moyen de 32 ans. La plupart des participantes étaient en couple (96,7 %), employées (93,3 %) et avaient un niveau de scolarité élevé (au moins jusqu' au lycée) (92,0 %).

Près de la moitié de notre cohorte ($N = 1571$, 47,5 %) avait des antécédents d'au moins un trouble psychiatrique ou addictologique, principalement un épisode dépressif caractérisé (35 %). Quarante-vingt-dix-huit femmes (3,0 %) ont signalé au moins une tentative de suicide. Les participantes avaient des antécédents personnels de trouble anxieux dans 16,0 % des cas, et de trouble du comportement alimentaire pour 4,1 % d'entre elles. Le trouble lié à l'usage de substances affectait 8,5 % des femmes, principalement le trouble lié à l'usage du tabac (7,1 %). Pendant la grossesse, 42 % des femmes ($n = 1\ 387$) ont bu au moins une fois de l'alcool et 0,32 % répondaient aux critères d'un trouble lié à la consommation d'alcool. Dans notre étude, 16 % des femmes avaient fumé du tabac et 0,85 % du cannabis pendant la grossesse.

La majorité (n = 2141, 64,7 %) des femmes avaient des antécédents familiaux au premier degré de troubles psychiatriques, les troubles de l'humeur étant les plus fréquents (signalés par 49,0 % des femmes),

Près de 300 femmes de la cohorte (9,0 %) ont signalé un traumatisme infantile.

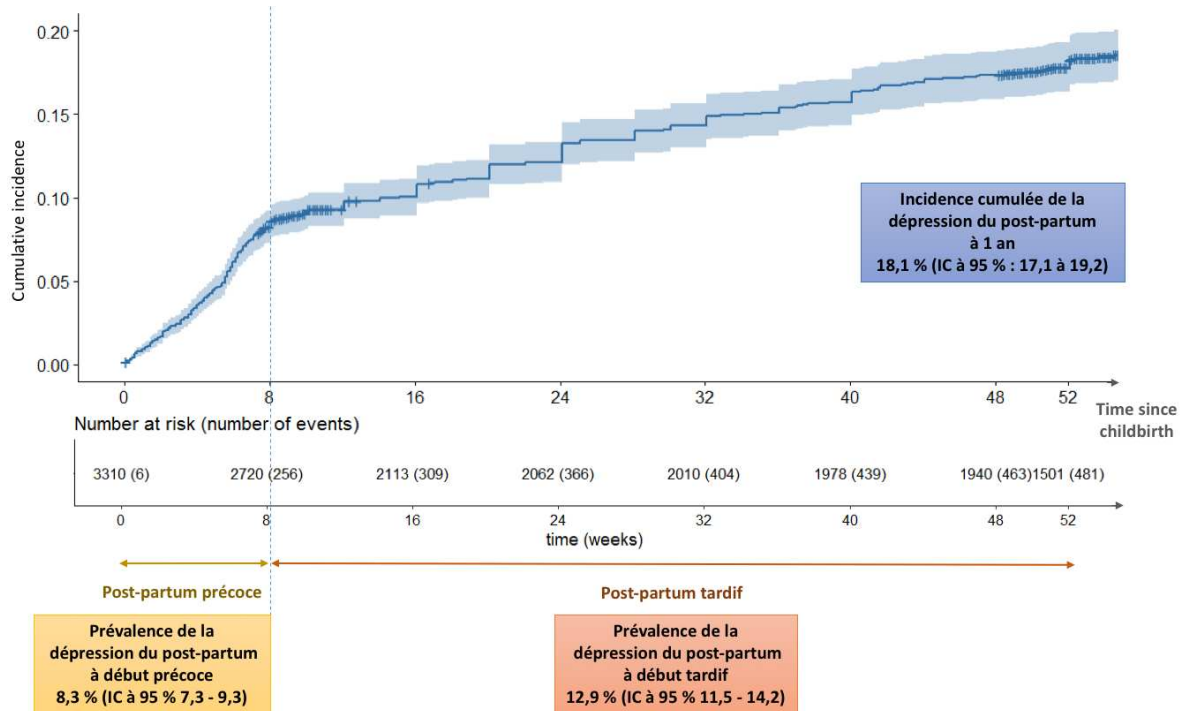
Pendant la grossesse, 47,7 % des femmes ont vécu un événement stressant, 30,2 % dans les 8 premières semaines et 43,9 % entre 8 semaines et un an post-partum.

Dans cette cohorte, les épisodes dépressifs incidents ont donc touché près d'une femme sur cinq au cours de la première année post-partum. Ces résultats sont cohérents avec différentes études internationales, évaluant la prévalence de la dépression du post-partum entre 10 et 20 % au cours de la première année post-partum (Ko et al. 2012; Heron et al. 2004; Shorey et al. 2018). Comme nous l'avons vu en introduction, ces variations peuvent être liées à différents facteurs. En particulier, nous avons choisi de distinguer deux temps d'évaluation dans le post-partum et utilisé un entretien semi-structuré pour le diagnostic reposant sur les critères internationaux pour la dépression, et non uniquement un auto-questionnaire de repérage de la dépression.

L'échantillon de femmes incluses dans IGEDEPP présente des caractéristiques sociodémographiques très favorables : les participantes avaient un niveau d'éducation élevé ; et la grande majorité d'entre elles travaillaient et étaient en couple. Par rapport à l'étude ALSPAC, une cohorte anglaise, les femmes d'IGEDEPP étaient plus susceptibles d'être en couple (96,7 % vs 79,4 %) (Fraser et al. 2013). Par rapport à l'enquête nationale périnatale française de 2016 (Blondel et al. 2017; French Ministry of Solidarities and Health 2017), un échantillon national des naissances, les femmes incluses dans l'IGEDEPP étaient plus âgées et avait un niveau d'éducation plus élevé. Malgré ses caractéristiques socio-économiques favorables, l'incidence de la dépression du post-partum reste élevée dans notre échantillon. D'ailleurs, une revue de la littérature récente a mis en évidence des résultats contradictoires concernant l'association entre le statut social et le risque de dépression du post-partum (Norhayati et al. 2015). Spécifiquement dans les pays développés, certains auteurs ont montré une association entre un faible niveau d'éducation ou de revenu et la dépression périnatale (Kim et al. 2008; Eastwood et al. 2012; Kozinszky et al. 2011), tandis que d'autres n'ont pas

trouvé cette association (Deng et al. 2014; Goker et al. 2012; Hamdan et al. 2012; Leigh et Milgrom 2008).

Figure 4 : Prévalence et incidence de la dépression du post-partum en fonction du temps.



Conclusion et perspectives :

Ce premier travail a permis de présenter notre cohorte IGDEPP, et de proposer un calcul de prévalence de la dépression du post-partum selon que son début soit précoce dans les premières semaines suivant l'accouchement, ou tardif jusqu'à un an (Tebeka, Le Strat, et al. 2020). Nous avons également proposé un calcul d'incidence cumulée pour évaluer la vitesse d'apparition de la maladie.

Nos travaux suivants vont s'attacher à distinguer la dépression du post-partum à début précoce et celle à début tardif.

Prevalence and incidence of postpartum depression and environmental factors: the IGEDEPP cohort

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ABSTRACT

Background: IGEDEPP (Interaction of Gene and Environment of Depression during PostPartum) is a prospective multicenter cohort study of 3,310 Caucasian women who gave birth between 2011 and 2016, with follow-up until one year postpartum. The aim of the current study is to describe the cohort and estimate the prevalence and cumulative incidence of early and late postpartum depression (PPD).

Methods: Socio-demographic data, personal and family psychiatric history, as well as stressful life events during childhood and pregnancy were evaluated at baseline. Early and late PPD were assessed at 8 weeks and 1 year postpartum respectively, using DSM-5 criteria.

Results: The prevalence of early PPD was 8.3% (95%CI 7.3-9.3), and late PPD 12.9% (95%CI 11.5-14.2), resulting in an 8-week cumulative incidence of 8.5% (95%CI 7.4-9.6) and a one-year cumulative incidence of PPD of 18.1% (95%CI: 17.1-19.2). Nearly half of the cohort (N=1571, 47.5%) had a history of at least one psychiatric or addictive disorder, primarily depressive disorder (35%). Almost 300 women in the cohort (9.0%) reported childhood trauma. During pregnancy, 47.7% women experienced a stressful event, 30.2% in the first 8 weeks and 43.9% between 8 weeks and one year postpartum. Nearly one in five women reported at least one stressful postpartum event at 8 weeks.

Conclusion: Incident depressive episodes affected nearly one in five women during the first year postpartum. Most women had stressful perinatal events. Further IGEDEPP studies will aim to disentangle the impact of childhood and pregnancy-related stressful events on postpartum mental disorders.

Keywords

- Postpartum
- Depression
- Prevalence
- Incidence
- Life events

INTRODUCTION

Pregnancy and postpartum comprise a timeframe in which the prevalence and the burden of depression is high (Howard et al., 2014; Mann et al., 2010; Tebeka et al., 2016). Postpartum depression (PPD) is a heterogeneous disease, both in terms of its symptoms as well as their onset (PACT Consortium, 2015; Putnam et al., 2017). Postpartum depression (PPD) is defined by international diagnostic criteria as a major depressive episode starting before the four (for DSM-5) or six week mark (for ICD-11) after delivery (American Psychiatric Association, 2013; World Health Organization, 2018). However, a broader definition, with a range up to one year postpartum is commonly used. This definition is also retained by the international Marce society of perinatal mental health (The International Marce Society, 2015). Although the definition remains controversial, some authors have proposed a definition of early PPD as beginning before the end of the first two months following birth, and late PPD as depression beginning between two months to one year after birth. (Gjerdingen et al., 2011; Norhayati et al., 2015).

PPD can have deleterious consequences for the mother. Suicide is the cause of more than 4% of maternal deaths (Metz et al., 2016). Forty percent of women who have experienced PPD will have a recurrence of depression within their lifetime (Howard et al., 2014); nearly 50% will experience another episode of PPD in subsequent pregnancies (Goodman, 2004). PPD is also associated with adverse outcomes for children (Netsi et al., 2018), including poor quality of early interactions with their mothers, pervasive effects upon their cognitive, emotional, and social development (Grace et al., 2003), and an increased risk for psychiatric disorders during infancy, childhood, adolescence and adulthood (Murray et al., 2011). PPD is therefore a major public health issue (Wisner et al., 2006).

PPD is considered to be a multifactorial disease, combining both environmental risk factors (including stressful life events), and genetic risk factors for depression (Howard et al., 2014). A better understanding of the pathophysiological mechanisms of PPD may help in targeting women at risk of PPD and developing programs in prevention and intervention. During the last decade, a wide range of research has helped to disentangle a number of factors associated with PPD, including pregnancy-related factors (gestational diabetes (Mak et al., 2018), hypertensive disorders (e.g. systolic blood pressure ≥ 140 mm Hg

or diastolic blood pressure ≥ 90 mm Hg, or proteinuria) (Strapasson et al., 2018) and stressful maternal experiences (such as sexual assault, physical violence, and emotional distress) (Zhang et al., 2018).

There are different methods to diagnose PPD: structured interviews, such as the Composite International Diagnostic Interview (Robins et al., 1988) or the Mini International Neuropsychiatric Interview (Lecrubier et al., 1997), semi-structured interviews such as the Structured Clinical Interview for DSM disorders (First, 2015), or Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994), or self-questionnaires such as Edinburgh Postnatal Depression Scale (EPDS) (Chaudron et al., 2010; Cox et al., 1987). Structured interviews administered by interviewers without any training; without a clinician's assessment, may induce an overestimation of depression (Levis et al., 2019, 2018). Self-questionnaires are easy to use and well accepted. EPDS is the most validated and widely used tool for peripartum depression in the world (Hewitt et al., 2010). However, it is a self-questionnaire validated only for PPD screening and includes different validated cutoff scores depending on whether it's being used in studies, across different countries, or in the ante or postnatal period of assessment (Hewitt et al., 2010; Norhayati et al., 2015; Smith-Nielsen et al., 2018). Although semi-structured interviews are time-consuming and require clinically trained interviewers, we favored this approach which allows for a reliable diagnosis, taking into account clinical judgment for each symptom of PPD.

Based on a large prospective multicentric cohort of women in the postpartum period, our aims were threefold: (1) to describe the IGEDEPP cohort (Interaction of Gene and Environment of Depression during PostPartum) developed to identify risk factors for PPD, (2) to estimate the cumulative incidence and prevalence of PPD at 8 weeks and one year after delivery, and (3) to estimate the prevalence of lifetime psychiatric disorders (mood, anxiety, eating and substance use disorders and suicide attempts) and the frequency of stressful events during childhood, pregnancy, and postpartum.

METHODS

Participants

IGEDEPP is a prospective cohort of 3,310 Caucasian women who gave birth in eight maternity departments in the Paris metropolitan area in France, between November 2011 and June 2016. The

women included in this cohort were aged over 18, Caucasian, French speaking, and were covered by French social insurance. The sample was restricted to Caucasian women to ensure ethnic homogeneity for genetic studies. Women were defined as Caucasian if they self-declared that their four grandparents were Caucasian. Exclusion criteria were delivery before 32 weeks of gestation, schizophrenia or mental retardation which were assessed clinically according to international criteria. Women meeting the inclusion criteria were visited by a clinician who presented the study at the maternity department between the second and the fifth day after delivery. After the patient provided consent, she had a blood test and a 30- to 90-minute interview with the clinician. No information was obtained from the medical record; all information was collected during the interview with the clinician. Acceptance rate was 61.2%. No data was collected on any woman who refused participation.

The research protocol (ClinicalTrials.gov Identifier: NCT01648816), including informed consent procedures, was approved by the French Ethics committee (Ile de France I) and Data Protection and Freedom of Information Commissions.

Measures

Women were evaluated by a clinician at three points over the course of one year. The interviewers were psychiatrists or psychologists who received specific training to administer the semi-structured interview of the DIGS, and to assess patients' psychiatric history, as well as their life events. They benefited from training on all scales of the study. The first face-to-face interview took place at the maternity department between the second and fifth day after delivery. The second and third interviews were conducted via phone calls at 8 weeks and one year postpartum. All assessments are summarized in table 1.

Screening tools and diagnosis of early and late PPD

All women were assessed for PPD in concordance with DSM-5 criteria for major depressive disorder (American Psychiatric Association, 2013). Depression was evaluated at three time points, using the DIGS: at inclusion for the diagnosis of current depression and a history of depression, at 8 weeks

postpartum for the diagnosis of early PPD, and at one year postpartum for late PPD. Late PPD was defined by the presence of a major depressive episode with onset between two months and one year postpartum. Women were assessed for the onset of depressive symptoms in the past 10 months and their duration. Thus, late PPD was assessed retrospectively one year after delivery, and could persist at the time of assessment or not.

All women also were screened for PPD at each of the three time points by the Edinburgh Postpartum Depression Scale (EPDS) (Cox et al., 1987; Guedeney and Fermanian, 1998), the most widely used self-administered questionnaire for PPD, and by two scales used in the general population for depression: the Hospital Anxiety and Depression Scale (HAD) (Zigmond and Snaith, 1983), a hetero questionnaire, and the Center for Epidemiologic Studies-Depression (CES-d) scale (Radloff, 1977), a self-administered instrument. Although all of the women in our sample had completed the EPDS at each of the three evaluations, the diagnosis of PPD according to DSM-5 criteria for major depressive disorder is based solely on the clinical evaluation of the DIGS interview.

To complete the mood assessment, we used the French version of the “maternity blues” questionnaire, a 28-item self-administered questionnaire to assess the intensity of postpartum blues on days 2 to 5 postpartum (Glangeaud-Freudenthal et al., 1995).

Sociodemographic Measures at the first evaluation

Age, marital status, educational level, employment, and health insurance status were systematically collected. Age at interview was categorized into: (i) 18–25, (ii) 26–34, (iii) 35–39, and (iv) 40 years or more. Marital status was assessed using six categories, grouped into two clusters: (i) widowed, divorced, separated, never married and (ii) married and common-law married. Educational level was classified into: (i) high school level or below, (ii) university level or higher. Employment status was categorized into: (i) employed and (ii) unemployed. Health insurance status was categorized into (i) covered under social security, the usual health insurance scheme and (ii) covered under universal healthcare system (PUMA) free healthcare available to low income families.

Lifetime psychiatric disorders assessed at the first evaluation

All women were evaluated by a trained clinician (psychologist or psychiatrist) using the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994; Preisig et al., 1999), a semi-structured interview assessing depression and other psychiatric or substance use disorders according to DSM-IV-TR criteria over the lifetime. Regarding the diagnosis of depression, we applied DSM-5 criteria for all depressive disorders including depression with mixed characteristics (which were precisely sought using of the DIGS), but excluding bereavement as a criterion (American Psychiatric Association, 2013). All clinicians were specifically trained to administer the DIGS interview. We reported lifetime prevalence for mood disorders (including major depressive episode, and bipolar disorder), anxiety disorders (including panic disorder, agoraphobia, social anxiety disorder, specific phobia, social phobia, generalized anxiety disorder and obsessive-compulsive disorder), substance use disorders (including those related to tobacco, alcohol, cannabis, cocaine, stimulants, opiates, hallucinogens and other drugs), as well as eating disorders (anorexia and bulimia). Regarding substance use, a pregnancy-specific assessment was proposed to assess tobacco, alcohol and cannabis use specifically in the first, second and third trimesters of pregnancy. Lifetime suicide attempts were also assessed.

First-degree family history (parents and siblings) of psychiatric disorders was obtained using the Family Informant Schedule and Criteria (FISC) (Andreasen et al., 1977) assessing mood disorders, anxiety disorders, schizophrenia, alcohol and substance use disorders for all first degree relatives. Participants reporting at least one first degree relative with a psychiatric disorder were considered as having a family history of the given disorder.

Stressful life events during childhood, pregnancy, and postpartum.

Childhood trauma was investigated using a self-administered questionnaire, the Childhood Trauma Questionnaire (CTQ), composed of 28 questions encompassing 5 different types of childhood trauma: sexual abuse, emotional or physical neglect and abuse (Bernstein et al., 2003). Cut-off scores were defined by Paquette et al. (Paquette et al., 2004) to determine the presence of abuse/neglect: > 10

for physical abuse and sexual abuse sub-scores, > 13 for physical neglect sub-scores, and > 15 for emotional abuse and emotional neglect sub-scores.

To identify stressful life events occurring during pregnancy and postpartum, we used the Paykel scale (Paykel, 1997), a 64 item questionnaire measuring the subjective impact of each event along with the extent of life change related to the event. These items are organized into categories (work, education, wealth, health, bereavement, relocation, romantic relationships, legal issues, family, marital and other). Stressful life events were defined as events rated by participants as having a “marked” to “severe” negative impact (impact score of 1 to 2). In other words, stressful events were defined by the subjective experience of the event; and not the objective severity of the life event itself. Paykel scales were administered at 3 time points: at the maternity department for the evaluation of stressful life events during pregnancy, by phone at 8 weeks and 1 year postpartum for the evaluation of stressful events during weeks 0-8 and 8-52 respectively. For each category, we reported the number and proportion of participants who declared at least one stressful event.

To complete the assessment of stressful life events, the BRIEF COPE was used to evaluate inappropriate coping strategies for stressful situations (Carver, 1997; Muller and Spitz, 2003).

Obstetrical characteristics during pregnancy and postpartum

Obstetric characteristics were collected at the maternity department by a hetero-questionnaire evaluating the following subjects: past history of pregnancy, use of assisted reproductive technology (ART), existence of multiple pregnancy, existence of a chronic underlying disease, medication or emergency consultation or hospitalization during pregnancy, and the reason for hospitalization: hypertension, threatened preterm delivery, gestational diabetes, thromboembolic event. Data on delivery included: labor onset (spontaneous or induced), mode of delivery (vaginal or cesarean (before or during labor)), use of obstetrical analgesia and perineal trauma (none, episiotomy, or perineal trauma if \geq 2-degree perineal tear). Prematurity (< 37 weeks of gestation), low birth weight (<2500g), presence of postpartum hemorrhage, use of the intensive care unit for the baby or the mother, and information on breastfeeding was collected.

At the 8 weeks postpartum assessment, information on the following postpartum events was collected: hospitalization for baby or mother, pain, incontinence, sexual activity and breastfeeding. At one year, we assessed postpartum events including hospitalization for baby or mother, breastfeeding and new pregnancy.

We asked the women about the impact of all obstetrical events: stressful obstetrical events are those with a “marked to severe” negative impact.

Statistical Analyses

The variables describing the included population were reported, for binary variables, as counts and percentages. For quantitative variables, descriptive statistics were mean and standard deviations or median and interquartile range. Cumulated incidence estimates were reported along with their 95% confidence intervals (95 % CI) derived by Kaplan-Meier survival analysis. Follow-up time for cumulative incidence started at delivery and ended at the date of last contact (for participants without depression) and at the reported beginning of symptoms for participants with depression. Comparisons of baseline characteristics between participants lost to follow-up and others were performed by logistic regression. Odd Ratios (ORs) and their 95 % CI are reported with the asymptotic p-value from Wald’s statistic.

All computations were done with the software R, version 3.4.

RESULTS

At the maternity departments, 3310 women were included. Of these 3015 (91.1%) were assessed at 8 weeks postpartum and 2351 (71.0 %) women were followed-up at 1 year postpartum (**Figure 1**).

Participants lost to follow-up were significantly younger ($p < 0.05$) and less educated ($p < 0.05$) than those who were not lost to follow-up. Other baseline characteristics were not significantly different among the two groups, including lifetime history of major depressive episode (**Supplementary tables 1 and 2**).

PPD prevalence and cumulative incidence (figure 2)

Among the 3015 women assessed at 8 weeks postpartum, 250 (8.3%, 95%CI 7.3-9.3) met criteria for early PPD. Among the 2351 women assessed at one year postpartum, 304 (12.9 %, 95%CI 11.6-14.3) met criteria for late PPD, 68 of whom already had early PPD. Before 8 weeks postpartum, 256 incident cases of PPD were recorded, resulting in a cumulative incidence of 8.5% (95%CI 7.4-9.6). The prevalence was heterogeneous among centers (**Supplementary table 3**). A total of 481 women presented with PPD during the first year after delivery and the one-year cumulative incidence of PPD was 18.1% (95%CI: 17.1-19.2). **Figure 2** presents the incidence curve over time during the first year. Among the women who completed the three assessments, 1875 were not diagnosed with a major depressive episode in the period of pregnancy and postpartum.

Sociodemographic characteristics at the first evaluation (table 2)

The majority of women in our sample were between 26 and 34 years old (62.7 %), with an average age of 32 years. Most of the participants were currently married or in domestic partnerships (common-law married) (96.7 %), employed (93.3 %), and had a high level of education (92.0 %).

Family and personal lifetime psychiatric history at the first evaluation (tables 3 and 4)

Nearly half of the women reported at least one lifetime psychiatric or addictive disorder (n=1571, 47.5%). More than one third of women had a history of mood disorder (n=1168, 35.3 %), mainly major depressive episode. Only 6 (0.2%) of our sample had a history of bipolar disorder. Major depressive episode during the current pregnancy concerned 3.7 % of the whole sample. Ninety-eight women (3.0 %) reported at least one suicide attempt. A personal history of anxiety disorder was reported by 546 (16.0 %) participants, including specific phobia (7.2 %), agoraphobia (5.1 %), social anxiety (4.2 %), generalized anxiety disorder (2.1 %), panic disorder (1.5 %) and obsessional compulsive disorder (0.2 %). A lifetime history of eating disorder was reported by 4.1 % of participants, including anorexia (3.7 %) and bulimia (1.2 %).

Substance use disorder affected 8.5 % of women, mainly tobacco use disorder (7.1 %). Excluding tobacco, substance use disorders were reported by 2.3 % of the sample: 1.7 % of women had a lifetime

history of cannabis use disorder, 0.6 % presented a lifetime history of alcohol use disorder and 0.4 % reported other lifetime substances use disorders (cocaine, stimulant, opioids, hallucinogens and others). During pregnancy, 42% of women (n=1387) drank at least once alcohol and 0.32% met criteria for an alcohol use disorder. In our cohort, 16% of women had smoked tobacco during pregnancy, while 0.85% of women reported having used cannabis, and 0.21% had a cannabis use disorder during pregnancy.

The majority (n=2141, 64.7 %) of women had a family history of psychiatric disorder with mood disorders being the most frequent (reported by 49.0 % of women), followed by family history of anxiety disorder (21.0 %), family history of alcohol use disorder (15.1 %) and family history of schizophrenia (1.4 %).

Stressful life events during childhood, pregnancy, and postpartum period (tables 5 and 6)

About one in ten woman (9.0 %) reported childhood trauma. The most frequent kind of trauma reported was emotional neglect (5.9 %), followed by sexual abuse (2.6 %), physical abuse (2.1 %), emotional abuse (2.0 %) and physical neglect (0.79 %) (**Table 5**).

During pregnancy, 85.0 % of women experienced at least one event listed on the Paykel scale. A total of 1578 (47.7 %) women experienced a stressful event with a high negative impact (**Supplementary table 4**). During the 8-week follow-up, 912 (30.2 %) women experienced at least one stressful event with a negative impact. During the 1-year follow-up, 1033 (43.9 %) reported at least one stressful with a negative impact.

Obstetrical characteristics during pregnancy and postpartum (table 6)

Assisted reproductive technology was necessary for 269 (8.1 %) women. Among our sample, 1242 (37.5 %) women were primiparous, 105 (3.2 %) had a multiple pregnancy and 439 (13.3 %) women had been hospitalized during pregnancy. In the IGEDEPP sample, 1982 (59.9 %) women had spontaneous labor onset; 2493 women (24.7 %) had a cesarean delivery. Among the women, 516 (15.6 %) intended to deliver with obstetrical analgesia but ultimately delivered without, 782 (23.6) had an episiotomy and 30 (0.9 %) had perineal trauma. Delivery events with a negative impact concerned 846 (25.6 %) of women. Those

events included preterm birth (4.8 %), low birth weight (6.3 %), intensive care for the baby or the mother (1.1 % each), and postpartum hemorrhage (4.6 %).

At 8 weeks, 637 (21.1 %) women had at least one postpartum event with a negative impact. The main events reported were hospitalization for the child (11.0 %) or the mother (1.3 %), pain or incontinence (25.7 %) and the absence of sexual activity (30.0 %). One year after birth, 419 (17.8 %) women had at least one postpartum event with a negative impact. The main events reported were hospitalization or disease of the child (15.9 %), or the mother (1.4 %). A new pregnancy concerned 4.1 % of women.

Breastfeeding after birth concerned 2372 women (71.7 %) and the median duration of breastfeeding was 12 weeks (interquartile range 7-24). The prevalence of breastfeeding was 52.8 % at 8 weeks and 8.2 % at one year postpartum.

DISCUSSION

This study aimed to describe IGEDPEP data for the first time. IGEDPEP is the largest prospective multicenter cohort to our knowledge of 3310 pregnant women followed-up for 1 year to determine the prevalence of early and late postpartum depression (PPD) during the first year after delivery. In the first postpartum year, the cumulative incidence of PPD was 18.1 %. Early PPD affected 250 women (8.3 %), and 304 women had late PPD (12.9 %). These results are consistent with different international studies, evaluating PPD prevalence between 10 and 20 % during the first year postpartum (Ko et al., 2012; Heron et al., 2004; Shorey et al., 2018). Many factors can explain this range: the studies are heterogeneous in terms of population, timing of assessment and diagnostic tools (Norhayati et al., 2015). For instance, we used a diagnosis based on clinical evaluation with DSM-5 criteria, whereas most studies rely only on a screening questionnaire, leading to possible fluctuations in PPD prevalence.

Our sample has very favorable socio-demographic characteristics: the women included had a high level of education; and the vast majority of them worked and was in a relationship. Compared with the ALSPAC study, an English cohort, the women in IGEDPEP were more likely to be in a relationship (96.7% vs

79.4%) (Fraser et al., 2013). Compared with the 2016 French National Perinatal Survey (Blondel et al., 2017; French Ministry of Solidarities and Health, 2017), a national sample of births, women included in IGEDEPP were older (mean age was 30.3 vs. 32 years old in our sample) and had a higher level of education (55.4% vs. 92%). Despite its favorable socio-economic characteristics, the incidence of PPD remains high in our sample. A recent literature review highlighted conflicting results for the association between social status and risk of PPD (Norhayati et al., 2015). In developed countries, some authors have shown an association between a low level of education or income and PPD (Eastwood et al., 2012; Kim et al., 2008; Kozinszky et al., 2011), while others did not find this association (Deng et al., 2014; Goker et al., 2012; Hamdan et al., 2012; Leigh and Milgrom, 2008).

Nearly half of the women reported at least one lifetime psychiatric disorder, and one third of the women had a history of mood disorder. Prior research from the EDEN mother-child French cohort) found a history of mental health problems for 11% at 12.6% of women of childbearing age (Melchior et al., 2012; van der Waerden et al., 2015). This prevalence was based on a single question about psychiatric history, which may explain why it is much lower than that of our cohort. Indeed, we found similar rates of personal psychiatric history to those described in the National Epidemiologic Study of Alcohol and Related Conditions (NESARC), a study of 1085 peripartum women representative of the United States population assessed with DSM criteria, (48 % in both samples). However, French women of the IGEDEPP study were more likely to report a personal history of mood depressive disorder (35 % vs. 22 %) and more familial history of mood disorder (49 % vs. 37 %) than US women (Tebeka et al., 2016). One of the explanations could be that the two population (US vs French) and the assessment were different (depression in the past year vs prospective assessment in the first year postpartum).

Moreover, the same percentage of women reported at least one stressor event during pregnancy (85 % vs. 82 %, respectively) in our sample and in NESARC study (Tebeka et al., 2016).

Our study has several strengths. First, to our knowledge, it is the largest multicenter prospective study of postpartum women which aims to evaluate the development of depression at 3 time points during the first year after birth. Moreover, depression diagnosis was established by a trained clinician using reliable DSM-5 criteria and does not rely solely on the use of a screening questionnaire, such as

EPDS. Furthermore, IGEDEPP provides an extensive assessment of a wide range of psychiatric disorders, including mood and anxiety disorders, substance use disorders and many stressful life events during childhood, pregnancy and one-year postpartum, as well as a broad assessment of obstetric events. Very few participants were lost to follow-up during the study: we had 91% available data at 8 weeks postpartum evaluation, and 71% at 1 year, increasing the external validity of these findings. However, because we have no data on those who refuse to participate to this cohort, we cannot avoid an inclusion bias of subjects with PPD that could change the incidence and prevalence.

Some limitations should be considered when interpreting these results. First, participants in the IGEDEPP study reported higher levels of education than in the general population (INSEE, 2018), a finding which has also been associated with genetic research participation (Hensley Alford et al., 2011; McQuillan et al., 2003). This limits the generalizability of our findings. The eight inclusion centers were in Paris or in the Paris suburbs. This population is not representative of France. A general population study comparing a population from Ile de France to one from low Normandy found differing rates of depression: severe depression during the last year was more common in urban areas, and severe lifetime depression was more frequent in individuals living in flats in large building complexes. However, after adjusting for sex, age, marital status and negative life events, there was no longer any difference in the prevalence of depression in the two populations (Kovess-Masfety et al., 2005). Further study should examine how to reach the population currently excluded from genetic studies. Second, the sample is composed only of Caucasian women, in line with the design of the IGEDEPP study which includes a genetic component. Our study did not include French women of non-Caucasian ascent or migrant women and as migration is a known risk factor of postpartum depression (Ahmed et al., 2008; Falah-Hassani et al., 2015), we may have underestimated the prevalence of PPD in the general French population and lost information on risk factors in this vulnerable sub-group. Third, we only included women aged 18 or more. Adolescent pregnancy is associated with an elevated risk of depression and other psychiatric disorders and is associated with specific social and environmental conditions. Further study should examine whether the evidence provided by the IGEDEPP cohort apply to adolescent pregnancy or not. In addition, we used the CTQ to evaluate childhood trauma. The CTQ has been validated in a population of women of childbearing

age, regardless of their pregnancy or postpartum status (Grassi-Oliveira et al., 2014; Paquette et al., 2004). According to a recent literature review, the CTQ is the most relevant tool for evaluating childhood trauma in the perinatal period (Choi and Sikkema, 2016). Finally, different clinicians have participated in the evaluation of patients, and although they have all benefited from specific training, we cannot exclude bias.

Incident PPD affects 18.1 % of women in the first year postpartum. Thanks to the evaluation of many different factors, including socio-demographics, family and personal psychiatric history, stressful life events during childhood, negative pregnancy, postpartum and obstetric events, the IGEDEPP study will be able to better characterize the factors associated with early and late PPD. In addition, genetic analyses with both gene candidates and a GWAS approach aim to clarify the genetic determinants of PPD. Finally, analysis of the interaction between genetic variants and life events will allow to accurately describe factors associated with PPD. Identifying a vulnerable population is necessary to develop prevention and intervention strategies during the pregnancy and postpartum period.

LIST OF ABBREVIATIONS

95%CI: 95% confidence interval

ART: assisted reproductive technology

CTQ: Childhood Trauma Questionnaire

EPDS: the Edinburgh Postnatal Depression

IGEDEPP: Interaction of Gene and Environment of Depression during PostPartum

ORs: Odd Ratios

PPD: Postpartum Depression

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	Baseline	At 8 weeks	At one year
Socio demographic assessment	X		
Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994)	X	X ^a	X ^b
Family Informant Schedule and Criteria (FISC) (Andreasen et al., 1977)	X		
Edinburgh Postpartum Depression Scale (EPDS) (Cox et al., 1987; Guedeney and Fermanian, 1998)	X	X	X
Hospital Anxiety and Depression Scale (HAD) (Zigmond and Snaith, 1983)	X	X	X
Maternity blues Questionnaire (Kennerley and Gath, 1989)	X		
Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003; Paquette et al., 2004)	X		
Scaling of life events (Paykel scale) (Paykel, 1997)	X	X	X
Obstetrical events	X	X	X
Brief COPE (Carver, 1997; Muller and Spitz, 2003)	X		
CES-d (Radloff, 1977)	X		

Table 1: measures made at baseline, 2nd and 3rd interviews

^a only depression assessment.

^b only depression and mania assessment.

Abbreviations: CES-d, Center for Epidemiologic Studies Depression Scale; COPE, Coping Orientation to Problems Experienced;

	N (%)
Age (y) ^a	
25 or less	158 (4.8)
26-34	2077 (62.7)
35-39	826 (25.0)
40 or more	248 (7.5)
Marital status	
Widowed, divorced, separated, never married	108 (3.3)
Married, common-law married	3202 (96.7)
Education level ^b	
University	3044 (92.0)
Primary or high school	261 (7.9)
Employment ^c	
Unemployed	222 (6.7)
Employed	3088 (93.3)
Health insurance ^b	
Social security	3281 (99.1)
Universal healthcare system (PUMA)	24 (0.7)

Table 2: Sociodemographic characteristics among IGEDEPP cohort respondents (N=3310)

^a Data missing for 1 participant; ^bData missing for 5 participants; ^cData missing for 1 participant;

Abbreviations: PUMA, Protection Maladie Universelle ;

	N (%)
Mood disorders (any)	1168 (35.3)
Major depressive episode	1166 (35.2)
Bipolar disorder	6 (0.2)
Suicide attempt	98 (3.0)
Anxiety disorders (any)	546 (16.0)
Obsessive-compulsive disorder	8 (0.2)
Panic disorder	51 (1.5)
Agoraphobia	169 (5.1)
Social anxiety disorder	138 (4.2)
Specific phobia	238 (7.2)
Generalized anxiety disorder	70 (2.1)
Eating disorders (any)	137 (4.1)
Anorexia	123 (3.7)
Bulimia	40 (1.2)
Substance use disorders (any)	280 (8.5)
Alcohol use disorder	20 (0.6)
Cannabis use disorder	55 (1.7)
Tobacco use disorder	235 (7.1)
Other substance use disorder	12 (0.4)

Table 3: Lifetime psychiatric history among IGEDEPP cohort respondents (N=3310)

	N (%)
Family history of mood disorder	1624 (49.0)
Family history of anxious disorder	696 (21.0)
Family history of schizophrenia	47 (1.4)
Family history of alcohol dependence or abuse	501 (15.1)
Family history of other substance use disorder	647 (19.5)

Table 4: Family history of psychiatric disorder among IGEDEPP cohort respondents
(N=3310)

	N (%)
Childhood stressful life event	298 (9.0)
Emotional abuse	100 (3.0)
Physical abuse	71 (2.1)
Sexual abuse	86 (2.6)
Emotional neglect	196 (5.9)
Physical neglect	26 (0.8)

Table 5: Childhood stressful life events among IGEDEPP cohort respondents (N=3310)

Events before and during pregnancy (N=3310)

Infertility	401 (12.1)
Assisted reproductive technology	269 (8.1)
Physical concomitant chronic disease	105 (3.2)
Primiparity	1242 (37.5)
Multiple pregnancy	105 (3.2)
Emergency consultation during pregnancy	1593 (48)
Hospitalization during pregnancy	439 (13.3)
Threatened preterm delivery	139 (4.2)
Hypertension during pregnancy	37 (1.1)
Gestational diabetes	59 (1.8)
Venous thromboembolic event	7 (0.21)

Delivery events (N=3310)

Spontaneous labor onset	1982 (59.9)
C-section delivery	817 (24.7)
Absence of an accompanying person	91 (2.5)
No obstetrical analgesia despite intention	516 (15.6)
Perineal Trauma	
None or minor perineal tear	1674 (50.6)
Episiotomy	782 (23.6)
Perineal trauma (\geq 2-degree perineal tear)	30 (0.9)
Newborn related events (preterm, low weight, NICU)	310 (9.4)
Maternal early postpartum events (hemorrhage, ICU)	180 (5.4)

Early postpartum events assessed at 8 weeks (N=3015)

Child hospitalization or disease	331 (11.0)
Maternal hospitalization or disease	38 (1.3)
Pain or incontinence	774 (25.7)
No sexual activity	904 (30.0)
No breastfeeding	1411 (46.8)

Late postpartum events assessed at one year (N=2351)

Child hospitalization or disease	373 (15.9)
Maternal hospitalization or disease	32 (1.4)
New pregnancy	97 (4.1)

Table 6: Pregnancy, delivery and postpartum events among IGEDEPP cohort respondents Abbreviations: GA, gestation age; NICU, newborn Intensive Care Unit; IUC, Intensive care unit.

	8 weeks follow-up (N=3015)	Lost to follow-up during the first 8 weeks (N=295)	p value
Age	32.7 (4.5)	32.1 (4.9)	0.025
Primiparous	1726 (57.2)	170 (58)	0.95
Marital status: Single	90 (3.0)	13 (4)	0.24
Education level: high School or less	223 (7.4)	38 (13)	0.001
Job status: unemployed	198 (6.6)	24 (8)	0.36
Current psychotropic medication			
Antidepressant	48 (1.6)	5 (2)	1
Antiepileptic	8 (0.3)	1 (0.3)	0.57
Antipsychotic	5 (0.2)	0 (0)	1
Other	3 (0.1)	1 (0.3)	0.31
Lifetime history of major depressive episode	1053 (34.9)	113 (38)	0.27
Major depressive episode during current pregnancy	110 (3.7)	14 (5)	0.43

Supplementary table 1: Comparison of patient's characteristics between participants lost to follow-up during the first 8 weeks (N=295) and participants evaluated at W8 (N=2351).

	One year follow-up (N=2351)	Lost to follow-up during fist year (N=959)	p value
Age	32.8 (4.4)	32.2 (4.7)	<0.001
Primiparous	1355 (57.6)	541 (56.4)	0.54
Marital status: Single	64 (2.7)	39 (4.1)	0.056
Education level: high School or less	147 (6.3)	114 (11.9)	<0.001
Job status: unemployed	151 (6.4)	71 (7.4)	0.34
Medication:			
Antidepressant	36 (1.5)	17 (1.8)	0.73
Antiepileptic	6 (0.3)	3 (0.3)	0.72
Antipsychotic	3 (0.1)	2 (0.2)	0.63
Other	3 (0.1)	1 (0.1)	1
History of depressive episode	812 (34.5)	354 (36.9)	0.21
History of depressive episode during the current pregnancy	83 (3.5)	41 (4.3)	0.36

Supplementary table 2: comparison between patients lost to follow-up during the first year (N=959) and patients with complete follow-up.

Centre	B	C	H	J	L	N	P	T	p (Chi-square)
Prevalence of PPD at W8 (%)	5.9	6.8	7.0	7.3	6.7	8.6	11.5	5.2	0.049

Supplementary table 3: Prevalence of PPD at W8 in the different centers participating in the study

Category	Whole pregnancy (N=3310)	Early post-partum (N=3015) ^a	Late post-partum (N=2351) ^a
	N (%)	N (%)	N (%)
Work	392 (11.8)	194 (6.4)	308 (13.1)
Education	38 (1.2)	18 (0.6)	30 (1.3)
Wealth	255 (7.7)	87 (2.9)	115 (4.9)
Health	355 (10.7)	117 (3.9)	256 (10.9)
Bereavement	202 (6.1)	83 (2.8)	179 (7.6)
Moving	161 (4.9)	71 (2.4)	95 (4.0)
Love relationship	36 (1.1)	27 (0.9)	27 (1.2)
Legal issues	60 (1.8)	22 (0.73)	26 (1.1)
Social or familial	443 (13.4)	248 (8.2)	199 (8.5)
Marital	207 (6.3)	153 (5.1)	249 (10.6)
Others	385 (11.6)	310 (10.3)	282 (12.0)
Any	1578 (47.7)	912 (30.2)	1033 (43.9)

Supplementary table 4: Adult stressful life events during pregnancy and postpartum period among IGEDEPP cohort respondents.

^aEarly post-partum was defined as 8 weeks postpartum, late post-partum was defined as ranging between two months and one year postpartum

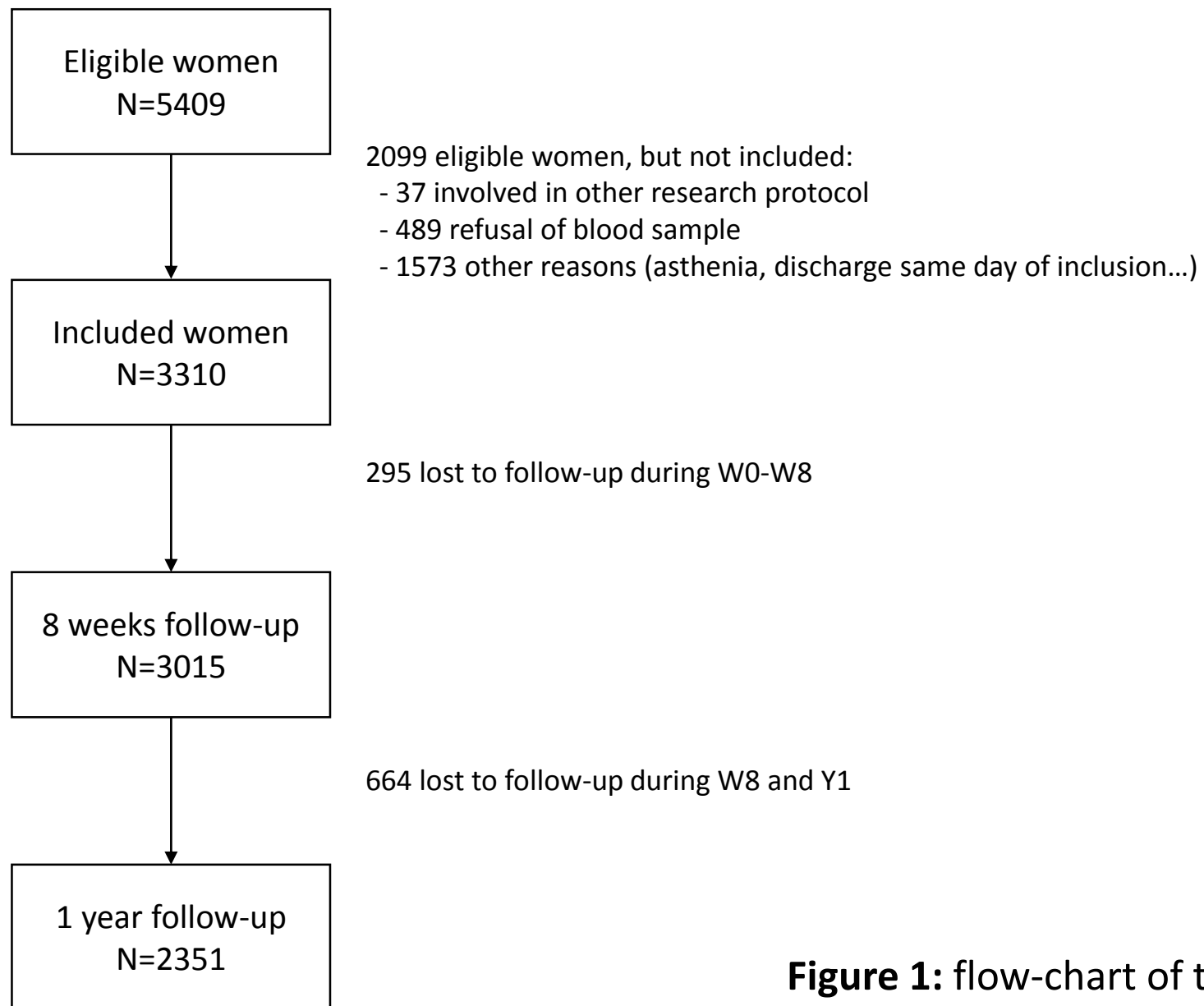


Figure 1: flow-chart of the study

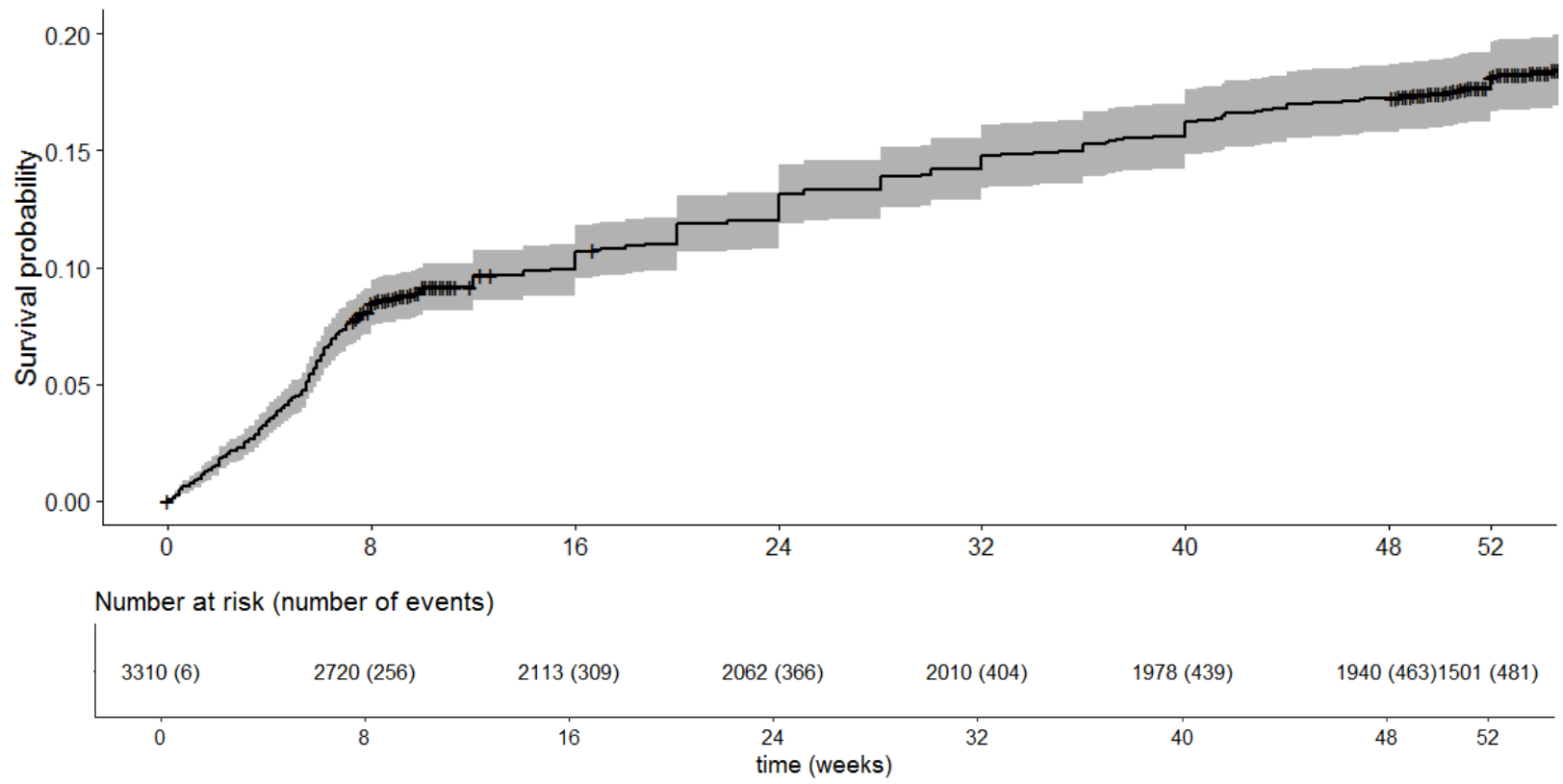
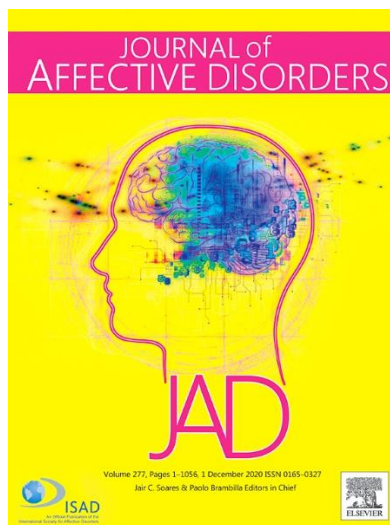


Figure 2: cumulative incidence of postpartum depression over time (weeks) since delivery
 Bands indicate 95% confidence interval, Crosses indicate censoring

II. Dépression du post-partum, facteurs environnementaux

II.A. Article 2 : Developmental trajectories of pregnant and postpartum depression
in an epidemiologic survey

ARTICLE 2



**Developmental trajectories of pregnant and postpartum depression
in an epidemiologic survey**

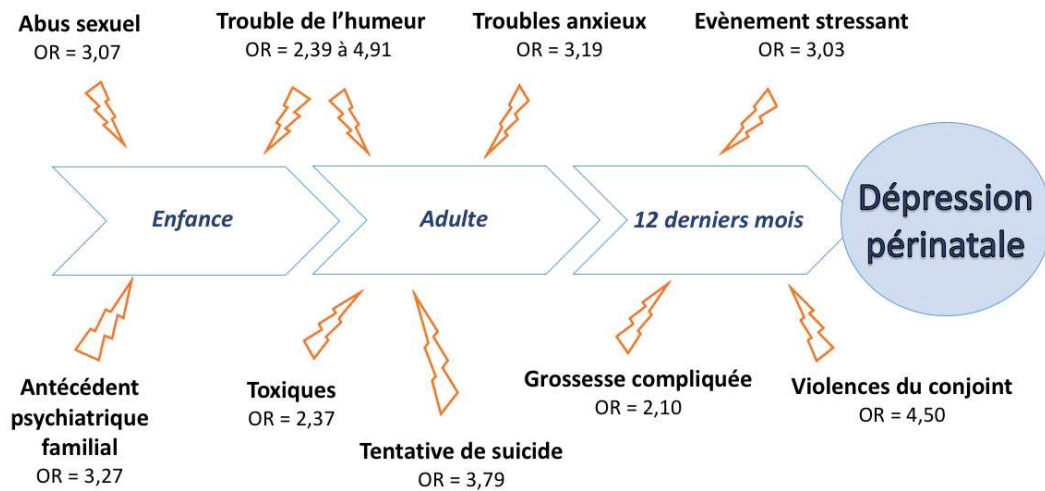
Sarah Tebeka, Yann Le Strat, Caroline Dubertret.

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Afin de mieux comprendre la dépression périnatale, nous avons conduit une étude visant à évaluer la prévalence et les déterminants de celle-ci, en population américaine. Pour cela, nous nous sommes appuyés sur la NESARC (cohorte prospective portant sur 34 653 participants représentative de la population américaine (cf. méthodologie p. 46). Toutes les femmes enceintes au cours de l'année précédant la deuxième évaluation ont été incluses. La dépression périnatale a été évaluée selon un entretien semi-structuré selon les critères diagnostiques internationaux à la vague 2. Tous les déterminants étudiés étaient évalués de façon rétrospective.

Dans l'échantillon de 1085 participantes enceintes ou dans le post-partum (<1 an) au cours de la vague 2, la prévalence de la dépression périnatale était de 10,8 %. Les femmes ayant une dépression périnatale rapportaient des taux plus élevés d'abus sexuels dans l'enfance (OR = 3,07 ; IC à 95 % 1,78-5,28), des antécédents familiaux de dépression (OR = 3,27; IC à 95 % 2,11-5,07), et des antécédents de troubles dépressifs à l'adolescence (OR = 3,83; IC à 95 % 1,83-8,02) et une faible estime de soi (OR = 3,07; IC à 95 % 1,78-5,29). Cinq troubles étaient spécifiquement associés à un taux plus élevé de dépression périnatale : un antécédent personnel de dépression (OR = 4,91; IC à 95 % 2,97-8,12), les troubles liés à l'usage de substances (OR = 2,37; IC à 95 % 1,42-3,97), les troubles bipolaires (OR = 2,39; IC à 95 % 1,19-4,85), les troubles anxieux (OR = 3,19; IC 95 % 1,93-5,26) et les antécédents de tentative de suicide (OR = 3,79; IC à 95 % 1,65-8,72). La dépression périnatale était également associée à un événement de vie stressant au cours de la dernière année (OR = 3,03; IC à 95 % 1,20-7,66), et en particulier à des violences physiques conjugales (OR = 4,50; IC à 95 % 2,38-8,52), et à des complications pendant la grossesse (OR = 2,10; IC à 95 % 1,28-3,44).

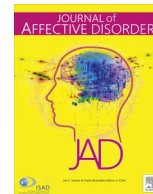
Figure 5 : Évènements de vie de l'enfance à la grossesse associés à la dépression périnatale dans la cohorte de la NESARC



Conclusion et perspectives

Ainsi, cette étude retrouvait des déterminants à la dépression périnatale à différents moments de la vie des femmes, allant du développement de la petite enfance et de l'adolescent à des événements négatifs plus récents. Pendant l'enfance, les deux principaux facteurs de risque sont des antécédents personnels d'abus sexuel et des antécédents familiaux de dépression. Le meilleur prédicteur de la dépression périnatale est une histoire personnelle de trouble psychiatrique, et en particulier un antécédent de dépression. Cela souligne la vulnérabilité préexistante de certaines femmes. Les événements stressants de la vie au cours de l'année écoulée, y compris le deuil et les violences conjugales, sont également des déterminants de la dépression périnatale.

La principale limite de ce travail concerne l'évaluation de la période périnatale qui ne permet pas de distinguer pas les femmes déprimées au cours de la grossesse de celles déprimées dans le post-partum. Nos travaux suivants vont permettre de distinguer la dépression périnatale en fonction de la date d'apparition du trouble dépressif.



Research paper

Developmental trajectories of pregnant and postpartum depression in an epidemiologic survey

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ABSTRACT

Objective: To estimate the prevalence and determinants for the peripartum depression.**Methods:** Data were extracted from the 2 waves of the National Epidemiologic Study of Alcohol and Related Conditions (NESARC), a representative sample of the US population corresponding to 34,653 participants. All women pregnant during the year before the second assessment were included. Peripartum depression was evaluated according a semi-structured interview at Wave 2. Risk factors covering life from childhood through adulthood, and including sexual abuse, family history of depression and psychiatric disorder lifetime were evaluated at wave 1. Stressful life event and obstetric factors were evaluated for the period of 12 months preceding the second interview.**Results:** In the sample of 1085 participants pregnant at wave 2, the prevalence of peripartum depression was 10.8%. Women with a peripartum depression reported higher rates of sexual abuse in childhood (OR=3.07), family history of depression (OR=3.27). A history of mental disorder was associated with a higher rate of peripartum depression (OR=3.43). Four disorders were specifically associated with higher rate of peripartum depression including depression (OR=4.91), substance use disorder (OR=2.37), bipolar disorder (OR=2.39) and history of suicide attempt (OR=3.79). Peripartum depression was associated with stressful life event in the last year (OR=3.03), and complications during pregnancy (OR=2.10).**Limitations:** Not distinguish between depressed women during pregnancy from postpartum depressed women.**Conclusion:** Depression affects more than one in 10 women during peripartum. The factors associated with peripartum depression are traumatic, personal or family history of mental disorder, in a timeframe covering life from childhood through adulthood.

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1. Introduction

Peripartum depression is considered as a major public health issue (Wisner et al., 2006). Depression is the second leading cause of disability among women during childbearing year (World Health Organization, 2001), with an increased risk during pregnancy and postpartum (O'Hara and McCabe, 2013). The prevalence of depression during peripartum ranges between 10% and 20% (Gavin et al., 2005; Mann et al., 2010), whereas the prevalence of depression in women in general population is less than 10%

(Kendler et al., 2002). Suicidal behavior is the main maternal complication of peripartum depression (Cantwell et al., 2011). The risk of recurrence after a postpartum depression is estimated at 40% (Wisner et al., 2004; Howard et al., 2014) and up to 50% during subsequent pregnancies (Goodman, 2004).

As a multifactorial disease, many studies have focused on the determinants of peripartum depression (Gaillard et al., 2014; Howard et al., 2014). A review highlighted many risk factors associated with depression during pregnancy and postpartum (Stuart-Parrigon and Stuart, 2014). This last work emphasizes the role of personal or family history of depression, the impact of a low socioeconomic status as well as the importance of interpersonal support (Stuart-Parrigon and Stuart, 2014). It also points out the caveats of the existing literature, including the non-representativeness of samples, the focus on a specific type of risk rather than a broad range of factors, or the use of a transversal design.

Kendler et al. (2002) developed an explanatory model of

Abbreviations: AOR, adjusted odd ration; CI, confidence interval; MDE, major depressive disorder; NESARC, National Epidemiologic Study of Alcohol and Related Conditions; OR, odd ratio

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depression in the general population through development periods, distinguishing factors related to childhood, teen age, adult age and during the year before the disorder. To our knowledge, this model has not been yet examined in peripartum depression.

The objective of this work is to determine risk factors for the peripartum depression, examining not only proximal risk factors (e.g. negative events occurring within the past year) but also childhood, adolescence and adulthood factors, allowing the assessment of the entire trajectory of a participant with peripartum depression. Using data from the 2 waves National Epidemiologic Study of Alcohol and Related Conditions (NESARC), we examined childhood, adolescent, and adult risk factors associated with the occurrence of peripartum depression in the literature in a subsample of pregnant or post-partum women.

2. Methods

2.1. Sample

The NESARC is a representative sample of the non-institutionalized US civilian population. Participants were evaluated twice: first between 2001 and 2002 (Wave 1) and then between 2004 and 2005 (Wave 2). Wave 1 targeted a civilian population over 18 years, with an overall response rate of 81%, corresponding to 43,093 participants. Wave 2 had 86.7% response rate, corresponding to 34,653 participants having completed both waves of interviews. Face-to-face interviews were conducted by members of the US Census Bureau. The research protocol, including informed consent procedures, received ethical approval from the US authorities. For this study, the sample consisted of all women of childbearing age 18–50 years old) who answered yes to the question “have you been pregnant in the last 12 months?” at the time of the second assessment, further considered in the paper as pregnant and postpartum women ($n=1085$). Therefore, the “past-year pregnant women” group includes both currently (wave 2) pregnant and postpartum women.

2.2. Measures

To make a longitudinal analysis, variables of interest were collected at wave 1 when available, while the outcome (peripartum depression) was measured three years later, at wave 2. Two variables were only available at wave 2 (but not measured at wave 1, namely sexual and physical abuse).

2.2.1. Diagnostic of major depressive episode at wave 2

The National Institute on Alcohol Abuse and Alcoholism's Alcohol Use Disorder and Associated Disabilities Interview Schedule–DSM–IV (AUDADIS–IV), a valid and reliable structured diagnostic interview, was used to assess major depressive disorder (MDE) during pregnancy or post-partum. MDE was diagnosed when at least 2 weeks of persistent depressed mood was present, accompanied by a total of at least 5 or more of the 9 DSM–IV symptoms of major depression during the episode. Social and/or occupational dysfunction had also to be present during the disturbance. MDE due to bereavement or physical illness were ruled out. The reliability of the AUDADIS–IV was shown to be high for MDE, with κ between 0.60 and 0.65.

2.2.2. Sociodemographic measures at wave 1

Race/ethnicity was categorized into: (i) White, (ii) Black, (iii) Hispanic/Latino, and (iv) Asian/Native Hawaiian/Pacific Islander/American Indian/Alaska Native. Age at interview was categorized into: (i) 18–24, and (ii) 25–50 years old. This allows highlighting the impact of young maternal age in peripartum depression.

Educational level was classified into: (i) high school or less, (ii) some college or higher. Familial income was classified into: (i) \$0–19,999, (ii) \$20,000–34,999, (iii) \$35,000–59,999, and (iv) \$60,000 or greater. Urbanicity was classified into: (i) rural or (ii) urban. Region of residence was classified into: (i) Northeast, (ii) Midwest, (iii) South, and (iv) West. Health insurance coverage was classified into (i) private, (ii) public, and (iii) none).

2.2.3. Childhood and adolescence measures

Family history of depression was assessed at wave 1 with a specific module of AUDADIS, including first-degree family history (parents and siblings). Participants who had experienced sexual or physical abuse during childhood were identified at Wave 2 by a positive answer to the questions “Have you experienced sexual violence, rape or unwanted sex?” and “Have you been assaulted, beaten, injured before the age of 18?” respectively. Participants who had experienced death of a parent during childhood were identified at Wave 1 by their positive answer to the question “one of your parents [biological/adoptive] is it died before your 18th birthday?”. Participants with low self-esteem were identified at Wave 1 by a positive answer to the question “Do you think you're not as good, as smart, as attractive as most people?”. Five questions measured family support before the age of 18. For example, participants were asked to rate on a 5-point Likert scale sentences like: “I felt there was someone in my family who wanted me to be a success”. Participants reporting less than 4 favorable answers were considered as having a lack of family support during adolescence. Early depression was considered as having major depression history before the age of 15.

2.2.4. Lifetime mental and physical disorders at wave 1

Psychiatric diagnoses were measured using the AUDADIS–IV. We reported lifetime prevalence at wave 1 for bipolar disorder (defined by a history of mania or hypomania), any anxiety disorders (including panic disorder, specific phobia, social phobia, and generalized anxiety disorder), substance use disorders (including abuse or dependence to alcohol, cannabis, sedatives, tranquilizers, opiates, stimulants, hallucinogens, cocaine (including crack cocaine), inhalants/solvents, heroin, and other drugs) and alcohol use disorder (including abuse and dependence), as well as personality disorders (paranoid, schizoid, histrionic, antisocial, avoidant, dependent and obsessive-compulsive).

Lifetime suicide attempts were screened at wave 1 with a single question.

Data on height and weight were self-reported at wave 1. BMI was calculated by dividing weight in kilograms by the square of the height in meters. Participants were considered overweight or obese if their BMI was 25.0 or greater. Overall health status was assessed using self-reported perception of the respondent's health. Respondents were asked, “In general, would you say your health is excellent, very good, good, fair or poor?” Health status was categorized into 2 categories: (i) excellent, very good or good and (ii) fair or poor.

2.2.5. Past-year predictors of peripartum MDE at wave 2

Stressful life events were evaluated for the period of 12 months preceding the second interview using the 12 questions of the Social Readjustment Rating Scale (Holmes and Rahe, 1967). Since bereavement has been described as associated with higher rates of post-partum depression, we examined this negative event independently. We examined various obstetric factors, including the number of children or the existence of complications in late pregnancy or childbirth. Furthermore, the existence of three physical comorbidities (diabetes, hypertension, or hypercholesterolemia) in the past 12 months was considered if participants reported positive answers to both questions (“did you have ...?”

and “Did a doctor confirmed the diagnosis?”). We reported 12 months prevalence for alcohol use disorder (including abuse and dependence). Finally, the relationship with the partner was assessed by marital status. We examined recent separation as well as physical or sexual violence by the partner. In addition, the presence of an alcohol use disorder for the partner was assessed with two specific questions.

2.3. Statistical analyses

Weighted estimates and standard errors (SEs) were computed using SUDAAN, version 11.01 (Research Triangle Park, NC). This software implements a Taylor linearization to adjust SEs of estimates for complex survey sampling design effects including clustering data.

Multivariate logistic regressions were conducted with simultaneous entry of sociodemographics covariates. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs), unstandardized linear regression coefficients and SEs are presented to reflect association strength and significance.

3. Results

3.1. Sample

Of the 34,653 participants, 14,564 were women in which 1085 have been pregnant within the year preceding the assessment.

Among the women who had been pregnant during the past year, 117 met criteria for MDE in the past 12 months (10.8%).

3.2. Demographics

The sociodemographic characteristics of both groups are summarized in Table 1. The majority of women was white, over 25 years old, educated and mainly lives in rural areas. The average age was 26.7 years (SD=5.9). Peripartum women with MDE were significantly more likely to belong to the younger group (OR=0.51; 95% CI=0.31–0.82) and were less educated (OR=0.51; 95% CI=0.30–0.87) than peripartum women without MDE. Black women were more represented in the depressed group than in the non-depressed group (OR=1.67; 95% CI = 1.04–2.69). Urbanicity, familial income, residential area, ethnicity and insurance status were not significantly different among the two groups.

3.3. Life events in childhood and adolescence

Traumatic events in childhood including sexual abuse, physical abuse, and loss of a parent, were reported by 15%, 3% and 6% of the women respectively. Women with a depressive episode in the peripartum most frequently reported sexual abuse in childhood even when adjusted for socio-demographic variables (AOR=3.07; 95% CI = 1.78–5.28) (Table 2).

More than a third of peripartum women (37.44%, SE: 1.77) mentioned a family history of depression. Having a first degree relative with a history of depression was significantly associated with an increased risk of peripartum depression (AOR=3.27; 95%

Table 1
Sociodemographic characteristics of peripartum women with or without Major Depressive Episode Major Depressive Episode in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

Characteristic	PP non MDE n=968	PP with MDE n=117	Bivariate association	
	% (SE)	% (SE)	OR	95% CI
Race/ethnicity				
White	66.1 (2.5)	60.3 (4.8)	Reference	
Black	12.1 (1.3)	17.3 (3.3)	1.60	0.95–2.68
Hispanic	15.4 (2.0)	18.5 (3.9)	1.34	0.79–2.30
American Indian/Alaska Native/ Asian/Native Hawaiian/Pacific Islander	6.4 (1.3)	3.9 (1.2)	0.64	0.21–1.96
Age (years old)				
18–24	36.0 (2.0)	53.1 (5.7)	Reference	
25–50	64.0(2.0)	46.9 (5.7)	0.51	0.31–0.82
Education				
High school or less	33.4 (2.0)	50.7 (6.3)	Reference	
Some college or higher	66.6 (2.0)	49.3 (6.3)	0.51	0.30–0.87
Income (\$)				
0–19,999	20.7 (1.5)	28.2 (4.8)	Reference	
20,000–34,999	20.7 (1.6)	29.9 (5.5)	1.03	0.55–1.93
35,000–59,999	25.9 (1.6)	19.6 (4.2)	0.55	0.29–1.07
≥ 60,000	32.8 (2.0)	22.3 (5.6)	0.50	0.25–1.00
Urbanicity				
Urban	33.7 (3.1)	32.9 (5.1)	Reference	
Rural	66.3 (3.1)	67.2 (5.1)	1.06	0.62–1.80
Region				
Northeast	18.5 (3.7)	12.9 (4.5)	Reference	
Midwest	27.5 (4.2)	26.9 (6.9)	1.35	0.60–3.04
South	29.8 (3.5)	36.5 (6.8)	1.79	0.78–3.83
West	24.2 (3.9)	23.6 (5.7)	1.39	0.60–3.21
Insurance				
None	21.6 (1.6)	30 (5.1)	Reference	
Public	11.0 (1.1)	12.4 (3.1)	0.84	0.43–1.63
Private	67.5 (1.8)	57.6 (5.5)	0.64	0.38–1.07

Abbreviations: Abbreviations: PP with MDE: Peripartum women with Major Depressive Episode; PP non MDE: Peripartum women without Major Depressive Episode; CI=confidence interval; OR=odds ratio; SE: Standard Error
Significant results in bold (p < 0.05).

Table 2

Childhood and adolescence predictors of Major Depressive Episode in peripartum women in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

Risk factors	PP non MDE n=968	PP with MDE n=117	Adjusted Odds ratios ^a	
	% (SE)	% (SE)	AOR	95% CI
Family history of MDD	35.9 (1.8)	59.1 (4.8)	3.27	2.11–5.07
Sexual abuse	13.2 (1.3)	32.8 (5.4)	3.07	1.78–5.28
Physical abuse	3.5 (0.8)	3.6 (1.6)	0.89	0.31–2.53
Parental loss	5.2 (0.8)	8.0 (3.1)	1.80	0.69–4.69
Low self-esteem	11.3 (1.2)	29.2 (5.1)	3.07	1.78–5.29
First depressive episode before 15	4.4 (0.8)	16.5 (4.2)	3.83	1.83–8.02
Lack of familial support	4.1 (0.75)	5.3 (2.4)	1.20	0.42–3.44

Abbreviations: PP with MDE: Peripartum women with Major Depressive Episode; PP non MDE: Peripartum women without Major Depressive Episode; CI=confidence interval; AOR=Adjusted odds ratio; SE: Standard Error

Significant results in bold ($p < 0.05$).

^a Adjusted for age, race, education, income, region, urbanicity, insurance.

CI=2.11–5.07).

Peripartum women with MDE reported a lower self-esteem during adolescence than peripartum women without MDE (AOR=3.07; 95% CI=1.78–5.29). The prevalence of early onset depression during adolescence was 5% in our sample consisting of 1085 peripartum women. This proportion was significantly higher in peripartum women with MDE than in peripartum women without MDE (16.5% vs 4.4%, $p < 0.001$).

The prevalence of a lack of family support during adolescence was low (4.3% of the entire sample), and not statistically significant different between peripartum women with and without MDE (Table 2).

3.4. Lifetime mental and physical predictors of MDE in peripartum

A history of mental disorder was consistently associated with a higher rate of MDE during peripartum (Table 3).

Nearly half of peripartum women present an axis 1 disorder diagnosis (48.85%, SE: 2.02). The existence of a psychiatric disorder

was associated with an AOR 3 times higher of peripartum depression after adjustment for sociodemographic variables (46.5% vs 70.7%, AOR=3.43; 95% CI=2.07–5.69). Anxiety disorder or substance use disorder over lifetime were significantly associated with peripartum MDE (AOR=3.19 and 2.37 respectively). However, alcohol use disorder was not associated with a significantly higher prevalence of peripartum depression (AOR=1.78, 95% CI=0.99–3.21). A history of bipolar disorder was also associated with higher rates of MDE in the peripartum (AOR=2.39; 95% CI=1.19–4.85).

Personality disorders were strong predictors of peripartum depression (AOR 4.21, 95% CI 2.53–7.20). These adjusted odds ratios vary widely from one personality disorder to another, ranging from non-significant 1.31 (0.15–11.37) in dependent personality disorder up to 8.40 (95% CI 3.23–21.82) in avoidant personality disorder.

A history of suicide attempt was more than 3 times more common in peripartum women with MDE than in peripartum women without MDE (12.0% vs 3.4%; AOR=3.79; 95% CI=1.65–8.72).

Table 3

Lifetime mental and physical predictors of Major Depressive Episode in peripartum women in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

Condition	PP Non MDE n=968	PP with MDE n=117	Adjusted Odds ratios ^a	
	% (SE)	% (SE)	AOR	95% CI
Psychiatric history				
Any lifetime axis I disorders (excluding MDE)	46.5 (2.13)	70.7 (4.7)	3.43	2.07–5.69
Any substance use disorder	33.8 (2.1)	49.5 (5.3)	2.37	1.42–3.97
Any alcohol use disorder LT	25.4 (1.9)	32.43 (5.3)	1.79	0.99–3.21
Any anxiety disorder	20.1 (1.5)	42.3 (5.8)	3.19	1.93–5.26
Bipolar disorder	7.7 (1.0)	18.7 (3.8)	2.39	1.19–4.85
Suicide attempt	3.4(0.7)	12.0 (3.7)	3.79	1.65–8.72
Any lifetime personality disorders (PD)	14.6 (1.3)	42.2 (5.5)	4.21	2.53–7.02
Antisocial PD	2.4 (0.5)	7.3 (3.0)	2.78	0.96–8.11
Avoidant PD	1.8 (0.5)	14.5 (4.7)	8.40	3.23–21.82
Dependent PD	0.8 (0.4)	1.1 (1.1)	1.31	0.15–11.37
Obsessive-compulsive PD	7.9 (1.0)	27.8 (5.0)	5.11	2.83–9.25
Paranoid PD	5.5 (0.8)	22.7 (5.1)	4.12	2.07–8.20
Schizoid PD	2.6 (0.6)	10.9 (3.5)	4.57	1.83–11.43
Histrionic PD	2.8 (0.7)	8.8 (3.5)	2.84	1.01–7.97
History of mood disorder				
Any lifetime history of MDE	18.6 (1.6)	47.8 (5.7)	4.91	2.97–8.12
Medical conditions				
Overweight or obesity at W1	39.2 (1.7)	48.0 (5.7)	1.30	0.78–2.18
Poor overall health	4.2 (0.7)	11.2 (3.7)	2.47	1.01–6.03

Abbreviations: MDE: Major Depressive Episode; PP with MDE: Peripartum women with Major Depressive Episode; PP non MDE: Peripartum women without Major Depressive Episode; CI=confidence interval; AOR=Adjusted odds ratio; SE: Standard Error

Significant results in bold ($p < 0.05$).

^a Adjusted for age, race, education, income, region, urbanicity, insurance.

Table 4
Past year predictors of Major Depressive Episode in peripartum women in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

Past-year condition	PP non MDE	PP with MDE	Adjusted Odds ratios ^a	
	% (SE)	% (SE)	AOR	95% CI
Past-year stressors				
Any stressful life-events	81.4 (1.4)	93.8 (2.6)	3.03	1.20–7.66
Bereavement	28.3 (1.8)	44.5 (6.3)	1.93	1.13–3.30
Relation with partner				
Past-year divorced or separated	4.0 (0.8)	7.2 (3.0)	1.68	0.63–4.49
Partner physical violence	5.4 (0.8)	22.7 (4.3)	4.50	2.38–8.52
Partner sexual abuse	1.0 (0.5)	2.6 (1.6)	2.49	0.59–10.46
Partner alcohol use disorder	2.9 (0.6)	4.3 (2.0)	1.65	0.56–4.80
Obstetrical factors				
Nulliparity	45.8 (1.9)	38.1 (5.6)	0.74	0.42–1.30
Pregnancy complication	29.4 (1.9)	45.3 (5.6)	2.10	1.28–3.44
Medical illnesses				
Diabetes	3.4 (0.7)	4.4 (2.2)	1.30	0.39–4.36
Hypertension	8.0 (1.0)	8.1 (2.4)	1.10	0.52–2.32
Hypercholesterolemia	3.0 (0.6)	9.1 (2.0)	3.98	1.80–8.83

Abbreviations: PP with MDE: Peripartum women with Major Depressive Episode; PP non MDE: Peripartum women without Major Depressive Episode; CI=confidence interval; AOR=Adjusted odds ratio; SE: Standard Error
Significant results in bold ($p < 0.05$).

^a Adjusted for age, race, education, income, region, urbanicity, insurance.

A personal history of depression involved nearly a quarter of our cohort (21.57%, SE: 1.58). This history was the strongest predictors of MDE during the peripartum period (AOR = 4.91; 95% CI=2.97–8.12).

Overweight at wave 1 was frequent in our sample of peripartum women (40.08%, SE: 1.68) but was not associated with a significantly higher risk of peripartum depression three years later.

The overall health was estimated as good for the majority of the women: only 4.2% of our cohort estimated having a poor condition. Women reporting poor health at wave 1 were more likely to present a MDE during peripartum three years later than their counterparts reporting fair to excellent health (AOR=2.47; 95% CI=1.01–6.03).

3.5. Past-year predictors of MDE in peripartum

Having experienced a stressful event in the previous year was common, and reported by 82% (SE: 1.37) of the women in our sample of women in peripartum (Table 4). Women reporting a stressful life event in the last 12 months were more likely to present MDE during the peripartum period (AOR = 3.03; 95% CI=1.20–7.66). This association was also significant in bereaved women (AOR=1.93; 95% CI=1.13–3.30).

Considering the relationship to the partner, 4.3% (SE: 0.78) of the women reported a separation during the previous year, 3.1% (SE: 0.6) reported that their partner had substance use disorder, 7.06% (SE: 0.89) reported having been victims of physical violence from their partner, and 1.1% (SE: 0.45) reported that they had been sexually abused by their partner. Among these characteristics of the relation to the partner, physical violence by the partner in the previous 12 months was significantly associated with higher rates of peripartum MDE (AOR=4.50; 95% CI=2.38–8.52).

In this sample, 45% (SE: 1.87) were nulliparous or primiparous.

Parity was not significantly associated with peripartum depression. One third of the women (30.98%, SE: 1.68) reported complicated pregnancy or delivery. Having had complications during pregnancy or childbirth was associated with a 2-fold increased risk of peripartum depression (AOR=2.10; 95% CI=1.28–3.44). Among the medical illnesses assessed (diabetes, high blood pressure, hypercholesterolemia), hypercholesterolemia was significantly associated with an increased risk of peripartum depression (AOR=3.98; 95% CI=1.80–8.83). However, alcohol use disorder in the past-12 month was not associated with peripartum depression (AOR 1.62; 95% CI 0.72–3.65).

4. Discussion

This prospective study aimed at studying the determinants associated with the peripartum depression at different times of their lives, ranging from early childhood and adolescent development to more recent negative events. In this two waves longitudinal survey, 10.8% of peripartum women had criteria for MDE, which is consistent with prior reports of peripartum depression prevalence in U.S (Howard et al., 2014).

During childhood, the two main risk factors are a personal history of sexual abuse and a family history of depression. These two life events are reported in the literature as risk factors for MDE in general (Howard et al., 2014), and are not specific of the peripartum period (Kendler et al., 2002).

Adolescence with a first depressive episode is associated with depression in the peripartum. Early onset of depression is associated with a more severe form of this condition, particularly with an important risk of recurrence in adulthood (Pelkonen et al., 2008). A low self-esteem was also a risk factor for peripartum depression in our study, a finding consistent with the literature examining its impact on depression, outside from the peripartum context (Pelkonen et al., 2003).

The strongest predictor of peripartum depression is a personal history of psychiatric disorder. History of depression lifetime was the most important risk factor with an adjusted odds ratio as high as 4.91. These determinants are consistent with those identified in the general population but also in pregnant women or in the postpartum period (Howard et al., 2014). This can be partly explained by pre-existing vulnerability, but also the frequent stopping treatment during pregnancy and postpartum which increases the risk of depressive relapse (Bennett et al., 2004). While the NESARC does not allow examining this possibility, further study should examine the impact of stopping antidepressant when pregnancy is discovered.

To our knowledge, our study is the first to examine the impact of a wide range of personality disorders on the risk of peripartum depression. While personality disorders were associated with high rates of peripartum depression, this risk varies widely between specific personality disorders, the higher risk being conveyed by avoidant personality disorder.

Overweight not associated with peripartum depression. While some studies suggest an association between overweight and peripartum depression, this finding may be related to the temporal proximity between the two assessments (onset of pregnancy) (Molyneaux et al., 2014).

A diagnosis of hypercholesterolemia in the last 12 months was associated with peripartum depression. To our knowledge, this association has never been shown in peripartum depression. Several studies have found a significantly lower cholesterol levels (Martínez-Carpio et al., 2009; Partonen et al., 1999), and a lower HDL-cholesterol levels (Lehto et al., 2010; Schwartz et al., 2014) in non-pregnant patients with MDE compared to participants without MDE. These findings warrant further examination of the

specificity of this association in the peripartum context.

Finally, stressful life events during the past year, including bereavement, are also determinants of depression in our study. These results are in line with the literature (Howard et al., 2014). Complications during pregnancy are also associated with a significantly higher risk of peripartum depression, in line with some previous studies (Le Strat et al., 2011). A history of physical abuse by the partner was also associated with higher risk of peripartum depression, again in line with existing literature (Howard et al., 2013).

The main strengths of this study are the sample representativeness, the large size of the sample and the validity of the psychiatric assessment, as well as the prospective nature of its design. The present study allows the evaluation of a large sample ($n > 1000$) representative of American women in the peripartum. The cumulative response rates to the two interviews NESARC were 70.2%, which is excellent for this type of study.

Moreover, comparing women with peripartum depression with women without depression in peripartum women is one of the highlights of our work. Previous studies comparing peripartum women with depression to the general population of women or women of childbearing age may underestimate the risks associated with the perinatal period (Howard et al., 2014).

Furthermore, the majority of risk factors during childhood, adolescence and adulthood was assessed during Wave 1, with an average of 3 years before MDE, which allowed to highlight a temporal relationship between the two events (Abbasi, 2015).

Finally, few studies assessed the determinants of peripartum depression in their entirety, which is tracing the life course of women from childhood to the last past year. We added to the analyses of more recent events happening during the last 12 months assessed during Wave 2. The NESARC thus provides a comprehensive assessment of life events at different times of life, and includes the assessment of a wide range of psychiatric disorders.

The NESARC is the largest representative survey of the US population interested in the perinatal period and risk. Despite this, some limitations should be considered when interpreting these results. First, our work does not distinguish between depressed women during pregnancy from depressed women during the postpartum period. Several studies in general population failed to show any differences in the prevalence of depression during pregnancy or the postpartum period (Le Strat et al., 2011). Moreover, almost half of postpartum depressive episodes begin in pregnancy (Heron et al., 2004), suggesting a continuum between these two disorders.

Second, although the NESARC is the largest epidemiological study on psychiatric evaluations in the United States, our difference detection power in the prevalence of rare life events is limited, and may partly explain the absence of significant association for some of the risk factors assessed.

Third, the sample does not provide information on adolescents or young mothers who may be at increased risk of developing perinatal mood disorders. It is at least plausible that depression during pregnancy in teenagers is associated with specific risk factors, and this should be the focus of future studies.

5. Conclusion

Depression affects more than one in 10 women during the peripartum. Our work confirms that the risk factors of perinatal depression are manifold and cover the entire life of women. Through the study of a representative cohort of the US population, we were able to trace the path of women from their childhood and adolescence to adulthood, including the most recent events. The

main factors associated with peripartum depression were traumatic life as well as personal or family psychiatric history.

Taking into account these factors allows a better understanding of the etiological mechanisms of peripartum depression. The present work may enable practitioners to provide better detection of women at risk.

Contributors

Sarah Tebeka drafted the initial manuscript, carried out the initial analyses, and approved the final manuscript as submitted.

Caroline Dubertret and Yann Le Strat revised the manuscript, and approved the final manuscript as submitted.

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- II.B. Article 3 : Correlates of early and late postpartum depression: results from the IGEDDEPP cohort

ARTICLE 3



**Correlates of early and late postpartum depression :
results from the IGEDDEPP cohort**

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Notre travail précédent semble révéler des trajectoires de vie associées à la dépression périnatale. De façon intéressante, plusieurs études se sont concentrées spécifiquement sur les facteurs associés aux différentes trajectoires de la dépression périnatale. Par exemple, l'étude de cohorte Française EDEN (2003-2011) distingue différentes trajectoires de symptômes maternels de dépression : aucun symptôme, des symptômes dépressifs persistants de niveau intermédiaire, des symptômes dépressifs élevés persistants, des symptômes élevés pendant la grossesse seulement et des symptômes élevés pendant la période préscolaire de l'enfant seulement (évaluation jusqu'à 5 ans post-partum) (van der Waerden et al. 2015). Une autre étude retrouvait elle trois trajectoire au cours de la grossesse : symptômes dépressifs faibles et stables (plus de 80 % de la population de l'étude), décroissants et croissants (Boekhorst et al. 2019)

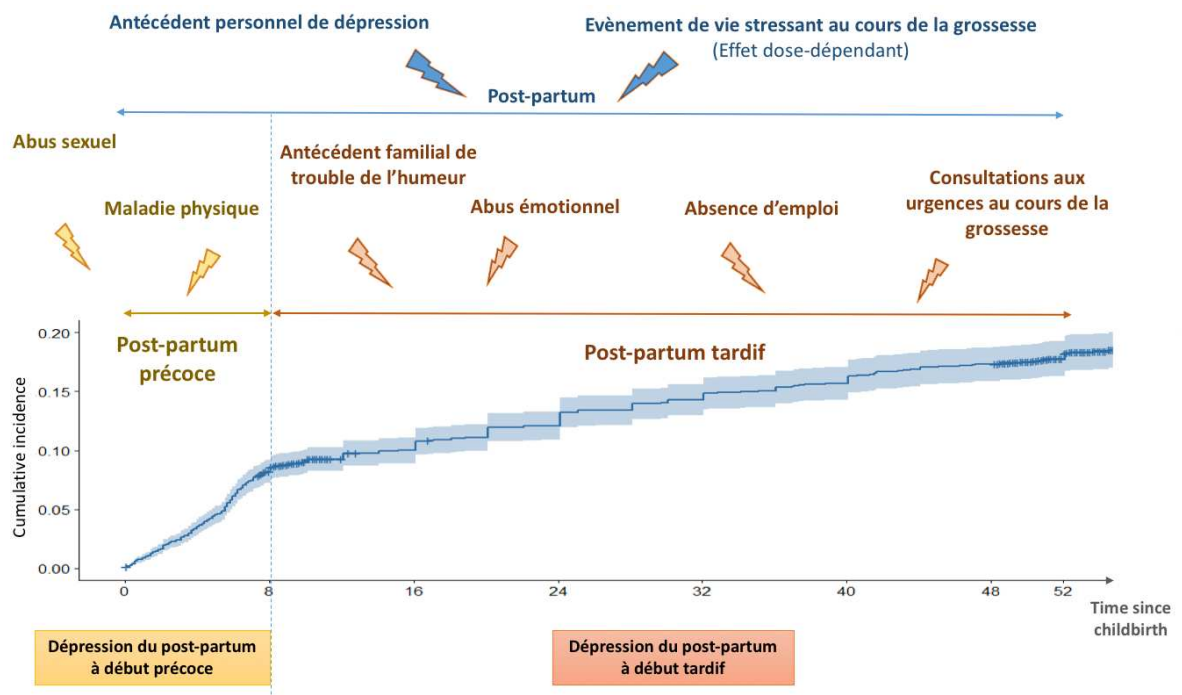
Une revue systématique analysant 11 études avec au moins 3 temps d'évaluation des symptômes dépressifs n'a pas permis de retrouver des caractéristiques démographiques, de personnalité ou cliniques différenciant systématiquement des groupes de femmes présentant des trajectoires de symptômes différentes (Baron et al. 2017). Alors que la dépression du post-partum est généralement considérée comme une maladie unique quel que soit le moment d'apparition des symptômes (The International Marce Society 2015), notre hypothèse est que les facteurs de risque peuvent différer entre dépression du post-partum à début précoce et tardif. En effet, l'état émotionnel, physique et biologique de la mère ainsi que l'environnement évoluent entre l'accouchement, les premières semaines post-partum et plusieurs mois après la naissance (Rossen et al. 2019). Il existe une interaction entre l'état émotionnel maternel, l'état émotionnel des enfants et leur lien, avec une influence mutuelle (Nath et al. 2020; Beck 2020; van der Waerden et al. 2015). Peu d'études examinent la distinction entre dépression du post-partum à début précoce et tardif avec une conception prospective (Heron et al. 2004; Woolhouse et al. 2012).

Ainsi, à partir de la cohorte IGEDEPP (cf. méthodologie p. 37), nous avons cherché à distinguer les facteurs associés à la dépression du post-partum de ceux associés à la dépression du post-partum à début précoce et tardif (Tebeka, Le Strat, et al. 2020). Nous avons proposé une étude cas-témoins niché dans la cohorte IGEDEPP, comparant les femmes avec une dépression du post-partum à début précoce ou tardif (les deux catégories étant exclusives), aux témoins qui étaient des femmes sans dépression pendant la grossesse ou la période post-partum.

Les événements de vie stressants de la vie pendant la grossesse avaient une relation dose-réponse avec la survenue d'une dépression du post-partum, et ce, quel que soit le délai de début par rapport au post-partum. Par contre, sur d'autres caractéristiques, la dépression du post-partum à début précoce et tardif présentait des modèles distincts. En effet, la dépression du post-partum à début précoce était indépendamment associée aux antécédents de dépression (aOR : 2,0, IC à 95 % : 1,5-2,6), d'abus sexuels pendant l'enfance (aOR : 2,0, IC à 95 % : 1,0-4,0), d'événement stressant grossesse (aOR : 1,8, IC à 95 % : 1,4-2,4) et à une maladie physique chronique concomitante pendant la grossesse (aOR : 1,5, IC à 95 % : 1,0-2,1) dans notre modèle multivarié. La dépression du post-partum à début tardif était, elle, indépendamment associée aux abus émotionnels pendant l'enfance (aOR : 2,6, IC à 95 % : 1,4-4,8), aux événement de vie stressant pendant la grossesse (aOR : 2,1, IC à 95 % : 1,6-2,8), au chômage (aOR : 2,0, IC à 95 % : 1,2-3,2), aux antécédents personnels et familiaux de trouble de l'humeur (aOR : 1,6, IC à 95 % : 1,2-2,1 et aOR : 1,4, IC à 95 % : 1,0-1,8) et aux consultations aux urgences pendant la grossesse (aOR : 1,4, IC à 95 % : 1,1-1,9).

Afin de mieux comprendre la dépression du post-partum et de développer des pratiques de prévention ciblées, nous avons choisi de distinguer la dépression du post-partum en fonction de l'apparition des symptômes, avec un seuil à 8 semaines post-partum, correspondant au pic de dépression du post-partum observé dans les premières semaines post-partum (Norhayati et al. 2015), mais également à la définition proposée par les nosographies internationales (American Psychiatric Association 2013; World Health Organization 2018).

Figure 6 : Facteurs associés à la dépression du post-partum selon le moment de survenue du trouble dans la cohorte IGEDEPP



Conclusion et perspectives :

Si la dépression du post-partum à début précoce et celle à début tardif partagent certains facteurs de risque communs, comme des antécédents personnels de trouble dépressif ou des événements de vie stressants pendant la grossesse, on peut distinguer début précoce et tardif par des corrélats socio-économiques, des événements de vie et des troubles psychiatriques associés. Nos résultats peuvent avoir des implications cliniques directes importantes. En effet, la prévention grâce à l'identification précoce des femmes à risque semble être une stratégie déterminante pour réduire l'incidence de la dépression périnatale (U.S. Preventive Services Task Force 2009; Siu et al. 2016).

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**Early and late-onset postpartum depression exhibit distinct associated factors:
the IGEDEPP prospective cohort study**

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Short title: Correlates of early and late-onset postpartum depression

ABSTRACT

Objective To identify risk factors for early and late-onset postpartum depression (PPD) among a wide range of variables including sociodemographic characteristics, childhood trauma, stressful life events during pregnancy and history of personal and family psychiatric disorders; and to assess the contribution of each risk factor.

Design Nested case-control in a prospective longitudinal cohort study.

Setting Eight maternity departments in Paris metropolitan area, France.

Sample 3310 women with deliveries between November 2011 and June 2016.

Methods Cases were women with early or late-onset PPD. Controls were women without depression during pregnancy or postpartum period. Logistic regression adjusted on socio-demographic variables were performed for each outcome and a multivariable model was proposed based on a stepwise selection procedure.

Main Outcome Measures Early and late-onset PPD assessed respectively at 2 months and one year postpartum.

Results: Stressful life events during pregnancy have a dose-response relationship with both early and late-onset PPD.

Conclusion: Early and late-onset PPD presented distinct patterns of correlates. These results have important consequences in terms of prevention and specific care.

Keywords

- Postpartum
- Depression
- Psychiatric history
- Stressful life events
- Childhood trauma

Tweetable abstract:

Early and late-onset postpartum depression are associated with stressful life events and psychiatric history.

INTRODUCTION

Postpartum depression (PPD) is a severe disease, associated with short-term complications such as suicide, and long-term deleterious consequences, including depressive recurrence (1,2). It affects between 10% and 20% of women in the year following delivery (2,3). Studies over the course of several decades identified consistently two distinct peaks of PPD (4–7): early-onset PPD is usually defined as beginning in the first 6 weeks after delivery, while late-onset PPD develops between the second month and the end of the first year postpartum (8–10).

Some studies reported sociodemographic and psychiatric risk factors, including extreme ages, primiparity or grand multiparity (more than 4 children), being single, and personal or familial psychiatric history (3,11–20). Stressful life events are also associated with higher rates of PPD, whether they occur during childhood, adulthood or during pregnancy (3,21). Obstetrical factors, such as unwanted pregnancy, emergency cesarean section, or complications of pregnancy, are also associated with PPD (17,22–24).

Differences in socio-demographic factors or depression history were found to contribute to the onset timing of perinatal depression (pregnancy or postpartum), establishing different trajectories of depression (4,25). Only a few studies have investigated the distinction between early and late-onset PPD with a prospective design (26,27). Several studies focused on factors associated with different trajectories of postpartum depression. For example, the EDEN mother-child birth cohort study based in France (2003-2011) distinguishes different trajectories (28).

A systematic review of eleven studies found no significant difference in socio-demographic or clinical characteristics between women with different trajectories of perinatal depressive symptoms (29). While PPD is usually considered as a single disease irrespective of the time of onset of symptoms (10), our hypothesis is that factors may differ between early and late-onset PPD. Indeed, the emotional and physical state of the mother as well as the environment change between the first weeks postpartum and several months after birth (30). There is an interaction between the maternal emotional state, children emotional state and their link, with mutual influence (31–33).

The aim of the present study is (i) to identify risk factors for both early and late-onset PPD among a wide range of variables including sociodemographic characteristics, personal and family history of psychiatric disorders, childhood trauma, and stressful life events during pregnancy, (ii)

to assess the contribution of each of these risk factors to the development of early or late-onset PPD.

MATERIALS AND METHODS

Participants

We performed a nested case-control study within the IGEDEPP prospective cohort. IGEDEPP enrolled 3310 Caucasian women in eight maternity departments in the Paris metropolitan area in France, between November 2011 and June 2016. Caucasian cohort participants were selected in order to remove potential confounding factors for genetic analysis. Other main inclusion criteria were: age over 18, and delivery after 32 weeks of amenorrhea. Exclusion criteria included mental retardation, dementia or schizophrenia. Women were included in the study at the maternity department between the second and the fifth day after delivery and were evaluated at three time points by specially trained clinicians, over the course of one year. The first assessment took place at the maternity department between the second and fifth day after delivery in a face-to-face interview; the second at 8 weeks postpartum, by phone; the third at one year postpartum, also by phone. Among the 3310 women, 91.1% (n=3015) were assessed at 8 weeks postpartum, and 71.0 % (n=2351) were assessed at 1 year postpartum. Clinical characteristics of the sample have been described in previous work (34).

The research protocol (ClinicalTrials.gov Identifier: NCT01648816) was approved by the Data Protection and Freedom of Information Commissions and the French Ethics Committee (Ile de France I). All women received oral and written information regarding the study and signed a consent form.

Measures

Sociodemographics and childhood trauma at the initial evaluation

Socio-demographic characteristics assessed at the initial evaluation included age, marital status, educational level, professional situation and health insurance status.

Childhood trauma (physical and sexual abuse, severe neglect) were assessed using the Childhood Trauma Questionnaire (CTQ), a validated self-administered questionnaire of 28 questions (35). To determine the presence of abuse/neglect, we used the cut-off scores

described by Paquette (36).

Stressful life events during pregnancy, assessed at the initial evaluation

The Paykel scale, a validated questionnaire of 64 questions each with a subjective score of the intensity of the impact, was used to identify stressful events (37). Stressful life events were based on subjective experience, as assessed during the initial evaluation. Events were considered as stressful if they had a negative impact considered "marked" or "severe" by the participant, considering the perceived stress. The Paykel scale was administered three time points: at the maternity department, at 8 weeks and at 1 year postpartum.

The 64 items are organized into 11 categories: work, teaching, wealth, health, bereavement, moving, love relationships, legal issues, family, conjugal and other.

While the Paykel scale has been translated and adapted to French, psychometric proprieties have not yet been described.

Obstetrical events at the initial evaluation

Obstetrical characteristics were assessed by a questionnaire at the maternity department, covering factors known to be associated with PPD in the literature (see details in (Tebeka et al. (34)). No information came from the obstetrical record.

Obstetrical events with a negative impact considered as "marked" or "severe" by the woman were considered as stressful.

Lifetime psychiatric disorder at the initial evaluation

During the first interview, personal psychiatric history was assessed by a trained clinician using the French validated version of the Diagnostic Interview for Genetic studies (DIGS), a semi-structured interview (38,39), adapted to DSM-5 criteria (40).

PPD was also diagnosed using a semi structured interview (the DIGS) (38,39), according to DSM-5 criteria for a major depressive episode (40). PPD was evaluated at two time points: at 8 weeks postpartum (early-onset PPD), and at one year postpartum (late-onset depression). Early-onset PPD was defined as beginning prior to the 6th week postpartum, and was diagnosed at 8 weeks, following DSM criteria. Late-onset PPD was defined as beginning between two months

and one year postpartum: women were assessed at the one-year follow-up for the onset and duration of depressive symptoms over the prior 10 months. Late-onset PPD was assessed retrospectively one year after delivery, and could persist at the time of assessment or not. For all women with PPD, the date of onset and the duration of symptoms were collected.

Family psychiatric history (1st degree relatives) was also assessed using the Family Informant Schedule and Criteria, a validated questionnaire (FISC) (41). The FISC has been translated and adapted to French.

Statistical Analyses

We performed a nested case-control study from the IGEDEPP cohort. We identified 250 cases of early-onset PPD, defined as meeting DSM-5 criteria for major depressive episode at the 8 weeks interview. Similarly, there were 235 cases of late-onset PPD, identified at the one-year visit. Categories were mutually exclusive, participants with early-onset PPD were not considered as having late-onset PPD even if they met criteria for PPD at the one-year visit (N=68). Women without any form of perinatal depression (i.e. neither during pregnancy nor in the first year postpartum) and with complete follow-up during one year were used as unmatched controls (N=1859) (figure 1).

Descriptive statistics for binary and categorical variables included sample sizes and percentages for each category and according to the case/control status. Multivariable logistic regressions were conducted to quantify the association between PPD and associated factors at a given time point. Odds-ratios (ORs), adjusted for socio-demographic variables (i.e. age, marital status, education level, and employment), are reported along with their 95% confidence interval (CI) and p-values. The significance threshold was set at .05. No imputation procedure for the replacement of missing data was performed.

We performed a backward stepwise logistic regression procedure using PPD as the dependent variables to minimize the Akaike Information Criterion. In the multivariable logistic regressions, initial candidate variables were socio-demographic variables and variables with a p-value below 0.2. The final step is reported using p-values, adjusted odd ratios (aOR) and 95% Confidence Intervals (CI). This approach is justified in this study by a large ratio between the number of observed events and candidate variables. We performed a penalized likelihood

approach (LASSO) as a sensitivity analysis: the optimal penalty was set with 10-fold cross-validation to optimize the AUC of the model. All pairwise interactions have been tested on the final model. All analysis were performed with R, v4.0.2.

RESULTS

EARLY-ONSET PPD

Sociodemographic characteristics and childhood trauma (table 1)

Being single was associated with early-onset PPD (OR=2.2, 95% CI 1.2-4.1, $p=.017$), as well as a lower level of education (primary or high school) (OR=1.8, 95% CI 1.1-2.8, $p=.011$), whereas being unemployed and age were not.

Childhood trauma was twice as common in women with early-onset PPD as in women without perinatal depression (aOR=2.2, 95%CI 1.5-3.3, $p<.001$). Regarding the different types of childhood trauma, emotional abuse, sexual abuse and emotional neglect were associated with early-onset (aOR=2.2, 95%CI 1.1-4.2, $p=.021$, aOR=2.8, 95%CI 1.5-5.4, $p=.002$ and aOR=2.2, 95%CI 1.4-3.5, $p<.001$ respectively), while physical abuse and physical neglect were not.

Stressful life events during pregnancy (table 2)

Having at least one stressful life event during pregnancy was associated with early-onset PPD (aOR=2.0, 95%CI 1.5-2.7, $p<.001$). More specifically, having at least one event related to relationship difficulties (separation or dispute) during pregnancy was associated with early-onset (aOR=2.8, 95%CI 1.8-4.3, $p<.001$). The number of stressful life events during pregnancy was also associated with an increased risk of early-onset PPD per additional stressful life event (aOR=1.5, 95%CI = 1.3-1.7, $p<.001$) (table 2). In another way, early-onset PPD was associated with exactly one stressful life event (aOR=1.6, 95%CI = 1.1-2.2, $p=0.006$), exactly two events (aOR=2.5, 95%CI = 1.7-3.6, $p<.001$), and three events and more (aOR=3.8, 95%CI = 2.4-6.0, $p<.001$) (Table S1).

Regarding stressful obstetrical events, early-onset PPD was associated with concomitant chronic physical disease, and emergency consultation during pregnancy (aOR=1.6,

95%CI 1.1-2.2, $p=.008$, and $aOR=1.4$, 95%CI 1.1-1.8, $p=.015$ respectively). Other stressful obstetrical events were not associated with early-onset PPD.

Personal and family lifetime psychiatric history (table 3)

A history of any psychiatric disorder was significantly associated with early-onset PPD ($aOR=2.2$, 95%CI 1.7-2.9, $p<.001$). Histories of depression and suicide attempt increased the risk twofold for early-onset PPD ($aOR=2.2$, 95%CI 1.7-2.9, $p<.001$; $aOR=2.3$, 95%CI 1.2-4.2, $p=.011$ respectively). History of any anxiety disorders (specific phobia, agoraphobia, social anxiety, generalized anxiety disorder or panic disorder) was associated with an increased risk of early-onset PPD ($aOR=1.6$, 95%CI 1.2-2.2 $p=.005$). A history of substance use disorders was significantly associated with higher risk of early-onset PPD ($aOR=1.8$, 95%CI 1.2-2.7, $p=.007$). Eating disorders and alcohol and cannabis use disorders were not significantly associated with early-onset PPD.

A family history of mood disorder was associated with early-onset PPD ($aOR=1.3$, 95%CI 1.0-1.7, $p=.049$), whereas family history of anxiety disorder, schizophrenia, alcohol dependence were not.

Stepwise regression model (table 4)

Sociodemographic variables and variables with a p -value below 0.2 in the univariate analysis (emotional abuse, physical abuse, sexual abuse, emotional neglect, infertility before conception, stressful life events during pregnancy, concomitant chronic physical disease, emergency consultation during pregnancy, and personal history of depression, suicide attempt, anxiety disorder, eating disorder, tobacco dependence and cannabis use disorder) were included in the model. In multivariable models, early-onset PPD was independently associated with a history of depression ($aOR:2.0$, 95%CI:1.5-2.6), sexual abuse during childhood ($aOR:2.0$, 95%CI:1.0-4.0), stressful life event during pregnancy ($aOR:1.8$, 95%CI:1.4-2.4) and physical concomitant chronic disease during pregnancy ($aOR:1.5$, 95%CI:1.0-2.1).

No significant interaction was found.

The LASSO sensitivity analysis led to a sparser model with only history of mood disorder, stressor event during pregnancy, emotional neglect and sexual abuse being included.

LATE-ONSET PPD

Sociodemographic characteristics and childhood trauma (table 1)

Being unemployed was associated with late-onset PPD (OR=2.1, 95% CI 1.3-3.3, $p=.001$), whereas being single, age, and educational level were not.

Childhood trauma was twice as common in women with late-onset PPD as in women without perinatal depression (aOR=2.1, 95%CI 1.4-3.2, $p<.001$). Each types of childhood abuse and emotional neglect were associated with late-onset PPD (emotional abuse aOR=3.6, 95%CI 2.0-6.4, $p<.001$; physical abuse aOR=2.8, 95%CI 1.3-5.6, $p=.006$; sexual abuse aOR=2.7, 95%CI 1.4-5.4, $p=.004$; and emotional neglect aOR=1.9, 95%CI 1.1-3.1, $p<.012$).

Stressful life events during pregnancy (table 2)

Having at least one stressful life event during pregnancy was associated with late-onset PPD (aOR=2.4, 95%CI 1.8-3.2, $p<.001$). More specifically, having at least one event related to relationship difficulties (separation or dispute) during pregnancy was associated with late-onset PPD (aOR=2.2, 95%CI 1.4-3.5, $p=.001$). The number of stressful life events during pregnancy was also associated with an increased risk of late-onset PPD per additional stressful life event (aOR=1.6, 95%CI = 1.4-1.8, $p<.001$) (table 2). In another way, late-onset PPD was associated with exactly one stressful life event (aOR=1.8, 95%CI = 1.3-2.5, $p<.001$), exactly two events (aOR=2.8, 95%CI = 1.9-4.2, $p<.001$), and three events and more (aOR=5.1, 95%CI = 3.2-8.0, $p<.001$) (Table S1).

Regarding stressful obstetrical events, late-onset PPD was associated only with emergency consultation during pregnancy (aOR=1.6, 95%CI 1.2-2.1, $p=.001$). Other stressful obstetrical events were not associated with either early or late-onset PPD.

Personal and family lifetime psychiatric history (table 3)

A history of any psychiatric disorder was significantly associated with late-onset PPD (aOR=1.7, 95%CI 1.3-2.2, $p<.001$). History of depression or suicide attempt increased the risk twofold for late-onset PPD (depression aOR=1.8, 95%CI 1.4-2.4, $p<.001$; suicide attempt aOR=2.4,

95%CI 1.3-4.6 p=.008). History of any anxiety disorders (specific phobia, agoraphobia, social anxiety, generalized anxiety disorder or panic disorder) was associated with an increased risk of late-onset PPD (aOR=1.5, 95%CI 1.1-2.1 p=.013). A history of substance use disorders was significantly associated with higher risk of late-onset PPD (aOR=1.8, 95%CI 1.1-2.7, p=.013), as well as cannabis use disorder (aOR=2.8, 95%CI 1.2-6.8, p=.019). Eating disorders and alcohol use disorder were not significantly associated with PPD.

A family history of psychiatric disorder was associated with a higher risk of late-onset PPD (aOR=1.6, 95%CI 1.2-2.1, p=.003). Women with late-onset PPD were significantly more likely to report specifically familial history of mood (aOR=1.7, 95%CI 1.3-2.2, p<.001), anxiety disorder (aOR=1.6, 95%CI 1.2-2.2, p=.003) and alcohol dependence or abuse (aOR=1.6, 95%CI 1.1-2.2, p<.012) than controls.

Stepwise regression model (table 4)

Sociodemographic variables and variables with a p-value below 0.2 in the univariate analysis (emotional abuse, physical abuse, sexual abuse, emotional neglect, sexual abuse, infertility before conception, stressful life events during pregnancy, emergency consultation during pregnancy, postnatal maternal complications and personal history of depression, suicide attempt, anxiety disorder, tobacco dependence, alcohol and cannabis use disorders, and a family psychiatric history of mood, anxiety disorders and alcohol dependence or abuse) were included in the model. Factors significantly associated with late-onset PPD in the final model included: emotional abuse during childhood (aOR:2.6, 95%CI:1.4-4.8), stressful life event during pregnancy (aOR:2.1, 95%CI:1.6-2.8), unemployment (aOR:2.0, 95%CI:1.2-3.2), personal and family history of mood disorder (aOR:1.6, 95%CI:1.2-2.1, and aOR:1.4, 95%CI:1.0-1.8), and emergency consultation during pregnancy (aOR:1.4, 95%CI:1.1-1.9).

There were no significant pairwise interaction.

The sensitivity analysis led to almost the same model. The only difference was that emergency consultation during pregnancy was not selected in the sensitivity analysis.

EARLY AND LATE-ONSET PPD

The comparison of women with early-onset PPD to women with late-onset PPD shows no significant difference (data available on request) except from early maternal postpartum events that were more likely to be reported by women with late-onset postpartum depression (aOR = 2.5; 95%CI 1.1-5.0, p =0.031).

DISCUSSION

Main Findings

This large prospective study aimed to determine and distinguish the main determinants of early and late-onset PPD. While both forms shared some common factors, several factors were specific to only one form of PPD. More specifically, early-onset PPD was independently associated with a personal history of depression, sexual abuse during childhood, stressful life events during pregnancy and concomitant chronic physical disease. Late-onset PPD was independently associated with emotional abuse during childhood, stressful life events during pregnancy, unemployment, personal and family history of mood disorder and emergency consultation during pregnancy.

Stressful life events during pregnancy were independently associated with both early and late-onset PPD in our cohort, in accordance with previous studies (2,42). However, the majority of women experience such stressful life events and most do not develop PPD. In the present study, we took into account the woman's subjective experience for each stressful life event and considered the perceived stress of each event. It is relevant to notice that stressful events occurring during pregnancy influence the risk of depression several months later, and not just as an immediate reaction. We also revealed a cumulative effect of these perceived stressful events. A cumulative effect of stressful life events in the year before pregnancy has been shown to have an impact on depression during pregnancy (43) , but to our knowledge had not been tested on PPD. This dose-effect relationship reflects an increased risk of both early and late-onset PPD with each additional perceived stressful event.

The impact of childhood trauma on PPD was controversial: some studies reported this association (44,45), while others did not (46,47). Our study not only confirms that childhood

trauma is associated with PPD, but also found that some CT appear to have a specific impact on early or late-onset PPD: sexual abuse was specifically associated with early-onset PPD, while emotional abuse was associated with late-onset PPD. Further research is needed to better understand this point.

As with early adversities, recent stressful events were also associated with PPD. Regarding obstetric factors before pregnancy, only a physical concomitant chronic disease was independently associated with early-onset PPD. Infertility and assisted reproductive technology were not associated with PPD, confirming recent findings (48,49). During pregnancy, we highlighted that consulting in emergency room is an important factor independently associated with late-onset PPD. An Australian study found consistent results, with more emergency room visits during pregnancy among women requiring hospitalization for PPD (50). In our study, perineal trauma and C-section were not associated with PPD. There are contrary data on perineal trauma. While Dunn et al. found an association between perineal trauma and PPD at 6 weeks and 3 months postpartum (51), recent study did not find it found no significant (52). The association between severe perineal trauma and early-onset PPD became significant in the group of women presenting low resilience (52). Resilience, considered as a moderator for both pain and depression, could modulate the link between trauma and PPD (53). Data on C-section are also conflicting, some data suggesting that emergency C-section were specifically associated with PPD (17,44,54).

Having a personal history of a psychiatric disorder was independently associated with a higher risk of both early and late-onset PPD, which is consistent with the literature (17). One of the most strongly associated factors was a personal history of depression, and the association persists in the final model. This results is in line with previous published data (2,3,17,55). Having a history of anxiety disorder was also associated with early and late-onset PPD although the final model did not retain it. The previous works find this association (15,56,57). As a potential explanation of our results, collinearity may exist between anxiety disorders and major depressive episodes, which are very often comorbid (58,59). In analyses adjusted on sociodemographic data, a history of attempted suicide was associated with the risk of early and late-onset PPD in our study. In a U.S. population study, a history of attempted suicide was associated with perinatal

depression with an adjusted OR of 3.79 (42). However, our final model did not retained history of attempted suicide. Lack of power could explain this result (history of attempted suicide concerned 14 women with early-onset PPD, 13 with late-onset PPD, and 44 controls).

Women with early and late-onset PPD were both more likely to report a family history of mood disorder than controls (53% and 60% vs. 47% respectively). There was a significant difference between women with both early and late-onset PDD and controls for family history of mood disorder disorders in our first analyses, adjusted for sociodemographic data. Our final model retained family history of mood disorder disorders only for late-onset PPD, suggesting a smaller effect of family history on early-onset PPD. A recent study based on Danish population-based registers found that parental psychiatric history of depression, bipolar disorder or schizophrenia was associated with postpartum psychiatric disorders, especially among women with personal psychiatric history (60). For women with a psychiatric history, the postpartum period appears to be a period of vulnerability for depression, suggesting that genetic factors may play a role in PPD.

Strengths and Limitations

The principal strengths of the present study are the prospective, multicenter design and the size of the sample. To the best of our knowledge, this is the largest sample to date to examine the determinants of PPD prospectively, with a good overall response rate at 1 year. In addition, all psychiatric diagnoses were based on a rigorous clinical assessment using DSM-5-criteria. Moreover, the evaluations at 8 weeks and then at 1 year postpartum make it possible to distinguish two types of PPD, with different determinants for early and late-onset PPD. Finally, IGEDEPP provides an extensive assessment of a wide range of determinants.

A main limitation of the study is the fact that all included women were Caucasian, due to the original objective of the cohort: studying genetic determinants of PPD. The women included also had a high level of education and favourable socio-economic conditions. The women were included in 8 maternity departments in Paris or the Parisian suburbs, which does not represent the French population. These points limit the generalizability of our findings. The assessment of late-onset PPD was retrospective. This may lead to underestimate the prevalence of late-onset PPD because of a recall bias. The prevalence of postpartum depression as well as prevalence of the psychiatric disorders assessed were consistent with other samples of women (34). No further

information was collected regarding access to psychiatric care. This should be the subject of future studies.

Interpretation

In order to better understand PPD and to develop targeted prevention practices, several studies attempted to define subtypes of PPD according to the time of onset, severity or predominant symptoms (29,61–63). In this study, we chose to distinguish PPD according to the onset of symptoms, with a cut-off at 8 weeks postpartum, corresponding to the peak of PPD observed in the first weeks postpartum (8). Early and late-onset PPD can be distinguished by socio-economic correlates, life events, and associated psychiatric disorders. Early and late-onset PPD also share some common risk factors, as stated the results of present study, e.g., a personal history of depressive disorder, or stressful life events during pregnancy.

Conclusions

This large, prospective, multicenter study highlights risk factors for PPD: a personal vulnerability, in addition to psychiatric history, and environmental factors, as well as childhood trauma and stressful life events during pregnancy. We distinguished different patterns of correlates for early and late-onset PPD. Early-onset PPD was particularly associated with a physical chronic disease, while late-onset depression was associated with unemployment, as well as obstetric factors like emergency consultation.

Our results had direct and important clinical implications. Indeed, prevention through earlier identification of at-risk women is the most important strategy in decreasing PPD incidence (64,65).

Whether personal biological vulnerability and stressful life events act independently or interact with one another should be the focus of further studies.

Disclosure of interests: The authors report no conflicts of interest.

Contribution to authorship:

S. Tebeka drafted the initial manuscript, and approved the final manuscript as submitted.

J. Mullaert carried out the initial analyses, revised the manuscript, and approved the final manuscript as submitted.

C. Dubertret designed the study, revised the manuscript, and approved the final manuscript as submitted.

A. Benachi, M. Dommergues, C. Dubertret, D. Luton, and L. Mandelbrot created and validated the questionnaire on obstetric characteristics.

A. Benachi, M. Dommergues, G Kayem, Y. Le Strat, J. Lepercq, D. Luton, L. Mandelbrot, Y. Ville, and N. Ramoz, revised the manuscript, and approved the final manuscript as submitted.

Details of Ethics Approval: The research protocol (ClinicalTrials.gov Identifier: NCT01648816), including informed consent procedures, was approved by the French Ethics committee (Ile de France I) on March 2011 (reference numbers: AOM10056, NI10018, IGEDEPP, ID-RCB 2010-AO1315-34) and Data Protection and Freedom of Information Commissions.

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Data availability statement :

The data that support the findings of this study are available from APHP. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of APHP

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Table 1. Association between post-partum depression and socio-demographic data and childhood trauma (CTQ)

	Early-onset PPD (N=250) N (%)	Late-onset PPD (N=235) N (%)	Controls (N=1859) N (%)	Early-onset PPD vs Controls aOR (95%CI) p-value	Late-onset PPD vs Controls aOR (95%CI) p-value
Age (years)					
<25	21 (8.4)	15 (6.4)	110 (5.9)	1.5 (0.9-2.4)	1.1 (0.6-1.9)
between 25 and 40	214 (85.6)	207 (88.1)	1656 (89.1)	1 (ref)	1 (ref)
>40	15 (6.0)	13 (5.5)	93 (5.0)	1.3 (0.7-2.1)	1.1 (0.6-2.0)
Marital status: single	13 (5.2)	6 (2.6)	46 (2.5)	2.2 (1.2-4.1)	1.0 (0.4-2.4)
Education level: Primary or high school	26 (10.4)	15 (6.4)	113 (6.1)	1.8 (1.1-2.8)	1.1 (0.6-1.8)
Unemployed	21 (8.4)	26 (11.1)	104 (5.6)	1.5 (0.9-2.5)	2.1 (1.3-3.3)
Childhood stressful life event (CTQ, N above threshold)					
- Emotional abuse	12 (4.9)	18 (7.7)	41 (2.2)	2.2 (1.1-4.2)	3.6 (2.0-6.4)
- Physical abuse	9 (3.6)	11 (4.7)	31 (1.7)	1.8 (0.8-4.0)	2.8 (1.3-5.6)
- Sexual abuse	14 (5.7)	12 (5.2)	35 (1.9)	2.8 (1.5-5.4)	2.7 (1.4-5.4)
- Emotional neglect	28 (11.3)	22 (9.4)	92 (5.0)	2.2 (1.4-3.5)	1.9 (1.1-3.1)
- Physical neglect	3 (1.2)	1 (0.4)	10 (0.5)	2.0 (0.5-7.4)	0.7 (0.1-5.9)
- Any trauma	41 (16.6)	35 (15.0)	138 (7.5)	2.2 (1.5-3.3)	2.1 (1.4-3.2)

Abbreviations: CTQ, Childhood trauma questionnaire; PPD: postpartum depression ;
aOR: OR adjusted for age, marital status, education level and employment

Table 2. Association between post-partum depression and stressor events during pregnancy

	Early-onset PPD N=250 N (%)	Late-onset PPD N=235 N (%)	Controls N=1859 N (%)	Early-onset PPD vs Controls		Late-onset PPD vs Controls	
				aOR (95%CI)	p-value	aOR (95%CI)	p-value
Stressful events during pregnancy							
At least one stressful event with negative impact during pregnancy (Paykel scale)	154 (61.6)	153 (65.1)	816 (43.9)	2.0 (1.5-2.7)	<.001	2.4 (1.8-3.2)	<.001
stressful event with negative impact during pregnancy (Paykel scale, aOR per additional event)				1.5 (1.3-1.7)	<.001	1.6 (1.4-1.8)	<.001
At least one event with negative impact relate-onsetd to couple dispute or separation	35 (14.0)	26 (11.1)	97 (5.2)	2.8 (1.8-4.3)	<.001	2.2 (1.4-3.5)	0.001
Obstetrical events before and during pregnancy							
Infertility	39 (15.6)	38 (16.2)	223 (12.0)	1.4 (1.0-2.0)	0.084	1.4 (1.0-2.1)	0.084
Assisted reproductive technology	23 (9.2)	25 (10.6)	156 (8.4)	1.1 (0.7-1.8)	0.642	1.3 (0.8-2.1)	0.254
Physical concomitant chronic disease	49 (19.6)	37 (15.7)	240 (12.9)	1.6 (1.1-2.2)	0.008	1.2 (0.8-1.8)	0.276
Primiparity	149 (59.6)	127 (54.0)	1077 (57.9)	1.1 (0.8-1.4)	0.647	0.9 (0.7-1.1)	0.291
Multiple pregnancy	10 (4.0)	7 (3.0)	65 (3.5)	1.2 (0.6-2.3)	0.663	0.9 (0.4-1.9)	0.701
Emergency consultation during pregnancy	134 (53.6)	133 (56.6)	846 (45.5)	1.4 (1.1-1.8)	0.015	1.6 (1.2-2.1)	0.001
Hospitalization during pregnancy	36 (14.4)	32 (13.6)	238 (12.8)	1.1 (0.8-1.6)	0.563	1.1 (0.7-1.6)	0.768
Delivery events							
C-section delivery	67 (26.8)	64 (27.2)	440 (23.7)	1.2 (0.9-1.6)	0.337	1.2 (0.9-1.6)	0.245
No obstetrical analgesia despite intention	40 (88.9)	48 (94.1)	283 (87.9)	1.1 (0.4-3.0)	0.853	2.2 (0.7-7.4)	0.205
Perineal trauma							
- None or minor perineal tear	187 (74.8)	179 (76.2)	1399 (75.3)	1 (ref)		1 (ref)	

- Episiotomy	60 (24.0)	54 (23.0)	441 (23.7)	1.0 (0.8-1.4)	0.822	1.0 (0.7-1.3)	0.847
- Perineal trauma (≥ 2-degree perineal tear)	3 (1.2)	2 (0.9)	19 (1.0)	1.2 (0.4-4.2)	0.764	0.8 (0.2-3.7)	0.824
Newborn relate-onsetd events (preterm, small for gestational age, NICU)	28 (11.2)	22 (9.4)	172 (9.3)	1.2 (0.8-1.8)	0.421	1.0 (0.6-1.6)	0.921
Early maternal postpartum events (hemorrhage, ICU)	10 (4.0)	19 (8.1)	110 (5.9)	0.7 (0.3-1.3)	0.211	1.4 (0.8-2.3)	0.188

Abbreviations: NICU, newborn Intensive Care Unit; PPD, postpartum depression; ICU, Intensive care unit.

aOR: OR adjusted for age, marital status, education level, and employment

Table 3. Association between post-partum depression and personal and family psychiatric history

	Early-onset	Late-onset	Controls	Early-onset PPD vs Controls		Late-onset PPD vs Controls	
	PPD	PPD	(N=1859)	aOR (95%CI)	p-value	aOR (95%CI)	p-value
	(N=250)	(N=235)	N (%)				
	N (%)	N (%)	N (%)				
Personal psychiatric history							
Any psychiatric disease	157 (62.8)	133 (56.6)	801 (43.1)	2.2 (1.7-2.9)	<.001	1.7 (1.3-2.2)	<.001
Major depressive episode	122 (48.8)	104 (44.3)	555 (29.9)	2.2 (1.7-2.9)	<.001	1.8 (1.4-2.4)	<.001
Suicide attempt	14 (5.6)	13 (5.5)	44 (2.4)	2.3 (1.2-4.2)	0.011	2.4 (1.3-4.6)	0.008
Any anxiety disorder	57 (22.8)	52 (22.1)	286 (15.4)	1.6 (1.2-2.2)	0.005	1.5 (1.1-2.1)	0.013
Any eating disorder	15 (6.0)	11 (4.7)	71 (3.8)	1.6 (0.9-2.9)	0.107	1.3 (0.7-2.4)	0.487
Any substance use disorder	31 (12.4)	27 (11.5)	128 (6.9)	1.8 (1.2-2.7)	0.007	1.8 (1.1-2.7)	0.013
Tobacco dependence	27 (10.8)	21 (8.9)	107 (5.8)	1.9 (1.2-2.9)	0.007	1.6 (1.0-2.6)	0.062
Alcohol use disorder	2 (0.8)	3 (1.3)	10 (0.5)	1.2 (0.2-5.7)	0.837	2.5 (0.7-9.3)	0.175
Cannabis use disorder	6 (2.4)	7 (3.0)	20 (1.1)	2.0 (0.8-5.1)	0.143	2.8 (1.2-6.8)	0.019
Family psychiatric history							
Any psychiatric disorder	169 (67.6)	171 (72.8)	1168 (62.8)	1.3 (1.0-1.7)	0.105	1.6 (1.2-2.1)	0.003
Mood disorder	132 (52.8)	140 (59.6)	871 (46.9)	1.3 (1.0-1.7)	0.049	1.7 (1.3-2.2)	<.001
Anxiety disorder	54 (21.6)	64 (27.2)	350 (18.8)	1.2 (0.9-1.7)	0.286	1.6 (1.2-2.2)	0.003
Schizophrenia	3 (1.2)	2 (0.9)	26 (1.4)	0.8 (0.2-2.8)	0.749	0.6 (0.1-2.6)	0.492
Alcohol dependence or abuse	41 (16.4)	45 (19.1)	242 (13.0)	1.3 (0.9-1.8)	0.223	1.6 (1.1-2.2)	0.012
Other substance use disorder	48 (19.2)	51 (21.7)	347 (18.7)	1.1 (0.8-1.5)	0.724	1.2 (0.9-1.7)	0.279

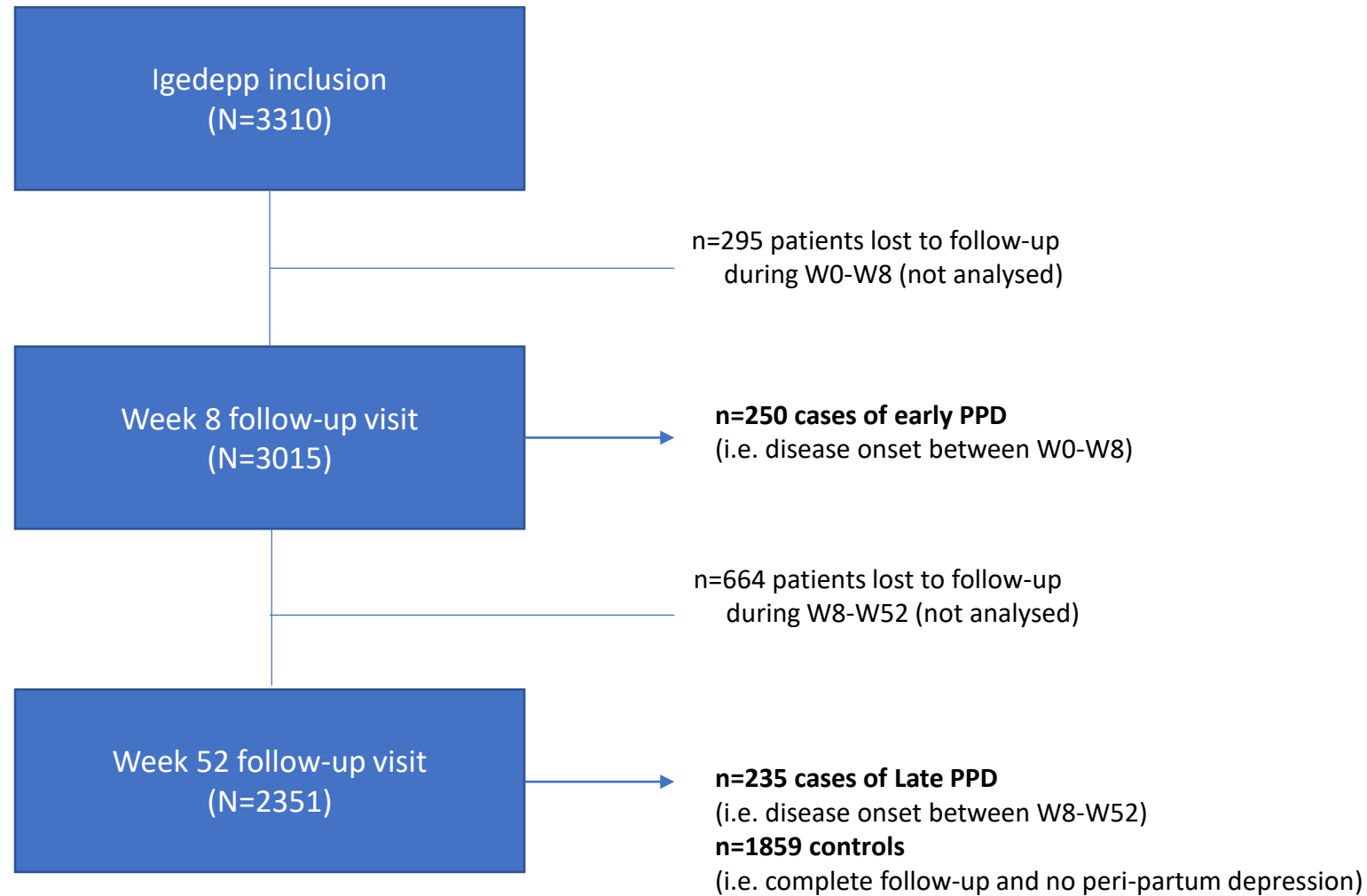
aOR: OR adjusted for age, marital status, education level and employment; PPD: postpartum depression.

Table 4. Multivariable models for early and late-onset postpartum depression

	Model 1:		Model 2:	
	Early-onset PPD vs Controls (N=2077)		Late-onset PPD vs Controls (N=2063)	
	aOR (95%CI)	p-value	aOR (95%CI)	p-value
Marital status: single	1.7 (0.9-3.2)	0.131		
Education level: Primary or high school	1.5 (1.0-2.5)	0.072		

Personal history of major depressive episode	2.0 (1.5-2.6)	<.001
Emotional neglect (CTQ)	1.6 (1.0-2.6)	0.054
Sexual abuse (CTQ)	2.0 (1.0-4.0)	0.045
Stressor event with negative impact during pregnancy (Paykel)	1.8 (1.4-2.4)	<.001
Physical concomitant chronic disease	1.5 (1.0-2.1)	0.035
Emergency consultation during pregnancy	1.2 (0.9-1.6)	0.118
Unemployed	2.0 (1.2-3.2)	0.004
Personal history of major depressive episode	1.6 (1.2-2.1)	0.002
Family history of mood disorder	1.4 (1.0-1.8)	0.028
Emotional abuse (CTQ)	2.6 (1.4-4.8)	0.002
Stressor event with negative impact during pregnancy (Paykel)	2.1 (1.6-2.8)	<.001
Emergency consultation during pregnancy	1.4 (1.1-1.9)	0.016

Abbreviations: aOR, adjusted odds-ratio; CTQ, Childhood trauma questionnaire; PPD, postpartum depression.



This article is protected by copyright. All rights reserved. **Figure 1. Flow chart of IGEDePP and selection of cases and controls**

- II.C. Article 4 : Childhood trauma and perinatal depression : data from the IGEDEPP cohort

ARTICLE 4



Childhood trauma and perinatal depression : data from the IGEDEPP cohort

Sarah Tebeka, Yann Le Strat, Bruno Etain, Margaux Ray, the IGEDEPP Study Group,
Jimmy Mullaert, Caroline Dubertret

Journal of Clinical Psychiatry, article in press

Concernant l'association entre traumatismes infantiles et dépression périnatale, les données actuelles sont imprécises et contradictoires. Ainsi, plusieurs études ont trouvé une association entre le risque de traumatismes infantiles et la dépression pendant la grossesse (Leeners et al. 2014; Rich-Edwards et al. 2011; Lara et al. 2015), avec un effet dose-réponse. Cependant, les études ultérieures ont donné des résultats contradictoires, certaines études n'ayant pas réussi à mettre en évidence cette association (Edwards et al. 2008; Dayan et al. 2010; Choi et Sikkema 2016). De même, les données sont hétérogènes concernant le lien entre traumatismes infantiles et la dépression post-partum (Choi et Sikkema 2016), des études montrant une association (Guintivano et al. 2018; S. Meltzer-Brody et al. 2018) alors que d'autres n'en retrouvent pas (De Venter et al. 2015; Robertson-Blackmore et al. 2013).

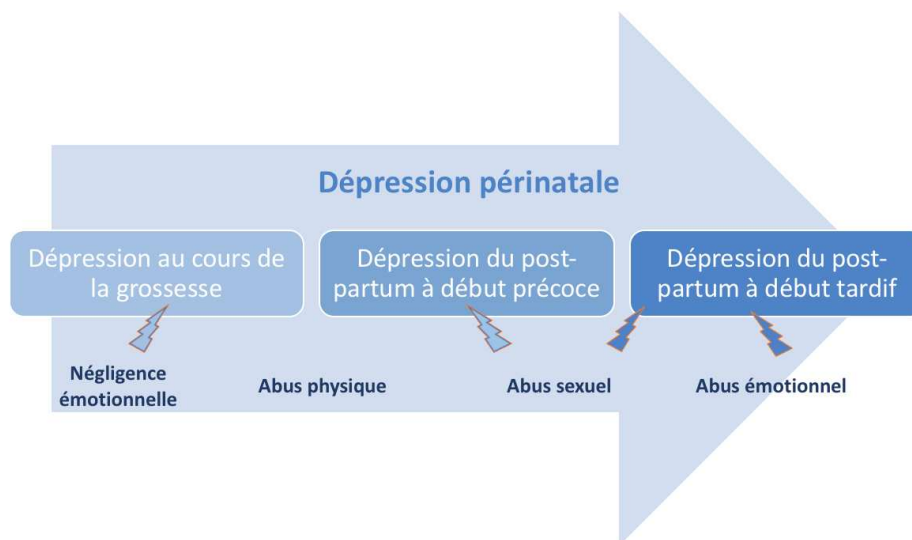
À partir de la cohorte l'IGEDEPP, une étude prospective multicentrique française, nous avons inclus les 3 252 femmes qui ont rempli le CTQ (sur 3310 femmes, 98.2 %), questionnaire sur les traumatismes dans l'enfance, au cours du séjour à la maternité (cf. méthodologie p. 37). La dépression périnatale était évaluée à trois temps : à la maternité pour évaluer la dépression de la fin de grossesse, à 8 semaines post-partum pour évaluer la dépression du post-partum à début précoce et un an post-partum pour la dépression du post-partum à début tardif.

Parmi les 3 252 femmes, 298 (9,2 %) ont déclaré au moins un traumatisme infantile. Les femmes avec un traumatisme infantile avaient un risque plus élevé de tout trouble psychiatrique (OR 2,1; IC à 95 % 1,6-2,8). La dépression périnatale, quelle que soit le moment de son apparition (pendant la grossesse, post-partum à début précoce ou tardif), était significativement plus fréquente chez les femmes avec un traumatisme infantile, et ce après ajustement pour les caractéristiques sociodémographiques et les antécédents personnels d'épisode dépressif caractérisé ($p < 0,001$). La dépression périnatale était plus fréquente chez les femmes avec un traumatisme infantile, quel que soit le type de traumatisme infantile (abus physique, sexuel ou émotionnel, ou négligence physique ou émotionnelle). Il y avait également un effet dose entre le nombre de types de traumatisme infantile et le risque de dépression périnatale. Certains traumatismes infantiles semblent avoir un impact sur le moment où débute la dépression : au cours de la grossesse ou dans le post-partum précoce ou tardif. Par exemple, alors que la négligence émotionnelle était associée à la dépression pendant la grossesse (OR 2,1, IC à 85 % 1,2-3,8), elle n'est pas associée de manière significative à la dépression au début ou à la fin du post-partum. Les abus sexuels étaient associés à la fois

à la dépression post-partum de début précoce et tardif, tandis que les abus émotionnels étaient spécifiquement associés à la dépression post-partum à début tardif.

La principale limite de ce travail est l'absence d'information sur l'âge du traumatisme infantile et sa durée. Bien que l'âge d'apparition de la maltraitance ne soit pas un facteur prédictif de symptômes de dépression pendant la grossesse (Atzl et al. 2019), d'autres études doivent confirmer ces résultats dans le post-partum.

Figure 7 : Association entre traumatismes infantiles et dépression périnatale dans la cohorte IGEDEPP




Conclusion et perspectives

Le traumatisme infantile serait associé à une dépression périnatale à chacun des trois moments de l'évaluation (pendant la grossesse, au début du post-partum et en fin de post-partum). À notre connaissance, il s'agit de la première étude qui distingue spécifiquement l'impact des types de traumatismes infantiles sur la dépression périnatale pendant la grossesse, en post-partum précoce ou tardif, dans un échantillon non clinique.

Ces résultats peuvent conduire à des soins anténataux, spécifiquement adaptés pour les femmes maltraitées ou négligées pendant l'enfance, afin de mieux dépister et prévenir la dépression périnatale.

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Childhood trauma and perinatal depression: data from the IGEDEPP cohort

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World count : 3109

ABSTRACT

Background: Childhood trauma (CT) is associated with an increased risk of major depressive disorder, but little is known about the impact of CT on depression during pregnancy and early and late postpartum. In the present study, we assessed whether CT is associated with perinatal depression considering different types of CT.

Methods: We used IGEDEPP, a French multicenter prospective cohort study, including 3,252 women who completed the Childhood Trauma Questionnaire at the maternity department between November 2011 and June 2016. Depression during pregnancy was assessed retrospectively at the maternity department using DSM-5 criteria. Early and late-onset postpartum depression were assessed at 2 months and one year postpartum respectively.

Results: Among the 3,252 women, 298 (9.2%) reported at least one CT. Women with CT had a higher risk of depression, anxiety and suicide attempts than women without CT (OR 2.1; 95%CI 1.6-2.8). Perinatal depression, was more frequent in women with CT than in women without, after adjusting for sociodemographic characteristic and personal history of major depression episode and considering all timing of onset (pregnancy, early or late postpartum) ($p < 0.001$). There was a dose effect between the number of CT type and the risk of perinatal depression.

Conclusion: Our results show that CT is associated with a depressive episode during adulthood, specifically in the perinatal period. It may lead to special prenatal care for women abused or neglected during childhood, to better screen and treat perinatal depression.

Trial registration: The research protocol was registered on ClinicalTrials.gov (Identifier: NCT01648816).

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Competing interests: none of the authors have any competing interests.

Ethics, consent and permissions

The research protocol including informed consent procedures, was approved by the French Ethics committee (Ile de France I) and Data Protection and Freedom of Information Commissions.

Authors' contributions:

S. Tebeka drafted the initial manuscript, and approved the final manuscript as submitted.

J. Mullaert carried out the initial analyses, revised the manuscript, and approved the final manuscript as submitted.

C. Dubertret designed the study, revised the manuscript, and approved the final manuscript as submitted.

Y. Le Strat, B. Etain and M. Ray revised the manuscript, and approved the final manuscript as submitted

Keywords

- Postpartum
- Pregnancy
- Depression
- Childhood trauma
- Women

INTRODUCTION

The perinatal period, including pregnancy and the first year postpartum¹, is associated with an increased risk for psychiatric disorders, especially mood disorders². Perinatal depression affects 10% to 20% of women^{2,3}. It is associated with adverse consequences for both the mother and her child, including a higher risk of suicide and an increased risk of developmental disorders^{2,4,5}. A personal or family history of depression, high levels of anxiety or depression during pregnancy, stressful life events, obstetrical complications and childhood trauma (CT) are considered as risk factors for perinatal depression^{3,6-15}.

According to child protection agencies, between 1.5% to 5% of children in Western countries are victims of child abuse¹⁶⁻¹⁸. Trauma during childhood is recognized as a major public health problem by the WHO¹⁹. However, these prevalence might be underestimated, with studies based on self-reported trauma suggesting a 34%- 48% range^{17,20,21}. Women report higher prevalence of CT than men and in particular more emotional and sexual abuses^{16,22,23}. Women are also more likely to experience multiple CT than men, and to report different types of abuse^{20,23}.

CT is associated with poor outcomes in adolescence and adulthood, with an increased risk of both physical and psychiatric disorders²⁴, including cardiovascular disorders²⁵, cancers²⁶, and premature death²⁷. CT is associated with an increased risk of major depressive disorder²⁸, post-traumatic stress disorder²⁹, substance use disorder³⁰ and is associated with a higher suicidality^{31,32}. In a prospective study, individuals who experienced CT were 2 times more likely to report a major depressive disorder, 2 times more likely to report suicidal ideation and 4 times more likely to report an anxiety disorder than individuals without CT³³. Patients with CT are more likely to report multiple psychiatric diagnoses than their counterparts without CT. More than 75% of individuals reporting both CT and a depressive episode also meet criteria for at least another psychiatric diagnosis^{23,32,34}. Moreover, psychiatric disorders in patients with

CT have a poorer prognosis than their counterpart without CT. In patients with both CT and a psychiatric disorder, the age at onset of the psychiatric disorder is younger, with greater symptom severity and a worse treatment response than in patients without a history of CT ³⁵⁻⁴³.

Several studies found an association between the risk of CT and depression during pregnancy ⁴⁴⁻⁴⁶, with a dose-response effect. For example, in a study by Robertson-Blackmore et al., women with 3 or more CT reported a 4-fold risk of depression during pregnancy compared to women without CT ¹⁰. However, subsequent studies yielded conflicting findings with some studies failing to find this association ⁴⁷⁻⁴⁹. On the other hand, there also are contradictory data regarding the impact of CT on postpartum depression ⁴⁹, with studies showing an association between CT and postpartum depression ^{6,9} while others not ^{10,50}.

These contradictory results could be explained by the small samples involved, preventing from distinguishing depression during pregnancy, early and late-onset postpartum depression, and rarely assessing the distinct subtypes of CT. Early-onset depression was defined as beginning prior to the 6th week postpartum, and was diagnosed at 8 weeks, following DSM criteria and corresponding to the peak of depression observed in the first weeks postpartum ^{51,52}. Late-onset PPD was defined as beginning between two months and one year postpartum. This definition is based on clinical practice, and is adopted by the Marce International Society for Perinatal Mental Health and the World Health Organization ^{1,53}.

Using data from the French Gene Environment Interaction in postpartum depression (IGEDEPP) study, we performed an intra-cohort case-control association study to fill the gaps in the literature. The aim of this study was to assess how CT is associated with women's history of depression, anxiety and/or suicide attempts by (i) comparing the sociodemographic characteristics and personal history of depression, anxiety and suicide attempts, and (ii)

assessing the prevalence of depression during pregnancy and early and late postpartum period in women with CT compared to women without. Our hypotheses were that (i) women with CT would be more likely to report depression, anxiety and suicide attempts than those without CT, (ii) the types of CT would be associated with depression depending on the timing onset (i.e. during pregnancy and postpartum).

METHODS

Participants

IGEDEPP is a large French multicenter cohort, composed of 3,310 European women in 8 maternity departments in the Paris metropolitan area, in France. Women were included between November 2011 and June 2016. Main inclusion criteria were: age >18, European ethnicity (required for further genetic studies in the IGEDPEPP Cohort) and coverage by French social insurance. Women who did not speak French, had an intellectual disability or schizophrenia, or who gave birth before 32 weeks of gestation were excluded. In the present work, we only included women who completed the Childhood Trauma Questionnaire (N=3,252).

Women were included and assessed between the 2nd and 5th day postpartum, at the maternity department by trained clinicians using a face-to-face interview. They were followed-up at 8 weeks and at 1 year postpartum, by phone.

All the details concerning this cohort are described in Tebeka et al ⁵⁴.

The research protocol (ClinicalTrials.gov Identifier: NCT01648816), including informed consent procedures, was approved by the French Ethic committee (Ile de France I) and the Data Protection and Freedom of Information Commission.

Measures

Assessment of childhood trauma at the first evaluation

The Childhood Trauma Questionnaire (CTQ) is a self-administered questionnaire used to assess CT; participants completed the CTQ during the first clinical assessment, at the maternity department. The CTQ included 28 items grouped into 5 subscales of trauma: sexual abuse (defined as a sexual contact with an adult or an older person) and emotional abuse (verbal assaults), emotional neglect (lack of love, nurturance or support), physical abuse (bodily assaults) and physical neglect (poor parental supervision and care)⁵⁵. The presence of trauma was determined according to validated cut-off scores of the CTQ. In the French version of the CTQ, sexual abuse, emotional neglect and abuse, physical neglect and abuse were considered as present if the score of the corresponding subscale is greater or equal than 11, 16, 11, 14 and 16, respectively²³. Alpha coefficients, estimated from our sample, were 0.51 (physical neglect), 0.85 (emotional neglect), 0.90 (sexual abuse), 0.78 (physical abuse) and 0.81 (emotional abuse) respectively.

Sociodemographic Measures at the first evaluation

Age, educational level, employment and marital status were collected at baseline. Age at interview was categorized into: (i) 18–25, (ii) 26-39, and (iii) 40 and more. Educational level was classified into: (i) high school or less, (ii) university.

Personal history assessed at the first evaluation

Psychiatric diagnoses were based on a semi-structured interview, the Diagnostic Interview for Genetic Studies (DIGS)^{56,57}, according to DSM-5 criteria⁵². The French validation study of the DIGS found excellent inter-rater reliability and a fair to good diagnostic reliability using a test-retest interval of six weeks⁵⁷. The interviewers were psychiatrists or psychologists who received specific training to administer the DIGS. We reported lifetime prevalence for major depressive episode, and anxiety disorders (including obsessional

compulsive disorder, panic disorder, agoraphobia, social anxiety disorder, specific phobia, social phobia, and generalized anxiety disorder). Lifetime suicide attempts were also assessed.

Perinatal depression assessed at 3 times

Perinatal depression was assessed according to the DSM-5 criteria, using the DIGS interview at three times (baseline, 8 weeks postpartum and 1 year postpartum). At baseline, clinicians retrospectively assessed depression during pregnancy by a face-to-face interview, using DIGS, at the maternity department, during days following birth. For women who were diagnosed for a depression during the assessment or in past months, the time at onset of the depressive episode was mentioned. Early-onset postpartum depression was defined as a major depressive disorder with an onset between delivery and 8 weeks postpartum, and assessed at 8 weeks by phone. Late-onset postpartum depression was defined as a major depressive disorder with an onset between 8 weeks postpartum and 1 year postpartum, and assessed at 1 year postpartum by phone.

Depression during pregnancy, early postpartum and late postpartum periods were not considered as mutually exclusive.

Perinatal depression was defined as major depressive disorder during either pregnancy, early postpartum and late postpartum periods.

Statistical Analyses

We reported variables describing the included population as counts and percentages for binary variables, and mean and standard deviations or median and interquartile range for quantitative variables.

We used the Student t-test (resp. Fisher exact test) to compare between quantitative scores (resp. proportions) across independent samples, and the Spearman correlation coefficient

to evaluated correlations between scores for different kind of trauma.

Odds ratios (OR) and their 95% confidence interval were estimated with logistic regressions and were reported with the asymptotic Wald p-value. We reported both univariate and multivariate analyses adjusted on sociodemographic variables, including age, education level, unemployment and marital status (model 1). An additional multivariate model included the same sociodemographic variables covariates and the lifetime history of major depressive episode (model 2).

We conducted a sensitivity analysis by excluding women with a depression at the time of the first assessment, considering that this could have an impact on the responses to the CTQ.

No replacement of missing data (e.g. for the perinatal depression) was done. All computations were done with the R software, version 3.6.1.

RESULTS

Among the 3,252 women who completed the Childhood Trauma Questionnaire, 298 (9.2%) reported at least one CT. There were no missing data for sociodemographic characteristics and personal history of depression, anxiety and suicide attempts.

Sociodemographic characteristics

The sociodemographic characteristics of the whole sample (N=3,252) are described in **Table 1**. Participants had an average age of 32 years old, with 12.2 % of women in our sample being less than 26 or more than 39. Women were mostly married or living common-law (96.9%), had a high level of education (92.1% reported at least a high school level) and most had a professional activity (93.2%).

Childhood trauma and associated factors

Emotional neglect was the most frequently observed type of CT (N=196, 6.0%), whereas physical neglect was the least (N=26, 0.8%). Concerning abuse, emotional abuse was

the most prevalent (N=100, 3.1%), followed by sexual abuse (N=86, 2.6%) and physical abuse (N=71, 2.2%).

More than one third of women who experienced at least one CT in our sample experienced at least two CTs (N=110, 3.4% of the total sample). All subtypes of CT score (when considered as continuous variables) were positively correlated with each other, and the Venn diagram shows co-occurrences of CT subtypes (**Figure 1**).

Women with a history of CT had different sociodemographic characteristics as compared to those without such a history (**Table 1**). They were more likely to be less than 26 years old (8.1% vs 4.5%; OR 1.8; 95%CI: 1.2-2.6) or more than 39 years old (11% vs 7%; OR 1.7; 95%CI 1.1-2.4). Women with a history of CT were also more likely to be single (6.7% vs 2.7%; OR 2.6; 95%CI 1.5-4.2), had a lower level of education (18.1% vs 6.8%; OR 3.0; 95%CI 2.2-4.2) and were more likely to have be unemployed (14.1% versus 6.1%, OR 2.5; 95%CI 1.8-3.6).

Personal history assessed at the first evaluation (Table 1)

Almost half of the women had a history of depression, anxiety disorders or suicide attempt (42.6%). Depression was the most common psychiatric disorder, reported by 35.2% of all women in the cohort. Sixteen percent had a history of anxiety disorder and 3.0% a history of attempted suicide.

Women with CT had a higher risk of either depression, anxiety or suicide attempts than women without CT (61.1% versus 40.8%; OR 2.3; 95%CI 1.8-2.9). A personal history of depression, anxiety disorder or a history of suicidal attempt were more frequent in women with CT (OR 2.2; 95%CI 1.7-2.7; OR 2.3; 95%CI 1.7-3.0 and OR 5.4; 95%CI 3.5-8.4 respectively).

Perinatal depression

Due to women being lost during the prospective follow-up of the IGEDEPP cohort, the perinatal depression status (early and late-onset depression) was unknown for 847 women, despite available CTQ data. Participants lost to follow-up were significantly younger and had a lower level of education than those who were not lost to follow-up. Other baseline characteristics were not significantly different among the two groups, including childhood trauma and lifetime history of major depressive episode (**Table 2**).

Among the 2405 women with known status for perinatal depression, one in 6 had a perinatal depression (N=574, 23.9%). Of them, 123 (21.4%) had a depression during pregnancy, 230 (40.0%) an early-onset postpartum depression and 221 (38.5%) a late-onset postpartum depression (**Table 3**).

Perinatal depression was overall more frequent in women with at least one CT than in their counterparts without such history (38.7% vs 22.3%, $p < 0.001$). This difference remained significant after adjusting for sociodemographic characteristic (aOR 2.0; 95%CI 1.5-2.7, $p < 0.001$), and for personal history of major depression episode (aOR 1.7; 95%CI 1.3-2.3, $p < 0.001$). Depression during pregnancy, early and late-onset postpartum, were all significantly associated with CT, independently from sociodemographic characteristics and personal history of depression (adjusted odds-ratio and confidence intervals respectively aOR 1.8; 95%CI 1.1-3.0, aOR 1.6; 95%CI 1.1-2.5, and aOR 1.8; 95%CI 1.2-2.8) (**Table 3**).

A sensitivity analysis excluding women with a depression at the time of the first assessment (N=49) showed consistent results (data available on request).

Perinatal depression was more common in women with CT, regardless of the type of CT (**Table 4**). This difference was significant for emotional, physical and sexual abuse and for emotional neglect ($p < 0.05$ for each). However, the types of CT showed specific associations with the different timing for perinatal onset (**Figure 2**). Emotional neglect was associated only

with depression during pregnancy (aOR 2.1; 95%CI 1.2-3.8, $p=0.0055$). Sexual abuse was associated with both early and late-onset postpartum depression (aOR=2.3; 95%CI 1.2-4.6; and aOR=2.4; 95%CI 1.2-4.9 respectively). Emotional abuse was only associated with late postpartum depression (aOR 2.7; 95%CI 1.4-5.1).

We finally found a dose effect between the number of CT type and the risk of perinatal depression (**Table 5**). Thus, compared to women without CT, women who reported exactly one type of CT had a higher risk of perinatal depression (aOR 1.6; 95%CI 1.1-1.3, $p=0.015$), while women reporting 2 or more types of CT having an even higher risk (aOR 2.1; 95%CI 2.3-3.3), even after adjustment on the history of depression and socio-demographic covariates.

DISCUSSION

This study examined the association between CT (including types of abuse and neglect) and perinatal depression, in a large prospective French cohort of women. To our knowledge, this is the first study assessing the impact of 5 different types of CT on perinatal depression during pregnancy, early and late-onset postpartum period, in a non-clinical sample.

In this study, women with CT presented more perinatal depression than women without CT, independently from the type of trauma. These results were significant for depression during pregnancy, early and late-onset postpartum depression assessed independently, and remained significant after adjustment for socio-demographic characteristics and previous history of depression. This suggests that trauma during childhood continues to be associated with the occurrence of a depressive episode later in adulthood, and more specifically in the perinatal period.

In our sample of women in perinatal period, 9.2% reported CT. This rate is lower than other samples of women of the same age category^{23,58}. For example, in a French, non-clinical

sample of women using the same scale and the same definition thresholds, Paquette et al found 34.8% of their sample reporting emotional neglect and 13.3% emotional abuse, higher than the 5.9% of emotional neglect and 3.1% emotional abuse respectively in the present work ²³. Likewise, Yildiz et al. also found higher levels of CT in 144 Turkish pregnant women compared to our IGEDEPP cohort ⁵⁸. The sample's characteristics can at least in part explain these differences. Women in Paquettes sample were younger and non-pregnant, while women in Yildiz' sample had a lower education level.

CT were significantly more frequent among socio-economically disadvantaged women (single, unemployed and with a lower level of education). These results are consistent with those of the literature which found an association between precariousness and CT. In addition, socio-economically disadvantaged women are more at risk of psychiatric disorders, and more specifically perinatal psychiatric disorders ^{3,8,59-62}.

CTs were significantly associated with a large range of lifetime psychiatric disorders: major depressive episode, anxiety disorder and suicide attempt. This is in line with other study that find an association between CT and depressive disorders, as well as a twice risk of suicide in adulthood ^{34,42,63-65}. In our cohort, 16.4% of women had a history of anxiety disorder, and those women were twice as likely to develop perinatal depression, which is consistent with the data of the literature ⁴⁹. While our focus was the link between different CT and perinatal depression, future studies should more specifically assess the relationship between perinatal anxiety disorder and CT. In addition, a history of depression was observed in 33% of the women in our sample. This is relatively high compared to other studies in the French population which found mental health problems in one in eight women, and compared to studies in the American population reporting 22% of women having a history of depression ^{3,66,67}. A hypothesis for these differences can be the methodology used in IGEDEPP. The use of a semi-structured interview by a specifically trained clinician to assess depression, anxiety and suicide attempts of the

women, may have increase the sensitivity of the diagnosis ^{68,69}. We showed that trauma during childhood is associated with perinatal depression independently from the depression history. The association between CT and perinatal depression remained significant after adjustment for history of major depressive disorders.

CT was associated with perinatal depression at each of the three times of assessment (during pregnancy, early postpartum and late postpartum). Interestingly, some CT appear to be associated with depression only at specific point during pregnancy and postpartum. For example, history of emotional neglect is associated with depression during pregnancy (OR 2.1, 85%CI 1.2-3.8), but not with depression during early or late-onset postpartum. This association of history of emotional neglect with depression during pregnancy have been confirmed by others ^{70,71}. Other studies found associations between history of sexual abuse and physical abuse and depression during pregnancy ^{10,72,73}, while this association is not significant in IGEDEPP. This might be due to the specific profile of IGEDEPP participants: the low prevalence of the CT and the high education level were negatively associated with history of sexual and physical abuse. History of sexual abuse was associated with both early and late-onset postpartum depression, while history of emotional abuse was associated specifically with late postpartum depression. Dennis et al also found an association between sexual abuse and early postpartum depression ⁷⁴, while other did not find this association with both early and late postpartum depression ¹⁰. Early postpartum depression was also associated with emotional abuse in a sample of low-income Australian women ⁴⁷. These comparisons with data from the literature should be taken with cautions, since CT was often assessed as a single dimension, or restricted to sexual or physical abuse, emotional abuse and neglect being less often described. In addition, the majority of studies were carried out on small samples, in clinical populations, mostly using self-questionnaire to define major depression rather than DSM criteria.

We also observed a dose-effect of the number of types of CT on the risk of perinatal depression. This is congruent with previous studies which found an association between the number of trauma type on depression during pregnancy¹⁰ and postpartum depression at 6 months⁷⁵.

The main limit is that our sample, although large, is not representative of the general population. Our sample consisted only of European women who gave birth in Paris area and had a higher education than the general population. However, our results remained significant after adjustment on sociodemographic characteristics, suggesting that these variables alone are unlikely to explain our findings. Further replication of these results in a more diverse sample, representative of the general population, is required to generalize our results. In addition, women with unknown clinical status due to premature lost to follow-up were not analyzed. Noteworthy, CT and peripartum depression were not associated with drop out (**Table 2**). A third limitation is that the CTQ assesses a range of traumatic events that may have occurred during childhood and early adolescence. However, the CTQ lacks any precise information about the age at which these traumas have occurred. While age of onset of maltreatment was not found to significantly predict depression symptoms during pregnancy⁷⁶, further studies should explore the importance of timing of traumatic events since the age at exposure (childhood or later during the adolescence) might influence the associations being observed in postpartum. Different questionnaires, including the Adverse Childhood Experiences (ACEs) Scale could provide additional information⁷⁷. Given the small size of each CT type subgroup, our results concerning the association between the type of CT and specific perinatal depression should therefore be replicated in larger samples.

Fourth, our study excluded women with any psychotic disorder, and included only 6 women diagnosed with bipolar disorders. Whether our findings can be replicated in such populations is yet unknown.

Finally, given the retrospective nature of CT assessment in our sample, no conclusion on causality between CT and post-partum depression should be drawn.

CT is associated with a depressive episode during adulthood, and more specifically in the perinatal period, whatever the timing of onset (during pregnancy, early or late-onset postpartum). There was also a dose effect between the number of CT type and the risk of perinatal depression. Our results may lead to special prenatal care for women abused or neglected during childhood, to better screen and treat perinatal depression. Indeed, our results support the benefit of a systematic evaluation of CTs at the beginning of pregnancy. This will allow the identification of women at higher risk of developing depression in the perinatal period, allowing appropriate care, and reducing the negative impact of depression ^{78,79}.

Clinical points

- The link between perinatal depression, including with a pregnancy, early or late-onset postpartum, and CT was unclear.
- Perinatal depression was more common in women with CT, regardless of the timing of onset of depression (during pregnancy, early or late postpartum), or the type of CT, with a dose effect between the number of CT type and the risk of perinatal depression.

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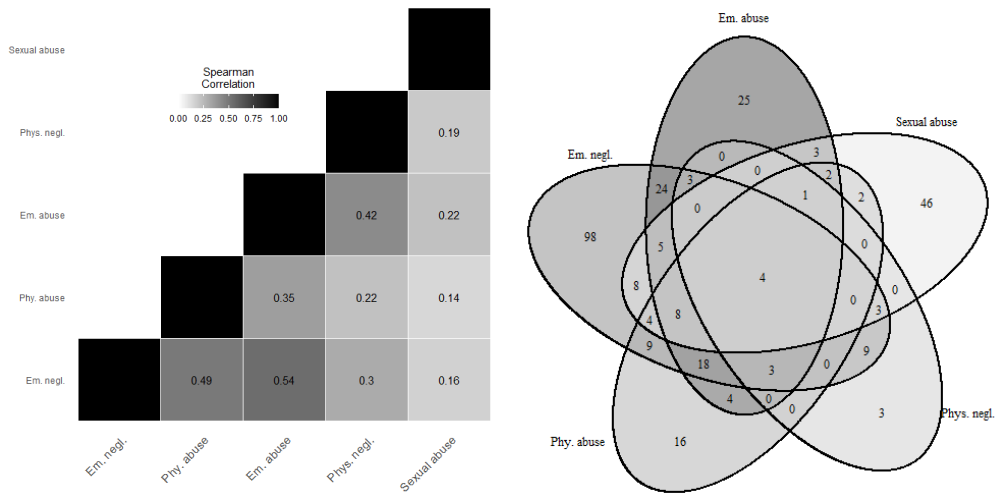


Figure 1: Structure between types of CTQ (N=3252)

Left : Spearman correlation, all combinations have $p < .001$

Right : Venn diagram, number indicates co-occurrences of every combination of CT

Abbreviations: Em. abuse = emotional abuse; Em. negl. = emotional neglect; Phy. abuse = physical abuse; Phys. negl. = physical neglect.

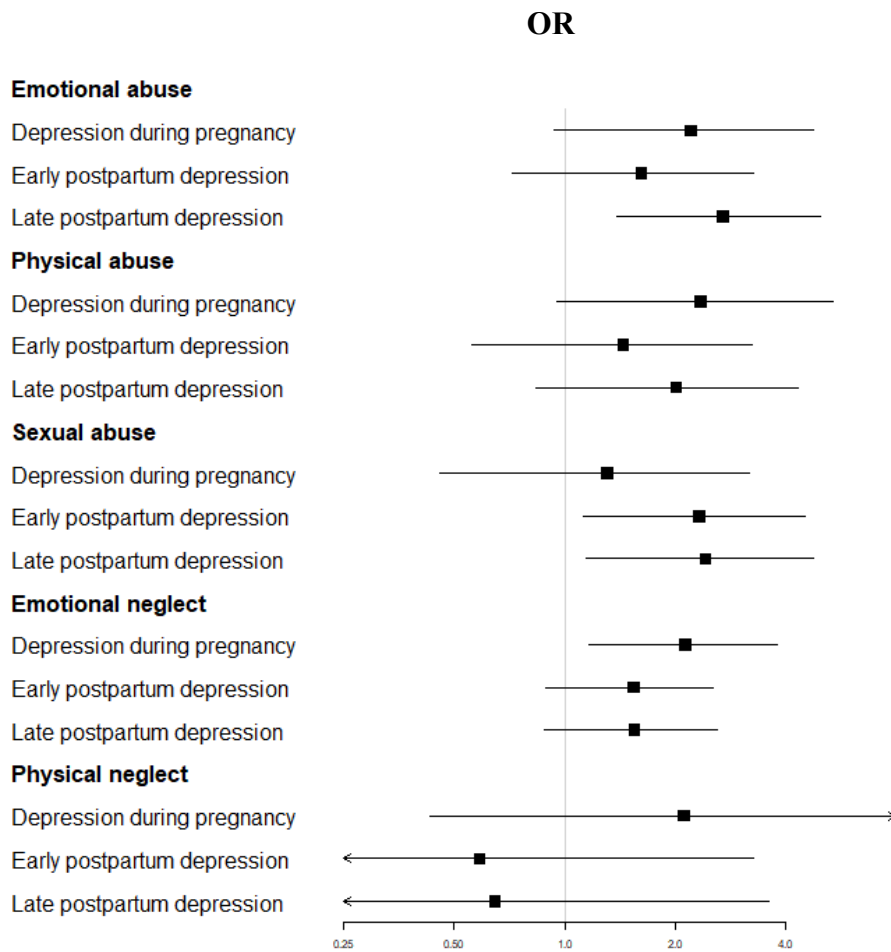


Figure 2: Forest plot showing association between each component of childhood trauma and peri-partum depression (N = 2405, reported OR correspond to multivariate model adjusted on sociodemographic characteristics and history of depression)

Table 1: Association between childhood trauma and socio-demographic data, and psychiatric history in participants evaluated at baseline

	All (N=3252) N (%)	CT (N= 298) N (%)	No CT (N= 2954) N (%)	CT vs no CT OR (95%CI)	p-value
Socio demographic characteristics					
Age (years)					
25 or less	156 (4.8)	24 (8.1)	132 (4.5)	1.8 (1.2-2.6)	0.0031
25<age<40	2856 (87.8)	241 (80.9)	2615 (88.5)	1 (ref)	
40 or more	240 (7.4)	33 (11.1)	207 (7.0)	1.9 (1.2-2.9)	0.0076
Marital status					
Married, common-law married	3152 (96.9)	278 (93.3)	2874 (97.3)	1 (ref)	
Widowed, divorced, separated, never married	100 (3.1)	20 (6.7)	80 (2.7)	2.6 (1.5-4.2)	<0.001
Education level:					
University	2996 (92.1)	244 (81.9)	2752 (93.2)	1 (ref)	
Primary or high school	256 (7.9)	54 (18.1)	202 (6.8)	3.0 (2.2-4.2)	<0.001
Employment:					
yes	3031 (93.2)	256 (85.9)	2775 (93.9)	1 (ref)	
no	221 (6.8)	42 (14.1)	179 (6.1)	2.5 (1.8-3.6)	<0.001
Psychiatric history					
no	1866 (57.4)	116 (38.9)	1750 (59.2)	1 (ref)	
any	1386 (42.6)	182 (61.1)	1204 (40.8)	2.3 (1.8-2.9)	<0.001
History of MDE					
no	2107 (64.8)	143 (48.0)	1964 (66.5)	1 (ref)	
any	1145 (35.2)	155 (52.0)	990 (33.5)	2.2 (1.7-2.7)	<0.001
History of anxiety disorder					
no	2719 (83.6)	212 (71.1)	2507 (84.9)	1 (ref)	
any	533 (16.4)	86 (28.9)	447 (15.1)	2.3 (1.7-3.0)	<0.001
History of suicidal attempt					
no	3156 (97.0)	266 (89.3)	2890 (97.8)	1 (ref)	
any	96 (3.0)	32 (10.7)	64 (2.2)	5.4 (3.5-8.4)	<0.001

Abbreviations: CI, confidence interval; CT, childhood trauma; OR, odd ratio; MDE, major depressive episode
Significant differences are in bold.

Table 2: Comparison of patient's characteristics between participants lost to follow-up for both evaluations (8 weeks and 1 year). Significant differences are in bold.

	8 weeks follow-up (N=2973) N (%)	Lost to follow-up before 8 weeks (N=279) N (%)	p value	1 year follow- up (N=2318) N (%)	Lost to follow-up before 1 year (N=934) N (%)	p value
Age (years)			0.0055			0.00029
age<25	207 (7.0)	33 (11.8)		144 (6.2)	96 (10.3)	
25≤age≤40	2627 (88.4)	229 (82.1)		2059 (88.8)	797 (85.3)	
age>40	139 (4.7)	17 (6.1)		115 (5.0)	41 (4.4)	
Marital status:			0.49			0.081
in relationship	2884 (97.0)	268 (96.1)		2255 (97.3)	897 (96.0)	
single	89 (3.0)	11 (3.9)		63 (2.7)	37 (4.0)	
Education level			0.0016			<0.001
higher than high school	2753 (92.6)	243 (87.1)		2172 (93.7)	824 (88.2)	
less than high school	220 (7.4)	36 (12.9)		146 (6.3)	110 (11.8)	
professional activity:			0.38			0.35
yes	2775 (93.3)	256 (91.8)		2167 (93.5)	864 (92.5)	
no	198 (6.7)	23 (8.2)		151 (6.5)	70 (7.5)	
Childhood Trauma:			0.39			0.9
yes	2705 (91.0)	249 (89.2)		2107 (90.9)	847 (90.7)	
no	268 (9.0)	30 (10.8)		211 (9.1)	87 (9.3)	
History of major depressive episode			0.22			0.23
yes	1936 (65.1)	171 (61.3)		1517 (65.4)	590 (63.2)	
no	1037 (34.9)	108 (38.7)		801 (34.6)	344 (36.8)	

Table 3: Association between childhood trauma and perinatal depression in participants with available outcome

	All (N=2405)	CT (N= 225)	No CT (N= 2180)	CT vs no CT		
	N (%)	N (%)	N (%)	OR (95%CI)	aOR (95%CI) ^a	aOR (95%CI) ^b
Perinatal depression						
No	1831 (76.1)	138 (61.3)	1693 (77.7)	1 (ref)	1 (ref)	1 (ref)
Any perinatal depression	574 (23.9)	87 (38.7)	487 (22.3)	2.2 (1.6-2.9)	2.0 (1.5-2.7)	1.7 (1.3-2.3)
Antenatal depression	123 (5.1)	24 (10.7)	99 (4.5)	3.0 (1.8-4.8)	2.7 (1.6-4.4)	1.8 (1.1-3.0)
Early postpartum depression	230 (9.6)	32 (14.2)	198 (9.1)	2.0 (1.3-3.0)	1.8 (1.2-2.7)	1.6 (1.1-2.5)
Late postpartum depression	221 (9.2)	31 (13.8)	190 (8.7)	2.0 (1.3-3.0)	1.9 (1.3-2.9)	1.8 (1.2-2.8)

Abbreviations: aOR, adjusted odd ratio; CI, confidence interval; CT, childhood trauma
Significant differences are in bold.

a: multivariate model adjusted on socio-demographic covariates (age, marital status, educational level and employment)

b: multivariate model adjusted on the history of MDE and socio-demographic covariates (age, marital status, educational level and employment)

Table 4: Association between each type of childhood trauma and perinatal depression

	Emotional abuse (N=100)		Physical abuse (N=71)		Sexual abuse (N=86)		Emotional neglect (N=196)		Physical neglect (N=26)	
	aOR (95%CI)	p-value	aOR (95%CI)	p-value	aOR (95%CI)	p-value	aOR (95%CI)	p-value	aOR (95%CI)	p-value
Perinatal depression	2.2 (1.3-3.5)	0.0021	1.9 (1.0-3.3)	0.033	2.1 (1.2-3.5)	0.0065	1.7 (1.2-2.4)	0.0055	1.1 (0.3-3.2)	0.96
Antenatal depression	2.2 (1.0-4.9)	0.054	2.3 (1.0-5.5)	0.051	1.3 (0.5-3.4)	0.59	2.1 (1.2-3.8)	0.012	2.1 (0.5-8.8)	0.31
Early postpartum depression	1.6 (0.8-3.4)	0.21	1.4 (0.6-3.4)	0.409	2.3 (1.2-4.6)	0.016	1.5 (0.9-2.6)	0.105	0.6 (0.1-4.8)	0.62
Late postpartum depression	2.7 (1.4-5.1)	0.0021	2.0 (0.9-4.5)	0.092	2.4 (1.2-4.9)	0.015	1.5 (0.9-2.7)	0.112	0.6 (0.1-5.3)	0.68

Abbreviations: aOR, adjusted odd ratio; CI, confidence interval

Significant differences are in bold.

Odds ratio for each trauma component compared to subjects with no trauma were adjusted on the history of MDE and socio-demographic covariates (age, marital status, educational level and employment)

Table 5: Association between the number of types of childhood trauma and perinatal depression (N=2405)

Perinatal depression	OR (95%CI)	aOR (95%CI) ^a	aOR (95%CI) ^b
No childhood trauma	1 (ref)	1 (ref)	1 (ref)
Exactly one type of childhood trauma	1.9 (1.3-1.8)	1.8 (1.2-1.7)	1.6 (1.1-1.3)
At least 2 types of childhood trauma	2.9 (2.6-4.6)	2.7 (2.5-4.2)	2.1 (2.3-3.3)

Abbreviations: aOR, adjusted odd ratio; CI, confidence interval

Significant differences are in bold.

a: multivariate model adjusted on socio-demographic covariates (age, marital status, educational level and employment)

b: multivariate model adjusted on the history of MDE and socio-demographic covariates (age, marital status, educational level and employment)

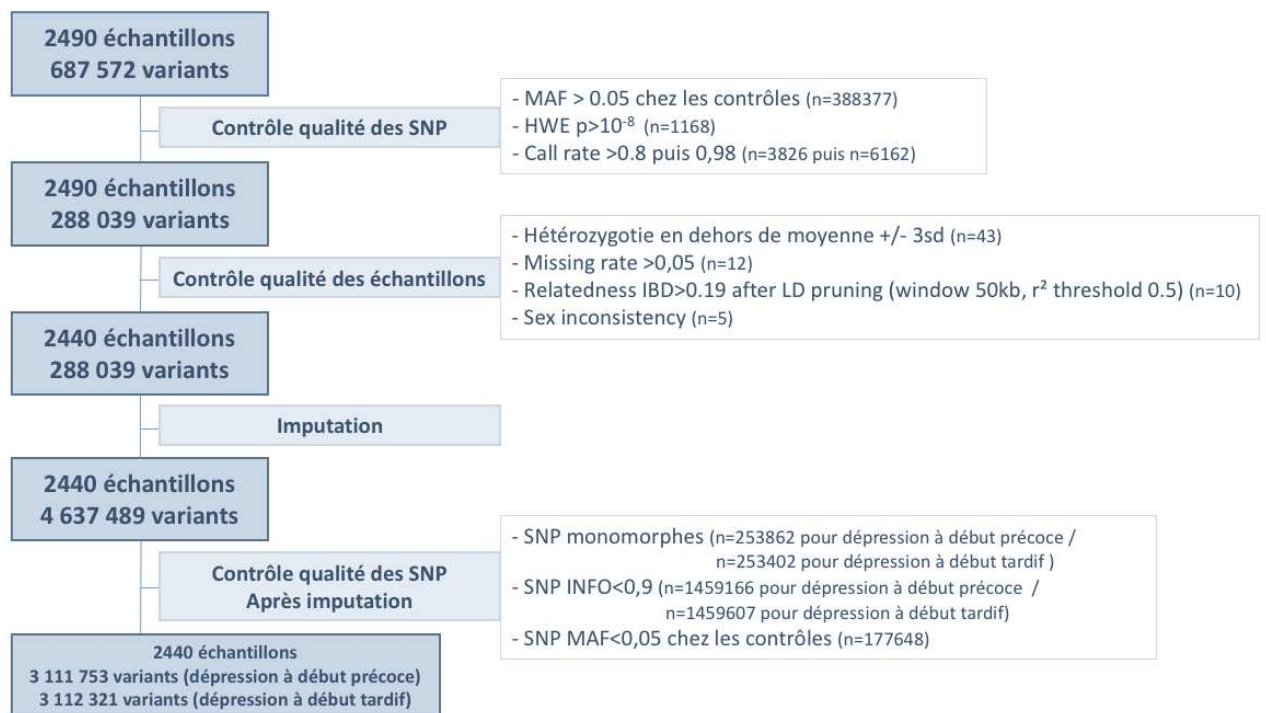
III. Dépression du post-partum : un GWAS

A partir de la cohorte IGEDEPP (cf. méthodologie p. 37), nous avons réalisé une analyse génétique pangénomique ou GWAS.

III.A. Contrôle qualité et imputation

Les différentes étapes du contrôle qualité ont diminué le nombre de variants de 687 572 à 288 039, puis le nombre d'échantillons de 2490 à 2440. Nous avons ensuite procédé à l'imputation sur les 22 chromosomes autosomiques et sur le chromosome X permettant d'analyser 4 637 489 variants. Nous avons achevé le contrôle qualité sur ces variants en considérant les échantillons finaux (dépression du post-partum à début précoce et contrôles d'une part, et dépression du post-partum à début tardif et contrôles d'autre part). Ces différentes étapes sont synthétisées dans la figure 8.

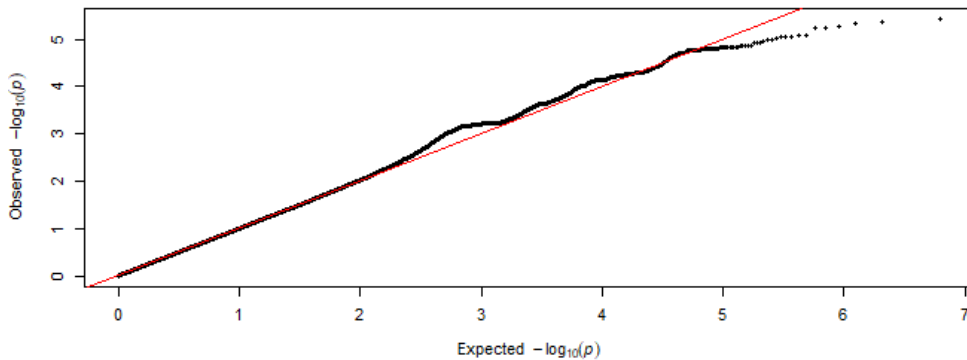
Figure 8 : Flow-chart du contrôle qualité et imputation du GWAS



III.B. Dépression du post-partum à début précoce

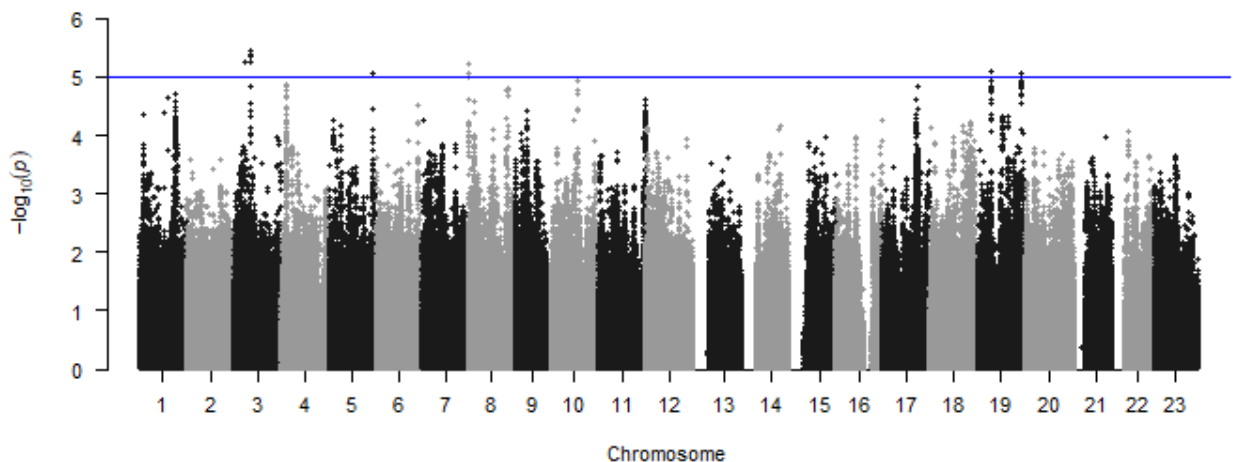
L'analyse comparant 3 111 753 variants des 234 cas de femmes présentant une dépression du post-partum à début précoce aux contrôles, ne trouvait aucun SNPs atteignant le seuil de significativité de 5×10^{-8} à l'échelle du génome (cf. figure 10).

Figure 9 : Quantile-Quantile Plot (Q-Q Plot) pour la dépression du post-partum à début précoce



Le Q-Q Plot représente les valeurs attendues et observées de P sur l'échelle log10 ; il indique la conformité des résultats observés à ce qui serait attendu sous l'hypothèse nulle, et en particulier l'absence de biais systématique dû, par exemple, à un facteur de confusion non pris en compte.

Figure 10 : Manhattan plot pour le GWAS concernant la dépression du post-partum à début précoce

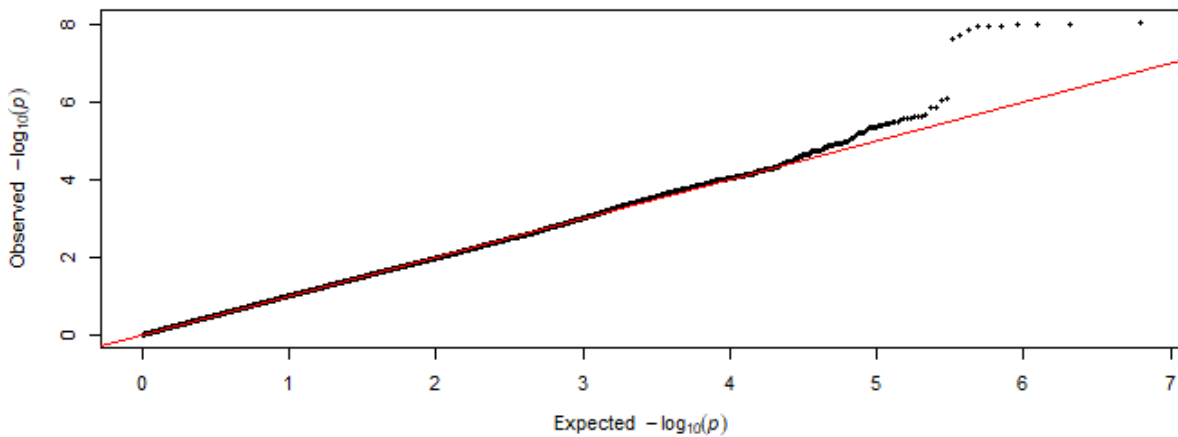


La ligne bleue montre un seuil à $p < 5 \times 10^{-5}$.

III.C. Dépression du post-partum à début tardif

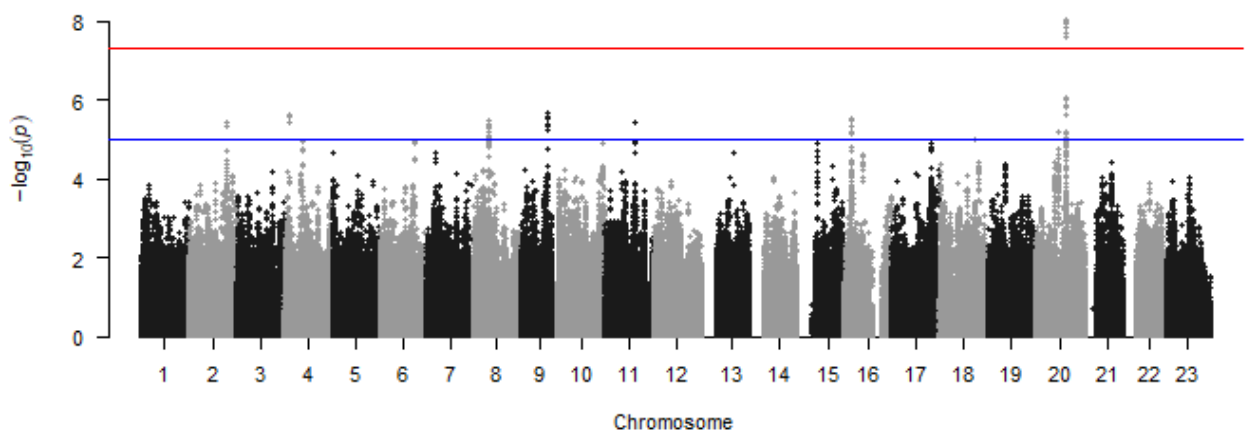
L'analyse comparant 3 112 321 variants des 223 cas de femmes présentant une dépression du post-partum à début tardif aux contrôles, identifiait 10 SNPs atteignant le seuil de significativité à l'échelle du génome (cf. figure 12).

Figure 11 : Quantile-quantile plot pour la dépression du post-partum à début tardif



Le Q-QPlots représente les valeurs attendues et observées de P sur l'échelle log10 ; il indique la conformité des résultats observés à ce qui serait attendu sous la valeur nulle.

Figure 12 : Manhattan plot pour le GWAS concernant la dépression du post-partum à début tardif



La ligne rouge montre le seuil de significativité à l'échelle du génome après correction ($P < 5 \times 10^{-8}$), la ligne bleue montre un seuil à $p < 5 \times 10^{-5}$.

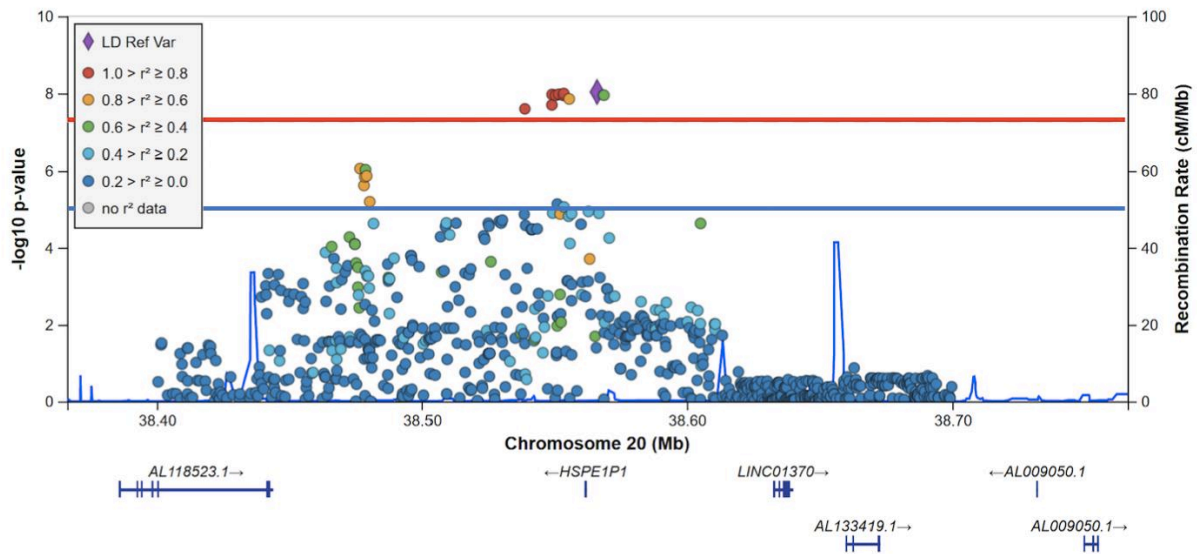
Ces 10 SNPs se situent sur le chromosome 20 et sont distants au maximum de 29 000 paires de bases (cf. tableau 2). Ils sont tous imputés et aucun n'est décrit dans la littérature.

Tableau 2 : Loci significatifs à l'échelle du génome pour la dépression du post-partum à début tardif.

CHR	SNP	BP	A1	A2	Fréquence chez les cas	Fréquence chez les témoins	INFO	OR	P
20	rs6065171	38538768	T	C	0.3333	0.4801	1.0223	0.545	2,55E-08
20	rs6028718	38548977	C	T	0.3315	0.4798	1.0285	0.543	2,02E-08
20	rs6028719	38549047	T	C	0.3248	0.4763	1.0336	0.5357	1,08E-08
20	rs6028721	38550395	C	G	0.3248	0.476	1.0319	0.536	1,13E-08
20	rs6028723	38551618	T	C	0.3248	0.4763	1.0327	0.5355	1,06E-08
20	rs11481519	38553325	A	AT	0.3245	0.4754	1.029	0.5355	1,14E-08
20	rs34294182	38553493	A	AC	0.3248	0.4763	1.0299	0.5345	1,02E-08
20	rs3038001	38555519	C	CAT	0.4303	0.5801	1.0313	0.5535	1,41E-08
20	rs6129447	38566077	A	C	0.3251	0.4766	1.0237	0.5325	9,28E-09
20	rs6028732	38568661	A	G	0.437	0.5861	1.0119	0.5478	1,13E-08

Parmi ces 10 SNPs, aucun n'est intronique. Ils encadrent un pseudo-gène : HSPE1P1 (Heat shock protein family E (Hsp10) member 1 pseudogene 1) (cf. figure 13). Ce gène jouerait un rôle dans la biotransformation ou le transport du citalopram, un antidépresseur de type inhibiteur de la recapture de la sérotonine (Ji et al. 2014). Nous n'avons trouvé dans cette région aucun autre gène ou ARN messenger.

Figure 13 : Diagramme d'association régionale, montrant les SNPs et leur association avec la dépression du post-partum à début tardif.



La ligne rouge montre le seuil de significativité à l'échelle du génome après correction pour les tests multiples ($p < 5 \times 10^{-8}$), la ligne bleue montre un seuil à $p < 5 \times 10^{-5}$.

Les SNPs sont colorés en fonction du niveau de déséquilibre de liaison (LD) entre chaque SNP et le top SNP (rs6129447).

Conclusion et perspectives

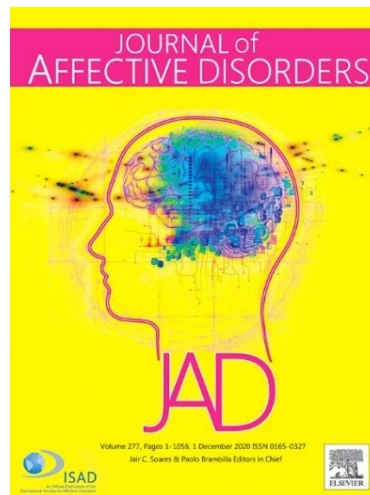
Ce premier GWAS portant spécifiquement sur la dépression du post-partum, cherchant à distinguer la dépression à début précoce et celle à début tardif, apporte un premier résultat significatif : une région du chromosome 20 comportant 10 marqueurs (SNPs imputés), encadrant le pseudogène HSPE1P1. Le génotypage de certains SNPs ainsi que la réplication des résultats sont des perspectives nécessaires à la poursuite de ce travail.

IV. Trouble bipolaire et périnatalité

IV.A. Article 5 : Is parity status associated with bipolar disorder clinical features, severity or evolution?

Et correspondance : Parity and bipolar disorder : new analyses

ARTICLE 5 ET CORRESPONDANCE



Is parity status associated with bipolar disorder clinical features, severity or evolution?

Sarah Tebeka, Yann Le Strat, Caroline Dubertret.

Journal of Affective Disorders, 2018; 225: 201-206

Parity and bipolar disorder : new analyses

Sarah Tebeka, Yann Le Strat, Caroline Dubertret.

Journal of Affective Disorders, 2018; 238: 489-490

Compte tenu de l'impact négatif de la grossesse et du post-partum sur le trouble bipolaire en période périnatale (risque de décompensation, davantage de comorbidité addictive, risque suicidaire plus élevé), nous nous sommes intéressés à l'impact des grossesses sur les caractéristiques du trouble bipolaire mais également son évolution sur trois ans.

Pour évaluer prospectivement l'association entre le nombre de grossesses passées et l'évolution du trouble bipolaire, nous nous sommes appuyés sur la NESARC (échantillon représentatif de la population américaine de 34 653 participants, cf. méthodologie p. 46) (Tebeka, Le Strat, et Dubertret 2018). Toutes les femmes avec un diagnostic de trouble bipolaire ont été incluses. Le nombre d'enfants et les caractéristiques du trouble bipolaire, c'est-à-dire le type de trouble bipolaire, l'âge d'apparition, l'hospitalisation et les tentatives de suicide, et la comorbidité psychiatrique au cours de la vie ont été évalués lors de la première évaluation (vague 1). Les épisodes thymiques (maniaque, hypomaniaque et dépressif) ainsi que les caractéristiques du trouble bipolaire ont également été évalués 3 ans plus tard, lors de la vague 2. Nous avons comparé les femmes ayant un enfant, deux enfants puis au moins 3 enfants aux femmes n'ayant pas eu d'enfant.

Parmi les 1190 femmes souffrant d'un trouble bipolaire, 27 % n'avaient pas d'enfant, 17 % en avaient un, 25 % en avaient deux et 31 % avaient trois enfants ou plus.

Les femmes ayant au moins deux enfants étaient plus susceptibles d'avoir un trouble bipolaire de type I et de présenter un épisode d'hypomanie au cours de suivi que les femmes sans enfant. Cependant, dans la NESARC, la parité n'était pas associée à d'autres caractéristiques du trouble bipolaire (âge de début, nombre d'épisode dépressif ou maniaque, hospitalisation pour dépression ou épisode maniaque, tentative de suicide ou idées suicidaires), ni aux comorbidités psychiatriques (trouble lié à l'usage de substance, trouble anxieux, trouble de la personnalité), ni à l'évolution du trouble sur 3 ans (incidence de manie, d'épisode dépressif, d'hospitalisation, de tentative de suicide ou de pensée suicidaire).

Nous avons réalisé des analyses de sensibilité sur deux sous-échantillons de notre population. D'une part, parmi les femmes qui ont été enceintes au cours des 3 ans de suivi, en comparaison aux femmes n'ayant pas déclaré de grossesse au cours du suivi, aucune différence significative sur l'évolution du trouble (incidence de manie, d'hypomanie, d'épisode dépressif, d'hospitalisation, de tentative de suicide ou de pensée suicidaire) n'était retrouvée.

D'autre part, nous nous sommes intéressés aux femmes en âge de procréer (18-50 ans). Dans cet échantillon, l'incidence de l'hypomanie se situait dans la même fourchette que celle observée dans l'ensemble de la population. En revanche, l'incidence des tentatives de suicide au cours du suivi était plus élevée chez les femmes ayant plus de deux enfants que chez les femmes sans enfant (OR = 3,28 ; IC 1,01-10,64). Aucune différence significative d'incidence n'a été observée sur l'incidence de la manie, la dépression, une hospitalisation ou les idées suicidaires.

Le Dr Sharma a commenté notre travail (Sharma 2018). Nous avons par la suite proposé une réponse à ce commentaire (Tebeka, Strat, et Dubertret 2018). La principale limite soulignée par le Dr Sharma était l'absence de prise en compte des traitements médicamenteux chez les participants. Nous avons analysé à nouveau nos données en fonction de la prescription d'un traitement médicamenteux pour le trouble considéré. Les femmes ayant plus de deux enfants étaient plus susceptibles de déclarer un traitement thymorégulateur que les femmes sans enfant à la vague 1 (aOR = 1,87, IC à 95 % 1,04-3,37). Aucune autre association significative entre la parité et la prescription de traitement n'a été établie.

De plus, cette nouvelle analyse montrait que plus de 30 % des femmes atteintes de trouble bipolaire ne bénéficiait pas de traitements psychotropes visant un trouble de l'humeur. La prescription de médicaments variait entre 42 et 65 % pour la dépression, et entre 15 % et 45 % pour la manie. Ces différences de traitement confirment que les femmes en âge de procréer souffrant de trouble bipolaire constituent probablement une population sous-diagnostiquée, quel que soit leur statut de parité (Drancourt et al. 2013).

Conclusion et perspectives :

La parité au-delà d'un enfant était associée au trouble bipolaire de type I et à davantage d'épisodes hypomaniaque au cours du suivi. Cependant, il n'y a pas d'association avec le nombre d'épisodes thymiques passés, le taux d'hospitalisation ou le risque suicidaire. Ainsi, nos résultats corroborent les études retrouvant que le nombre de grossesses antérieures était associé à un taux plus faible de troubles mentaux en population générale (Viguera et al. 2011; Power et al. 2013), et avec une morbidité moindre (Munk-Olsen, Jones, et Laursen 2014; Munk-Olsen et al. 2006); de façon plus spécifique au trouble bipolaire, la multiparité était

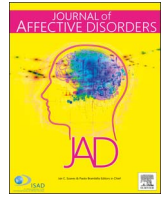
associée à une prévalence moindre d'épisodes maniaques et psychotiques (Di Florio et al. 2014).

Une des limites de ce travail est que la NESARC ne fournit pas d'informations sur le fait que le trouble bipolaire débute dans le post-partum ou non. En effet, l'apparition en période périnatale pourrait augmenter la spécificité diagnostique, améliorer la prédiction et modifier l'évolution du cours de la maladie. Nous nous sommes intéressés à cette question dans le travail suivant, à partir de la cohorte FACE-BD.



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Research paper

Is parity status associated with bipolar disorder clinical features, severity or evolution?

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ABSTRACT

Objective: To assess prospectively the association of the number of past pregnancies on the evolution of bipolar disorder (BD).

Methods: Data were drawn from the 2 waves of the National Epidemiologic Study of Alcohol and Related Conditions (NESARC), a representative sample of the US population of 34,653 participants. All women diagnosed with BD were included. The number of children and BD's characteristics, i.e. BD type, age of onset, hospitalization and suicide attempt, and lifetime psychiatric comorbidity were assessed at wave 1. Mood episode and BD's characteristics were also assessed at wave 2.

Results: In the sample of 1190 women with BD, 27% had no child, 17% had one, 25% had two 31% had three children or more. Women with at least two children were more likely to have BD I, to report hypomania and suicide attempt during the follow-up than women without child. Parity was not associated with other characteristics of BD, nor with the severity and course of the illness.

Limitations: Not provide information on pregnancies not ending to a delivery.

Conclusion: Parity is associated with a higher incidence of hypomania and suicide attempt during a 3-years follow-up in women with BD.

1. Introduction

Bipolar disorder (BD) is a severe and chronic affective disorder which affects both women and men, with an early age of onset. BD is the seventh leading cause of disability and premature mortality in women of childbearing age (The World Health Organization, 2001).

Peripartum period, which includes pregnancy and the first year following delivery, is known to be at risk for psychiatric disorders in general, and more specifically for BD (Tebeka et al., 2016). Peripartum is associated with a higher risk of either first episode or recurrence of BD (Laursen, 2012; Sharma and Pope, 2012; Jones et al., 2014; Parial, 2015; Pope et al., 2014). More than 50% of the women with BD will present peripartum depression during their lifetime (Maina et al., 2014; Viguera et al., 2011). Hypomanic, manic or mixed episodes can also occur in the postpartum period (Maina et al., 2014; Viguera et al., 2011; Doyle et al., 2012) and usually with an earlier onset during postpartum than postpartum depression (Di Florio et al., 2013).

Perinatal mood episodes can be complicated by a poor quality of early maternal-child relationship, inadequate neonatal care, and may

affect child's development (Kingston et al., 2012; Johnson et al., 2014). Perinatal mood episodes in BD are more likely to be longer, treatment-resistant and more likely to be with associated addictive comorbidities than mood episodes occurring during non-perinatal periods (Battle et al., 2014). During the post-partum period, women with BD are more likely to be hospitalized than women with other psychiatric disease (Munk-Olsen et al., 2009). Post-partum is also marked by a higher rate of hospitalization in patients with BD compared to non-post-partum periods (Munk-Olsen et al., 2009).

Occurrences of mood episode in the peripartum period are a risk factor for recurrences during subsequent pregnancies (Freeman et al., 2002; Pope et al., 2014).

Having in mind the negative impact of pregnancy and post-partum on bipolar disorder course, it is somehow counterintuitive that, in numerous cross-sectional studies, the number of past-pregnancies (e.g. parity) is associated with a lower rate of mental disorders in the general population (Viguera et al., 2011), and with a lower burden of disease in BD (Munk-Olsen et al., 2006) (Munk-Olsen et al., 2014). Indeed, multiparity is associated with lower prevalence of manic and psychotic

Abbreviations: AOR, adjusted odd ratio; BD, bipolar disorder; CI, confidence interval; MDE, major depressive disorder; NESARC, National Epidemiologic Study of Alcohol and Related Conditions; OR, odd ratio; SA, Suicide attempt

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episodes, but not with a lower prevalence of depressive episodes (Di Florio et al., 2014).

To our knowledge, no study assessed prospectively the association of the number of past pregnancies on the evolution of BD. Using a large US epidemiological survey, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), the aim of our work was to determine if parity status was associated with clinical features, severity or recurrences of BD.

2. Methods

2.1. Sample

The NESARC is a nationally representative sample of the US civilian population. It includes 34,653 civilian non-institutionalized people, over 18 years, evaluated two times: at first between 2001 and 2002 (Wave 1) and a second evaluation between 2004 and 2005 (Wave 2). We used participants who completed both waves of interviews, which results in a cumulative response rate of 70.2% for both waves 1 and 2. Members of the US Census Bureau conducted face-to-face interviews. The research protocol, including informed consent procedures, received ethical approval from the US Census Bureau and the Office of Management and Budget.

For this study, the sample consisted of all women who were diagnosed with BD, defined by a history of mania or hypomania, according to the Alcohol Use Disorder and Associated Disabilities Interview Schedule–DSM-IV (AUDADIS-IV).

More details on sampling and weighting procedures can be found elsewhere (National Institute on Alcohol Abuse and Alcoholism, 2005).

2.2. Measures

2.2.1. Number of children

Number of children was assessed at wave 1 with one direct question. Number of children was categorized into: no child, one child, two children and more than two children.

2.3. Sociodemographic measures

Race/ethnicity was separate into 5 groups (White, Black, American Indian /Alaska native, Hispanic/Latino, and others). Age at interview was classified into 4 groups (18–24, 30–44, 44–64 and more than 65 years old). Marital status was classified into 3 groups (married, never married and widowed/separated/divorced). Educational level was categorized in 3 groups (less than high school, high school and some college or higher). Familial income was divided in 4 groups (\$0–19,999, \$20,000–34,999, \$35,000–59,999, and \$60,000 or greater). Urbanicity was categorized into rural or urban. Region of residence was separate into 4 groups (Northeast, Midwest, South, and West). Health insurance coverage was separate into 3 groups (private, public, and none).

2.4. Diagnostic of bipolar disorder and its characteristics

The AUDADIS-IV is a valid and reliable structured diagnostic interview, used to assess lifetime mania, hypomania and major depressive episode (MDE) at wave 1, according to DSM-IV criteria. BD type 1 (BD1) was defined as lifetime mania. BD type 2 (BD2) is defined as lifetime hypomania in the absence of lifetime mania. BD was defined as BD1 or BD2.

The age of onset of BD was defined as the age at earliest episode. The number of each kind of mood episode is evaluated with a single question for each.

Hospitalization for MDE or mania was assessed with one question for each.

Suicide was assessed if respondents endorsed a period of depressed

mood and/or anhedonia for at least 2 weeks. Participants were asked whether they ever “attempt suicide” or “think about committing suicide?”. Participants were considered as having lifetime history of respectively “suicidal attempt” or “suicidal ideation” if they respond yes. Psychiatric diagnoses were also measured using the AUDADIS-IV. We considered three lifetime psychiatric comorbidity at wave 1: any substance use disorders (including abuse or dependence to alcohol, cannabis, sedatives, tranquilizers, opiates, stimulants, hallucinogens, crack/cocaine, inhalants/solvents, heroin, and other drugs), any anxiety disorders (including panic disorder, specific phobia, social phobia, and generalized anxiety disorder), and any personality disorders (paranoid, schizoid, histrionic, antisocial, avoidant, dependent and obsessive-compulsive).

2.5. Three-year course of bipolar disorder

Three-year incidence of at least one MDE, mania and hypomania was assessed at wave 2, using the AUDADIS-IV. Questions on hospitalization, suicide attempts and suicidal ideation were assessed for the period between the two interviews using the same wordings than during the first interview.

2.6. Statistical analyses

Weighted percentages, means and standard-errors (SEs) were computed using SUDAAN, version 11.01 (Research Triangle Park, NC). Because of the weighting and clustering used in the NESARC design, SUDAAN implements a Taylor linearization method.

We divided women sample of the NESARC into 4 independent groups as follows: (1) women without child, (2) women with one child, (3) women with two children and (4) women with three or more children.

We compared these groups according to (1) severity criteria including: type of BD, age of onset, number of episode(s), hospitalization, suicide attempts and psychiatric comorbidities; (2) evolution criteria including: incidence of mood episode, hospitalization, suicide attempts. Women without child were considered as the reference group.

Multivariate logistic regressions were conducted with simultaneous entry of sociodemographic characteristics (Pignon et al., 2017). Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were derived to presented to reflect association strength and significance.

As a sensitivity analysis, we compared women reporting a pregnancy within the 3 years of follow-up with those reporting no pregnancy within this timeframe. Similarly, we re-analyzed our results in the subsample of participants in childbearing age (aged 50 year old or less).

3. Results

3.1. Sample

Of the 34,653 participants, 14,564 were women in which 1190 met criteria for. Among them, 322 had no child (27%), 199 had one child (17%), 299 had two children (25%) and 370 had three children or more (31%). *Age-adjusted prevalence for bipolar disorder by parity was 5.65% (SE: 0.36%) in women with no child, 5.44% (SE: 0.51%) in women with one child, 5.81% (SE: 0.42%) in women with two children and 6.23% (SE: 0.54%) in women with 3 children or more.*

3.2. Sociodemographic characteristics

The sociodemographic characteristics are summarized in Table 1. The majority of women was white, married, less than 44 years old with, educated and mainly lives in rural areas. All women with BD and with children (1, 2 or more) were less likely to be never married, more likely to be older than 29 years old, and more likely to benefit from a public

Table 1

Sociodemographic characteristics of women with bipolar disorder without child, with 1 or 2 children and with more than 2 children in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

Characteristic	No child n = 322 % (SE)	1 child n = 199 % (SE)	2 children n = 299 % (SE)	> 2 children n = 370 % (SE)	1 child vs. no child OR (CI 95%)	2 children vs. no child OR (CI 95%)	> 2 children vs. no child OR (CI 95%)	
Race/ethnicity								
White	71.75 (3.20)	72.28 (4.77)	71.43 (3.05)	62.77 (3.56)	1.00	1.00–1.00	1.00	1.00–1.00
Black	10.60 (1.72)	11.40 (2.62)	13.20 (2.07)	17.25 (2.28)	1.07	0.58–1.96	1.25	0.77–2.03
American indian /Alaska native	3.05 (1.44)	4.73 (2.20)	3.35 (1.81)	6.55 (1.79)	0.54	0.45–5.32	1.10	0.25–4.92
Asian/Native Hawaiian / Pacific Inslander	4.40 (1.65)	3.57 (1.98)	2.93 (1.06)	0.24 (0.23)	0.81	0.19–3.39	0.67	0.26–1.71
Hispanic / latino	10.19 (1.97)	8.02 (1.91)	9.08 (1.73)	13.19 (2.40)	0.78	0.44–1.39	0.90	0.48–1.66
Age (years old)								
18–29	67.44 (3.13)	43.73 (4.39)	20.49 (2.59)	11.10 (1.82)	1.00	1.00–1.00	1.00	1.00–1.00
30–44	21.61 (2.77)	34.42 (4.30)	44.92 (3.89)	40.98 (2.87)	2.46	1.49–4.05	6.84	4.11–11.40
45–64	10.41 (1.55)	20.47 (3.91)	27.94 (3.32)	38.12 (2.95)	3.03	1.62–5.67	6.84	5.52–14.13
> 65	0.54 (0.34)	1.39 (0.66)	6.65 (1.75)	9.81 (1.84)	3.92	0.79–19.57	40.17	9.99–161.47
Marital status								
Married	32.37 (3.00)	56.29 (4.27)	65.80 (3.03)	63.36 (3.03)	1.00	1.00–1.00	1.00	1.00–1.00
Widowed, separated, divorced	8.75 (1.64)	19.81 (3.06)	27.19 (2.90)	30.46 (2.96)	1.30	0.71–2.40	1.53	0.89–2.62
Never married	58.88 (3.32)	23.91 (3.53)	7.01 (1.23)	6.18 (1.34)	0.23	0.14–0.29	0.06	0.04–0.10
Education								
Less than high school	0.88 (0.49)	3.06 (1.53)	1.31 (0.66)	9.88 (2.36)	1.00	1.00–1.00	1.00	1.00–1.00
High school	33.14 (3.18)	45.35 (4.39)	44.96 (3.52)	42.86 (2.99)	0.39	0.08–1.84	0.91	0.20–4.17
Some college or higher	65.98 (3.29)	51.59 (4.09)	53.73 (3.57)	47.26 (3.41)	0.22	0.05–1.07	0.54	0.12–2.57
Family income (\$)								
0–19,999	26.60 (2.85)	29.82 (4.30)	29.80 (3.08)	37.57 (3.13)	1.00	1.00–1.00	1.00	1.00–1.00
20,000–34,999	24.53 (2.84)	25.22 (4.05)	24.66 (2.87)	18.88 (2.26)	0.92	0.48–1.75	0.90	0.57–1.42
35,000–59,999	24.95 (2.77)	25.41 (3.93)	22.12 (2.88)	18.92 (2.50)	0.91	0.50–1.64	0.79	0.47–1.33
≥ 60,000	23.92 (2.99)	19.55 (3.78)	23.42 (2.90)	24.63 (3.08)	0.73	0.35–1.51	0.87	0.50–1.53
Urbanicity								
Urban	34.19 (3.58)	27.11 (3.71)	28.16 (3.47)	27.17 (3.10)	1.00	1.00–1.00	1.00	1.00–1.00
Rural	65.81 (3.58)	72.89 (3.71)	71.84 (3.47)	72.83 (3.10)	1.40	0.91–2.16	1.33	0.93–1.90
Region								
Northeast	17.85 (3.85)	15.96 (4.01)	17.43 (3.65)	17.82 (4.09)	1.00	1.00–1.00	1.00	1.00–1.00
Midwest	24.83 (4.34)	27.70 (4.88)	25.18 (4.41)	23.98 (3.82)	1.25	0.60–2.59	1.04	0.59–1.82
South	31.79 (4.62)	32.53 (4.90)	36.29 (4.30)	39.46 (4.29)	1.14	0.58–2.26	0.59	0.67–2.03
West	25.53 (4.67)	23.82 (5.42)	21.11 (3.79)	18.74 (3.41)	1.04	0.53–2.06	0.45	0.45–1.59
Insurance								
None	25.85(3.08)	22.36 (4.14)	21.93 (3.15)	20.94 (2.57)	1.00	1.00–1.00	1.00	1.00–1.00
Public	8.64 (1.61)	19.21 (3.46)	16.18 (2.27)	26.00 (2.83)	2.57	1.26–5.25	2.21	1.11–4.41
Private	65.51 (3.26)	58.43 (4.32)	61.89 (3.06)	53.06 (3.17)	1.03	0.60–1.77	1.11	0.66–1.88

Abbreviations: CI = confidence interval; OR = odds ratio; SE: Standard Error.

Significant results in bold (p < 0.05).

Table 2
Bipolar disorder's characteristics at wave 1 of women with bipolar disorder without child, with 1 or 2 children and with more than 2 children in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

Characteristics	No child n = 322 % (SE)	1 child n = 199 % (SE)	2 children n = 299 % (SE)	> 2 children n = 370 % (SE)	1 child vs. no child aOR (CI 95%)	2 children vs. no child aOR (CI 95%)	> 2 children vs. no child aOR (CI 95%)
Type of BD							
I	50.29 (2.98)	63.83 (4.38)	65.12 (3.08)	67.46 (3.23)	1.61	1.76	1.97
II	49.71 (2.98)	36.17 (4.38)	34.88 (3.08)	32.54 (3.23)	1.00	1.00	1.00
Age at onset (mean (SE))	18.91 (0.62)	22.70 (1.32)	24.69 (0.90)	25.64 (0.80)	1.01	1.01	1.02
Number of episode (mean (SE))	9.59 (0.62)	9.60 (0.86)	9.41 (0.66)	10.21 (0.62)	1.00	1.00	1.00
MDE	15.64 (1.30)	15.27 (2.04)	14.53 (1.46)	18.45 (1.60)	1.00	1.00	1.00
Hospitalization							
MDE	13.70 (2.58)	21.50 (3.86)	16.63 (3.01)	25.57 (3.46)	1.48	0.58	1.06
Mania	6.40 (1.40)	7.79 (2.06)	6.30 (1.71)	11.32 (2.19)	0.73	0.43	0.72
Suicide							
Suicide attempt	14.78 (2.50)	16.68 (3.02)	17.40 (2.74)	20.28 (2.66)	0.98	0.97	1.43
Thought without SA	25.62 (2.99)	31.79 (4.80)	32.22 (3.95)	23.61 (3.05)	1.38	1.33	0.63
Comorbidity							
Any substance disorder	57.49 (3.15)	61.12 (3.80)	62.97 (3.45)	59.46 (3.11)	0.96	1.09	1.03
Any anxiety disorder	48.76 (3.32)	50.99 (4.40)	58.95 (3.37)	59.14 (3.31)	0.80	1.14	1.24
Any personality disorder	51.55 (3.49)	58.02 (4.39)	50.43 (3.75)	55.57 (3.26)	1.36	1.05	1.21

Abbreviations: CI = confidence interval; AOR = Adjusted odds ratio; SE: Standard Error; MDE: Major Depressive episode; SA: Suicide attempt.
^aAdjusted for age, race, education, marital status, income, region, urbanicity, insurance.
 Significant results in bold (p < 0.05).

assurance than the bipolar women with no child. Women with BD and with 3 children and more were more likely to be black, older, single or divorced and less educated than the bipolar women with no child. Urbanicity and region were not significantly different among the groups.

3.3. Bipolar disorder characteristics and comorbidities

In the sample, 61.2% of women met criteria for BD I, other met criteria for BD II. 61.3% started their disease with a MDE. The mean age of onset was 22.9 years old. 19.5% had already been hospitalized for an MDE or mania and 17.0% reported suicide attempt (Table 2). Comorbidities rates were high, with 60.0% of women having substance use disorder, 55.0% having anxiety disorder and 53.5% having personality disorder (Table 2).

Women with at least two children were more likely to have BD I than women without child (OR: 1.76; CI 95%: 1.10–2.82 and OR: 1.97; CI 95%: 1.19–3.25 respectively for women with two children and more than two children) (Table 2). Parity status was not significantly associated with different rates of hospitalization for MDE, hospitalization for mania, suicide attempt, thought of suicide. Parity status was not significantly associated with different prevalence rate of psychiatric lifetime comorbidity, such as drug disorders, anxiety disorders or personality disorders (Table 2).

3.4. Parity and three-year course of bipolar disorder

Women with 2 children and more were more likely to experiment a hypomanic episode during the 3-years of follow-up than women without child (Table 3). They were also more than 2 times more likely to report hypomania during the follow-up (OR: 2.54; CI: 1.12–5.75) and women with 3 children or more were more than 3 times more likely to report hypomania during the follow-up (OR: 3.76; CI: 1.61–8.78) than women without child.

Considering other evolution criteria including, parity status was not associated with a significantly different incidence of MDE, incidence of mania, hospitalization, incidence of suicide attempt or thought of suicide.

3.5. Sensitivity analysis

Women who were pregnant within the 3 years of follow-up reported no significant difference incidence of mania, hypomania, MDE, hospitalization, suicide attempt or thought of suicide compared to those who reported no pregnancy within this timeframe (Supplementary Table S1).

In the subsample of participants aged 50 years old or less, the incidence of hypomania was within the same range as that observed in the whole population. The incidence of suicide attempt during the 3-year follow-up was higher in women having more than two children compared to women with no child (OR: 3.28; CI 1.01–10.64). No significant difference incidence was founded of mania, MDE, hospitalization, or thought of suicide (Supplementary Table S2).

4. Discussion

This study examined the characteristics and the course of BD in women, according to their number of children. To our knowledge, this is the first study that specifically examines the impact of parity on BD's course using a prospective design.

The characteristics of the sample of women with BD in our study were consistent with these observed in the literature. Women were more likely to have a BD I, presented a rate of psychiatric comorbidities of 50% and a rate of suicide attempts of 20% (Kawa et al., 2005; Viguera et al., 2001; Barnes and Mitchell, 2005).

The main finding of our study is that parity was positively

Table 3

Incidence of mood episode and complications between wave 1 and wave 2 in women with bipolar disorder without child, with 1 or 2 children and with more than 2 children in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

Characteristic	No child n = 322	1 child n = 199	2 children n = 299	> 2 children n = 370	1 child vs. no child		2 children vs. no child		> 2 children vs. no child	
	% (SE)	% (SE)	% (SE)	% (SE)	aOR (CI 95%)		aOR (CI 95%)		aOR (CI 95%)	
Depressive episode										
MDE	31.63 (3.17)	31.23 (4.49)	41.01 (3.55)	34.09 (3.40)	0.81	0.46 – 1.43	1.32	0.82 – 2.11	0.72	0.39 – 1.34
Manic episode										
Mania	9.44 (1.94)	12.89 (2.87)	15.53 (2.73)	14.98 (2.20)	1.53	0.71 – 3.32	1.21	0.60 – 2.46	1.76	0.78 – 3.98
Hypomania	7.86 (1.75)	8.18 (2.44)	7.77 (1.86)	8.47 (1.61)	1.92	0.81 – 4.59	2.54	1.12 – 5.75	3.76	1.61 – 8.78
Hospitalization (Yes/No)										
MDE	10.12 (3.47)	13.75 (4.57)	7.26 (2.27)	22.81 (4.85)	0.66	0.21 – 2.02	0.51	0.14 – 1.89	2.73	0.95 – 7.84
Mania	7.42 (3.24)	2.47 (1.54)	3.34 (2.04)	7.04 (2.32)	0.30	0.04 – 2.29	0.92	0.14 – 5.84	1.16	0.23 – 5.86
Suicide attempt (Yes/No)										
Suicide attempt	8.17 (3.36)	6.79 (2.83)	6.70 (2.15)	6.51 (2.26)	1.02	0.27 – 3.89	1.10	0.38 – 3.13	2.44	0.91 – 6.53
Though without SA	27.28 (4.51)	23.76 (5.35)	31.35 (4.00)	34.18 (4.82)	0.95	0.41 – 2.19	1.39	0.67 – 2.85	2.18	0.99 – 4.77

Abbreviations: CI = confidence interval; AOR = Adjusted odds ratio; SE: Standard Error; MDE: Major Depressive episode; SA: Suicide attempt.

^aAdjusted for age, race, education, marital status, income, region, urbanicity, insurance.

Significant results in bold ($p < 0.05$).

associated with hypomanic episode during the 3-years of follow-up. Women having 2 children or more were more than 2 times more likely to report hypomania during the follow-up than women without child, this odds being as high as 3 for women with 3 children or more. Otherwise, in the subsample of women in childbearing age, the incidence of suicide attempt during the 3-year follow-up was higher in women having more than two children compared to women with no child (OR: 3.28; CI 1.01–10.64).

Parity was not associated with other characteristics of BD, nor with the severity and course of the illness. More specifically, the number of episode, the rates of hospitalization or the risk of suicide attempt did not differ as a function of parity status.

The literature shows conflicting data on this subject. While peripartum periods appear to convey an important risk of BD's relapse, with an increased risk of depression, mania, or psychotic episodes (Pope et al., 2014), multiparity seems to be a protective factor for BD (Viguera et al., 2011).

Our work partly contributes to the comprehension of the relationships between peripartum mood episodes and parity. Although the literature reports a higher risk of mania or MDE in peripartum in women with BD, the effect of parity seems to be limited to an increased number of hypomanic episodes in a three-year follow-up.

We can suggest several hypotheses for this explaining our results.

First, women with BD are less likely to have children than women in the general population, and this negative association is particularly strong if BD is associated with psychiatric comorbidity (Power et al., 2013), or if BD is considered as severe or unstable (Viguera et al., 2011; Laursen and Munk-Olsen, 2010). Women with BD experiencing a severe mood episode following their first pregnancy are less likely to have other children (Pope et al., 2014). In addition, women with BD may choose not to have children for many reasons, including real or supposed treatment's adverse effect on fetal development and real or supposed impact of pregnancy on the course of BD (Viguera et al., 2002)

Furthermore, women with childbearing wishes could be more likely to be clinically stable before, particularly if they have already been pregnant (Di Florio et al., 2014; Wesseloo et al., 2016).

While our study does have important strengths, including representativeness, large size, prospective design and validity of the psychiatric assessment, some limitations should be considered while interpreting these results.

First, women aged less than 18 were not included in the NESARC. Given the prevalence of teenage pregnancy in the US (Hamilton et al., 2015), further study should examine the impact of pregnancy in adolescent with bipolar disorder.

Second, the NESARC does not provide information on postpartum

onset bipolar disorder. Peripartum onset can increase diagnostic specificity, improve the prediction of prognosis and assist in treatment selection. Further epidemiologic survey should take this point into account in order to measure the burden associated with the disease in women with previous postpartum episode. Another limitation is that the NESARC design does not establish whether recurrences occurred during postpartum period. This does not allow to draw any causal relationship between parity and its association with mood disorders. Third, the NESARC does not provide information on treatment maintenance during pregnancy. Discontinuation of mood stabilizer during pregnancy is a well-known major risk factor of relapse during peripartum period (Khan et al., 2016). Among other limitations, the study does not provide information on pregnancies not ending to a delivery. This includes miscarriages or abortions, women with psychiatric disorders having high rates of abortion compared with the general population (Laursen and Munk-Olsen, 2010).

In this large prospective survey in US women with BD, we provide description of the association of parity with the clinical characteristics of BD, its course and comorbidities. While parity is associated with a higher incidence of hypomania during a 3-years follow-up, it was not associated with other clinical characteristics of the disease.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jad.2017.08.042>.

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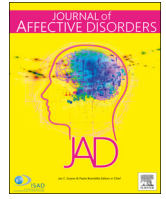
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Parity and bipolar disorder: New analyses



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We thank Dr. Sharma for the comments of our recent work on the association of parity status with bipolar disorder (BD) clinical features, severity and evolution (Tebeka et al., 2018; Sharma, 2018). In this work, we described the characteristics of BD, and compared them according to their parity (number of children). We found that in women with BD, parity was associated with a higher incidence of hypomanic episodes during 3-years follow-up, but not with other BD's characteristics or psychiatric comorbidities.

Dr. Sharma pointed out two limitations in our work.

First, our study did not consider drug treatments in participants. We agree and therefore reanalyzed our data according to the prescription of a drug treatment for the considered disorder. Women with more than two children were more likely to report an antimanic drug than women with no children at wave 1 (aOR = 1.87, 95% CI 1.04–3.37). This is consistent with our finding that women with more than 2 children were more than 3 times more likely than women without child to report hypomanic episodes during the follow-up (OR: 3.76; CI: 1.61–8.78) (Tebeka et al., 2018). No other significant association between the parity and treatment prescription was founded (Table 1). Importantly, this new analysis showed that more than 30% of women with bipolar disorder are untreated for a mood episode: drug prescription ranges between 42 and 65% for MDE, and between 15% and 45% for mania. These treatment gap confirm that women of childbearing age with bipolar disorder constitute an underdiagnosed, understudied and undertreated population, regardless of their parity status (Drancourt et al., 2013).

Dr. Sharma also emphasizes that the definition used by the NIAAA in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) is not consistent with the DSM-5 definition. While DSM-IV-TR only was available when the second wave of the survey was conducted in 2004–2005, we nevertheless agree with Dr. Sharma that “at least some of these patients would be classified as having other specified bipolar and related disorder rather than BD II”. We therefore reanalyzed our data to examine the proportion of women who could have been classified as having BD II according to DSM-IV-TR criteria. On the 481 women classified as such in the subsample of our

study, as high as 58% also meet the criteria for BD II according to DSM-IV-TR. We also reanalyzed our data excluding the 216 women (42%) considered as having BD II while not meeting DSM-IV-TR criteria for the considered disorder, and found no major differences (data available on request).

Having these limits in mind, the association of parity with specific features of bipolar disorder suggests further investigation.

Contributors

Sarah Tebeka drafted the initial manuscript, carried out the initial analyses, and approved the final manuscript as submitted.

Caroline Dubertret and Yann Le Strat revised the manuscript, and approved the final manuscript as submitted.

Role of the funding source

No funding was secured for this study.

The authors have no financial relationships relevant to this article to disclose.

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Access to data: Yann Le Strat had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.05.039.

Abbreviations: AOR, adjusted odd ratio; BD, bipolar disorder; CI, confidence interval; MDE, major depressive disorder; NESARC, National Epidemiologic Study of Alcohol and Related Conditions; OR, odd ratio; SA, suicide attempt

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Table 1

Prescription of medicine by a doctor to improve mood between wave 1 and wave 2 in women with bipolar disorder without child, with 1 or 2 children and with more than 2 children in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

Characteristic	No child	1child	2 children	> 2 children	1 child vs no child		2 children vs. no child		>2 children vs. no child	
	<i>n</i> = 322 % (SE)	<i>n</i> = 199 % (SE)	<i>n</i> = 299 % (SE)	<i>n</i> = 370 % (SE)	aOR (IC 95%)		aOR (IC 95%)		aOR (IC 95%)	
Drug prescription for MDE at wave 1	41.68 (4.00)	62.34 (5.24)	56.69 (3.85)	65.03 (3.49)	1.55	0.85–2.83	0.67	0.11–4.11	1.26	0.69–2.32
Drug prescription for mania or hypomania at wave 1	14.88 (2.22)	22.74 (3.86)	26.85 (2.88)	36.87 (3.31)	1.36	0.69–2.66	1.37	0.77–2.45	1.87	1.04–3.37
Drug prescription for MDE at wave 2	43.98 (5.84)	65.19 (6.64)	62.38 (5.00)	56.43 (5.04)	1.54	0.63–3.77	1.15	0.52–2.52	0.87	0.34–2.25
Drug prescription for mania or hypomania at wave 2	29.16 (5.94)	43.38 (8.56)	43.70 (7.21)	44.91 (5.89)	0.64	0.19–2.10	1.29	0.35–4.76	0.77	0.29–2.06

Abbreviations: CI = confidence interval; aOR = odds ratio; SE: standard error; MDE: major depressive episode.

^a Adjusted OR for age, race, education, marital status, income, region, urbanicity, insurance.

Significant results in bold ($p < 0.05$).

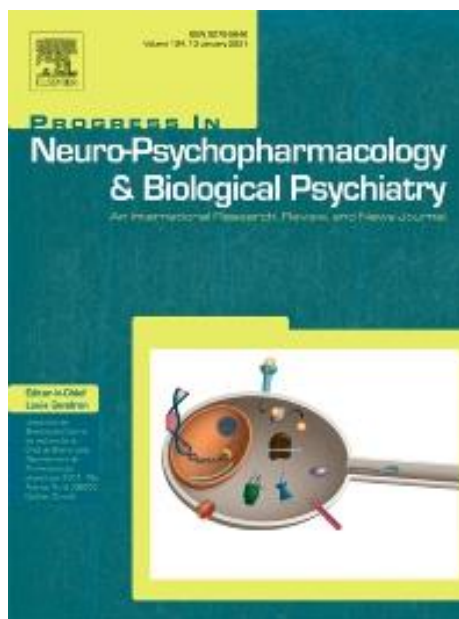
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IV.B. Article 6 : Clinical characteristics of bipolar disorders with postpartum depressive onset

ARTICLE 6



Clinical characteristics of bipolar disorders with postpartum depressive onset

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Des corrélats cliniques de la polarité du premier épisode dans le trouble bipolaire ont été décrits. En particulier, la polarité au début du trouble est un bon prédicteur de la polarité d'autres épisodes au fil du temps (Daban et al. 2006; Perugi et al. 2000; Turvey et al. 1999). Un début dépressif est deux fois plus fréquent qu'un début maniaque et il est associé à plus de chronicité et de cyclicité (un nombre plus élevé d'épisodes totaux, une durée plus longue de la maladie, un nombre plus élevé d'épisodes dépressifs, plus de tentatives de suicide, un début de maladie plus tardif) (Daban et al. 2006; Perugi et al. 2000).

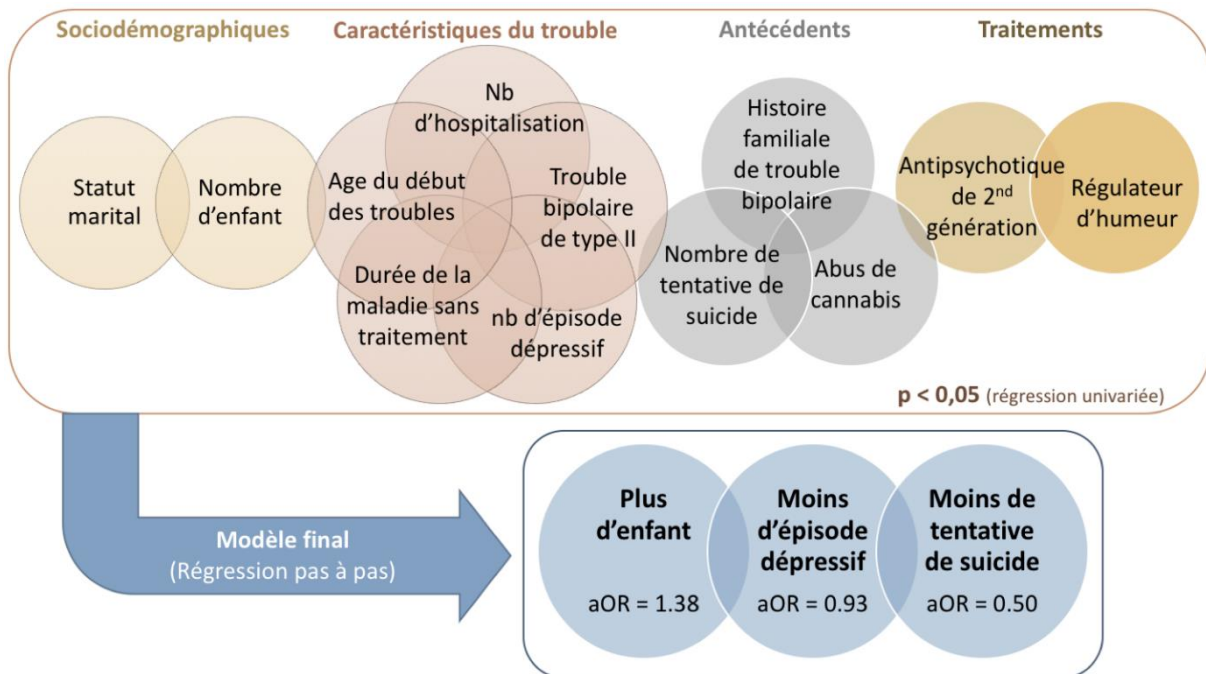
Par ailleurs, et comme nous l'avons détaillé plus haut, parmi les épisodes thymiques, la dépression est la manifestation la plus courante dans la période post-partum (Samantha Meltzer-Brody et al. 2018). Ainsi, nous avons proposé dans ce travail de comparer les caractéristiques sociodémographiques et cliniques d'un large échantillon de femmes souffrant de trouble bipolaire ayant débuté par un épisode dépressif caractérisé, pendant ou en dehors de la période post-partum.

Pour cela, nous nous sommes appuyés sur la cohorte multicentrique française FACE-BD (cf. méthodologie p. 44). Nous avons considéré toutes les femmes ayant débuté leur trouble bipolaire par un épisode dépressif caractérisé et ayant au moins un enfant. Nous avons comparé deux groupes selon la période de début de trouble : pendant ou en dehors de la période post-partum, défini ici par les 6 mois suivant l'accouchement.

Parmi les 759 femmes ayant débuté leur trouble bipolaire par un épisode dépressif caractérisé, 93 (12,2 %) ont eu un début post-partum. En comparaison à celles qui ont débuté par un épisode dépressif caractérisé en dehors du post-partum, les femmes ayant débuté leur trouble bipolaire par une dépression du post-partum avait une vie de famille plus stable, plus d'enfants, un âge plus avancé au début du trouble bipolaire, plus de trouble bipolaire de type II, moins d'antécédents de tentatives de suicide, moins d'épisodes dépressifs et plus de traitements de stabilisateur de l'humeur.

Les analyses ont également montré que les femmes ayant débuté leur trouble dans le post-partum avaient significativement plus d'enfants, moins d'épisodes dépressifs au cours de leur vie et un taux plus faible d'antécédents de tentatives de suicide par rapport aux femmes avec un début en dehors de la période post-partum.

Figure 14 : Caractéristiques démographiques et cliniques des femmes souffrant d'un trouble bipolaire à début dépressif, selon que le trouble ait commencé dans le post-partum ou non dans la cohorte FACE-BD.

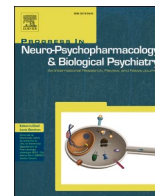


Conclusion et perspectives :

Nos résultats suggèrent que les femmes débutant un trouble bipolaire par une dépression du post-partum ont une évolution plus favorable de la maladie, en particulier moins de tentative de suicide et moins d'épisodes dépressifs au cours de la vie. Cela peut refléter que ces femmes représentent un sous-groupe phénotypiquement homogène, avec des caractéristiques spécifiques. Dans ce travail, nous retrouvons que la parité est un marqueur de bon pronostic d'évolution du trouble bipolaire, comme le suggéraient nos travaux précédents en population américaine (Tebeka, Le Strat, et Dubertret 2018; Tebeka, Strat, et Dubertret 2018). D'autres travaux, proposant un suivi prospectif au long court, pourraient permettre d'étudier au mieux cette hypothèse.

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Clinical characteristics of bipolar disorders with postpartum depressive onset

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ABSTRACT

Background: Postpartum period is associated with an increased risk of bipolar disorder diagnosis and relapse, mainly major depressive episode. Onset during this period might be associated with specific characteristics.

Aim: To compare the socio-demographic and clinical characteristics of parous women presenting with bipolar disorder and an index depressive episode occurring during or outside the postpartum period.

Methods: Using the multicenter cohort FACE-BD (FondaMental Academic Centers of Expertise for Bipolar Disorders), we considered all women who started their BD with a major depressive episode and have at least one child. We compared two groups depending on the onset: in or outside the postpartum period.

Results: Among the 759 women who started BD with a major depressive episode, 93 (12.2%) had a postpartum onset, and 666 (87.8%) had not. Women who started BD in the postpartum period with a major depressive episode have a more stable family life, more children, an older age at onset, more Bipolar 2 disorder, less history of suicide attempts, less depressive episodes and more mood stabilizer treatments as compared to those who started with a major depressive episode outside the postpartum period. The multivariable logistic regression showed that women with an onset in the postpartum period had significantly more children, less lifetime depressive episodes and a lower rate of history of suicide attempts as compared to women with an onset outside the postpartum period.

Discussion: Our results suggest that women starting their BD with postpartum depression have a more favorable course of BD, especially less history of suicide attempt and less lifetime depressive episodes.

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1. Introduction

Bipolar disorders (BD) are severe mood disorders, affecting 1 to 3% of the general population (Merikangas et al., 2011). BD usually begin in young adults before the age of 25, and affect men and women equally (Ferrari et al., 2016). Woman gender is associated with certain clinical features such as an increased risk of Bipolar 2 disorder, rapid cycling and mixed episodes (Di Florio et al., 2013). Moreover, the postpartum period is often marked by mood episodes; and women with BD can present with a post-partum onset (Jones et al., 2014). In general, BD is one of the leading causes of disability and premature death among women of childbearing age (Ferrari et al., 2016; The World Health Organization, 2001). The postpartum period is associated with an increased risk of a major depressive episode (Munk-Olsen et al., 2012; Parial, 2015; Pope et al., 2014; Sharma and Pope, 2012). After a postpartum depression, the risk of further conversion to a diagnosis of BD is more than twice as high as after a major depressive episode occurring outside the peripartum context (Liu et al., 2017; Munk-Olsen et al., 2012). In BD, a depressive onset is more common than a (hypo)manic onset (Cremaschi et al., 2017; Tundo et al., 2015).

Postpartum depression can be severe both for the mother and the baby. Indeed, severity of symptoms in the postpartum period more often requires hospitalizations (Munk-Olsen et al., 2009). Women with BD also present an increased risk of suicide (Tebeka et al., 2018a, 2018b) and more addictive comorbidities (Battle et al., 2014; Masters et al., 2019) compared with women in general population. Perinatal mood episodes can also complicate pregnancy (more gestational hypertension and antepartum hemorrhage) and are associated with low birth weight and inadequate neonatal adaptation (Johnson et al., 2014; Kingston et al., 2012; Rusner et al., 2016). Perinatal mood episodes can also negatively impact the early maternal-child interactions (Anke et al., 2019).

Clinical correlates of first-episode polarity in bipolar disorder have been described (Daban et al., 2006). In particular, the polarity at onset is a good predictor of the polarity of further episodes over time (Daban et al., 2006; Perugi et al., 2000; Turvey et al., 1999). A depressive onset is twice as frequent as manic onset and is associated with more chronicity and cyclicality (a higher number of total episodes, a longer duration of illness, a higher number of depressive episodes, more suicide attempts, a later illness onset) (Daban et al., 2006; Perugi et al., 2000). In particular, depression is the most common manifestation in the postpartum period (Meltzer-Brody et al., 2018).

Despite the obvious impact of bipolar disorder during the postpartum period, little is known about clinical characteristics and prognosis of women presenting with an index major depressive episode in the postpartum period; no previous study has explored this specific phenotype. The aim of our study is therefore to compare the socio-demographic and clinical characteristics in a large cross-sectional sample of women whose bipolar disorder began with a major depressive episode, in or outside the postpartum period.

2. Method

2.1. Study design and sample

The FACE-BD (FondaMental Academic Centers of Expertise for Bipolar Disorders) is a multicenter cross-sectional study. Outpatients with BD (types I, II and not otherwise specified) were recruited within a national network of 12 Expert Centers, set up by the FondaMental Foundation (www.fondation-fondamental.org). This network was created in 2007, funded by the French Ministry of Research and further supported by the French Ministry of Health.

The patients were referred by their psychiatrist or general practitioner for assistance in the diagnosis and management of patients with BD. All participants had a clinical, thorough and standardized assessment by trained clinicians. All assessment has been previously described in details (Henry et al., 2011).

The assessment protocol, including a letter of information for patients, was approved by the institutional review board (CPP-Ile de France IX, January 18th, 2010), in accordance with French laws for non-interventional studies. Anonymized data are stored in a national database that was approved by the French body overseeing the safety of computerized databases (Commission Nationale de l'Informatique et des Libertés, DR-2011-069).

In order to preserve a homogeneous sample, we considered for this study all parous women with a diagnosis of BD according to DSM-IV criteria (types I, II, and not otherwise specified (NOS)) who started their BD with a major depressive episode. We excluded unparous women: they had not experienced the postpartum period.

We distinguished two groups: women with a depressive onset in the postpartum period (within the six months following birth) and women with a depressive onset outside the postpartum period (ante-natal or after the postpartum period as defined above), according to women's self-declaration.

2.2. Measures

2.2.1. Sociodemographic measures

Sociodemographic characteristics were systematically recorded: age at the interview, education level, work and marital status.

Educational level was classified into: (i) less than high school, (ii) high school graduate or higher. Marital status was classified into (i) in couple (married or in common-law), (ii) single (single, widowed, separated or divorced).

2.2.2. Clinical assessment

Diagnoses of BD were determined using the Structured Clinical Interview for DSM-IV-R (SCID) (First, 2015). We also detailed the main characteristics of BD as follow: the age at onset, the age at the first treatment, the duration of untreated illness, the duration of the disease, the type of BD (I, II or NOS), the number of lifetime episodes (depressive, (hypo)manic or mixed, according to DSM-IV-R criteria) and hospitalizations, the number of episodes with psychotic characteristics and rapid cycling.

We also evaluated: number of suicide attempts, lifetime psychiatric comorbidities (anxiety disorders, eating disorders), substance use disorders (current tobacco use, alcohol abuse, cannabis abuse, and other abuses (sedative, stimulant, opioid, cocaine and hallucinogen drug)), sleep disturbances (Pittsburgh Sleep Quality Index, PSQI) (Buysse et al., 1989), obesity (Body Mass Index, BMI > 25) and C Reactive Proteine (CRP) abnormalities (>3).

The family history of mood disorders was also systematically collected.

Current mood state was assessed with the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) and the Young Mania Rating Scale (YMRS) (Young et al., 1978) (Young et al., 1978).

Childhood trauma was assessed using the CTQ (Childhood Trauma Questionnaire) (Bernstein et al., 2003; Paquette et al., 2004). The CTQ distinguishes 5 types of trauma: emotional, physical and sexual abuses as well as emotional and physical neglects.

Global functioning was assessed using the Functioning Assessment Short Test (FAST), including autonomy occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time (Rosa et al., 2007). High total score indicates bad functioning.

2.2.3. Treatments

Medical treatments were collected by self-report, following 5 pharmacological classes (first and second generation antipsychotics, antidepressants, lithium, mood stabilizers, anxiolytics), the number of psychotropic drugs and adherence to the treatment according to the Medication Adherence Rating Scale (MARS) score (Misdrabi et al., 2004; Thompson et al., 2000).

2.2.4. Statistical analysis

We analyzed the subsample of women with at least one child and with depression as a first episode. Socio-demographic and clinical characteristics as well as current medications are described by medians (interquartile range) for continuous data, given that most had non-gaussian distributions (Shapiro-Wilk test p -value <0.05), and percentage for categorical variables. Comparisons of all these characteristics between BD women with and without postpartum onset were performed using Chi-square for categorical variables and Student t -test or Wilcoxon Mann-Whitney test for continuous variables (depending of the variables distribution).

All variables with p values <0.2 in univariate analysis were included in a multivariate logistic regression analysis using a backward stepwise method. Statistical analyses were performed with SAS (release 9.3; SAS Statistical Institute, Cary, NC). All statistical tests were two-tailed, with α level set at 0.05.

3. Results

3.1. Sample

Of the 1912 women included in the 12 French FACE-BD centers, 960 (50.2%) had at least one child among which 119 (12.4%) had a postpartum onset (Fig. 1). The majority of women had a depressive onset ($N = 759$, 80.3%). Women with a first (hypo)manic episode corresponded to 17.0% ($N = 161$) of women in our study, and those with a first mixed episode were 25 (2.6% of our population). The polarity of the first episode of BD was not significantly different according to the PP onset status (Supplementary Table S1).

Among the 759 women with a depressive onset who were considered for this study, 93 (12.2%) present with a postpartum depressive onset, and 666 (87.8%) had not. Only 26 women (3.4%) had an (hypo)manic or mixed episode postpartum onset; they were not included in our analyses.

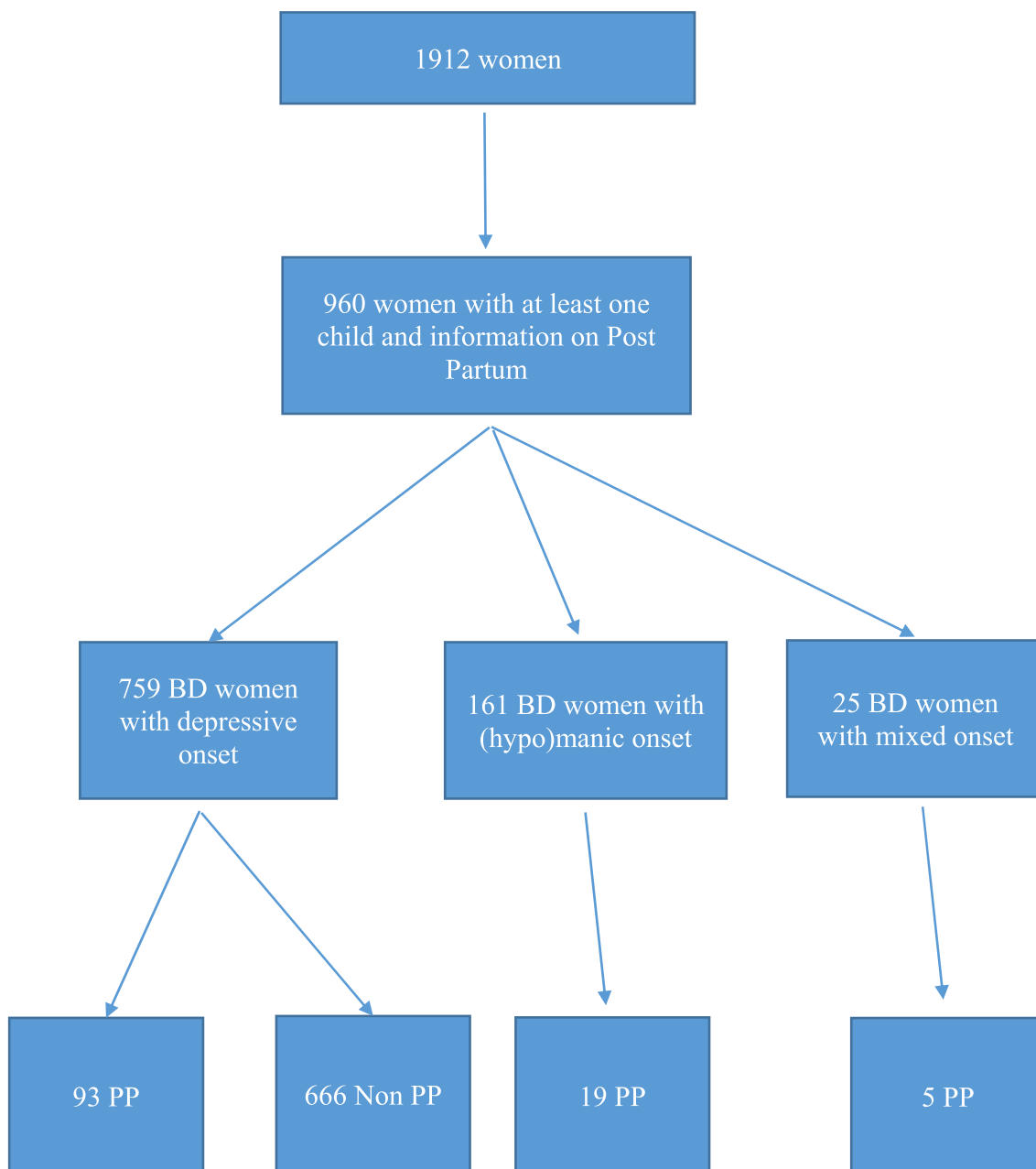


Fig. 1. Flowchart.

3.2. Demographics characteristics

The sociodemographic characteristics of both groups are summarized in Table 1. The mean age of the sample was 47.2 (10.5). Half of these women were working (51.5%). The majority of them had a high level of education (67.8%) and was living in couple (68.5%).

There was no significant difference between women with and without a postpartum depressive onset in terms of age, education level, work status and number of children. Women with a postpartum depressive onset were significantly more frequently in couple (80.3% vs. 66.9%, $p = 0.018$).

3.3. BD characteristics

Women with a postpartum depressive onset started their BD on average 5 years later than women without (median: 28 vs. 22 years old, $p < 0.001$). They tended to have a lower duration of untreated illness and a shorter duration of illness than women without postpartum onset, with no significant difference on these two points.

Women with a postpartum depressive onset had significantly more BD type II (58.1% vs. 47.2%, $p = 0.049$), and were less likely to have attempted suicide at least once (35.6% vs. 50.3%, $p = 0.009$). Although the number of lifetime mood episodes (all polarities combined) was not different in our 2 groups, women with a postpartum onset had significantly less depressive episodes than the others (median: 4 vs. 3, $p = 0.006$). There was no significant difference between the two groups in terms of BD type (BD type I 30.1% vs. 38.7%; BD type NOS 11.8% vs. 14.1%), lifetime number of (hypo) manic or mixed episodes and hospitalizations, number of suicide attempts, episode with psychotic characteristics, rapid cycling, or current mood state.

Family history of BD was not different between the 2 groups. Women with and without postpartum onset didn't show any difference in their functioning.

There was no significant difference between our 2 groups regarding childhood traumas, even when considering the trauma subtypes (emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect).

3.4. Comorbidities

Women with a postpartum depressive onset used less tobacco (32.9% vs. 38.3%), had less lifetime substance abuse, in particular less alcohol abuse (15.3% vs. 19.8%), less cannabis abuse (3.6% vs. 10.0%), and less eating disorders (24.0% vs. 20.0%) than women without. These differences were not significant.

There was no significant difference between the two groups regarding lifetime anxiety disorders, sleep disturbances, BMI and CRP.

3.5. Treatments

Regarding treatments, women with a postpartum depressive onset received significantly more mood stabilizers than women without (64.9% vs. 50.0%, $p = 0.017$). There was no difference regarding other classes of treatment (first- and second-generation antipsychotics, antidepressants, lithium and anxiolytics), the mean number of psychotropic drugs or adherence to treatment.

3.6. Multivariable logistic regression analysis

The following variables were included as independent variables in the stepwise logistic regression (all variables with p values < 0.2 in univariate analysis): marital status, number of children, age at BD onset, duration of untreated illness, duration of illness, BD type II, number of lifetime depressive episodes and number of lifetime hospitalizations, family history of BD, number of suicide attempts, cannabis abuse, use of second generation antipsychotics and mood stabilizer.

Table 1

Demographic and clinical characteristics of women with BD according to the presence of absence of a postpartum depressive onset (In women with at least one child and with a first depressive episode $n = 759$).

	BD women with a postpartum depressive onset		p value
	No ($n = 666$)	Yes ($n = 93$)	
	87.8%	12.2%	
Demographic characteristics			
Age, median (IQR)	46.2 (39–55)	46.4 (40–54)	0.512
High Education level, n (%)	386 (67.8)	49 (67.1)	0.902
Working, n (%)	288 (51.3)	40 (52.6)	0.832
Living in couple, n (%)	386 (66.9)	61 (80.3)	0.018
Number of children, median (IQR)	2 (1–2)	2 (2–3)	0.071
Disease characteristics			
Age of BD onset (years), median (IQR)	22 (17–31)	28 (26–31)	<0.001
Age at first treatment, median (IQR)	28 (21–37)	30 (25.5–35.5)	0.583
Duration of untreated illness, median (IQR)	0 (0–8)	0 (0–5)	0.068
Duration of illness, median (IQR)	20.7 (13.5–29.7)	18.7 (12.3–24.7)	0.079
Bipolar 2 disorder, n (%)	314 (47.2)	54 (58.1)	0.049
Bipolar subtype, n (%)			
Type 1	258 (38.7)	28 (30.1)	0.140
Type 2	314 (47.2)	54 (58.1)	
Type NOS	94 (14.1)	11 (11.8)	
Number of lifetime episodes, median (IQR)	7 (4–12)	6 (3–10)	0.160
Number of lifetime depressive episodes, median (IQR)	4 (2–7)	3 (1–5)	0.006
Number of lifetime manic and hypomanic Episodes, median (IQR)	2 (0–4)	2 (0–4)	0.884
Number of lifetime mixed episode, median (IQR)	0 (0–0)	0 (0–0)	0.569
Number of lifetime hospitalizations, median (IQR)	2 (1–4)	1 (0–3)	0.143
Episode with psychotic characteristic, n (%)	159 (24.5)	24 (27.0)	0.619
Family history of BD, n (%)	361 (55.6)	41 (46.6)	0.110
Suicide attempt (at least one), n (%)	329 (50.3)	32 (35.6)	0.009
Number of suicide attempt, median (IQR)	2 (1–4)	2 (1–3)	0.429
Rapid cycling, n (%)	124 (20.8)	16 (20.5)	0.958
Depressive symptoms (MADRS), median (IQR)	8 (3–16)	8 (4–15)	0.593
Maniac symptoms (YMRS), median (IQR)	1 (0–4)	0.5 (0–3)	0.501
Functioning (FAST), median (IQR)	20 (9–34)	18 (11–32)	0.961
Childhood trauma (CTQ), median (IQR)	43 (33–54)	42.5 (33.5–52.5)	0.958
- Emotional abuse, median (IQR)	10 (7–10)	10 (6–14)	0.539
- Physical abuse, median (IQR)	5 (5–7)	5 (5–7)	0.599
- Sexual abuse, median (IQR)	5 (5–8)	5 (5–8.5)	0.845
- Emotional neglect, median (IQR)	13 (9–17)	13 (9–18)	0.524
- Physical neglect, median (IQR)	7 (5–9)	6 (5–8)	0.130
Comorbidities			
Lifetime Anxiety disorders, n (%)	306 (49.6)	49 (55.1)	0.335
Lifetime eating disorders, n (%)	150 (24.0)	17 (20.0)	0.419
Lifetime substance abuse, n (%)	173 (27.4)	17 (20.0)	0.146
Alcohol abuse, n (%)	125 (19.8)	13 (15.3)	0.322
Cannabis abuse, n (%)	63 (10.0)	3 (3.6)	0.069
Other*, n(%)	47 (7.5)	2 (2.3)	0.106
Current daily tobacco smoking, n (%)	246 (38.3)	29 (32.9)	0.330
Sleep disturbances (PSQI), median (IQR)	7 (4–10)	7.5 (5–11)	0.325
BMI, median (IQR)	25 (22–28)	25 (22–28)	0.614
High CRP (>3), n(%)	127 (28.0)	15 (24.2)	0.532
Treatments			
Adherence to medication (MARS score), median (IQR)	7 (6–8)	8 (6–9)	0.274
First Generation Antipsychotics, n (%)	122 (25.2)	20 (27.0)	0.738
	164 (33.9)	18 (24.3)	0.102

(continued on next page)

Table 1 (continued)

	BD women with a postpartum depressive onset		p value
	No (n = 666)	Yes (n = 93)	
	87.8%	12.2%	
Second Generation Antipsychotics, n (%)			
Antidepressants, n (%)	228 (47.1)	34 (45.9)	0.852
Lithium, n (%)	147 (30.4)	22 (29.7)	0.911
Mood stabilizers, n (%)	242 (50.0)	48 (64.9)	0.017
Anxiolytics, n (%)	175 (36.2)	27 (36.5)	0.956
Number of psychotropic medications, median (IQR)	2 (1–3)	2 (2–3)	0.377

In bold, results significant with a $p < 0.05$ (with no correction for multiple testing).

Abbreviations: BD, Bipolar Disorder; BMI, Body Mass Index; CTQ, Childhood trauma questionnaire; FAST, Functioning Assessment Short Test; MADRS, Montgomery Åsberg Depression Rating Scale; MARS, Medication Adherence Rating Scale; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; YMRS, Young Mania Rating Scale.

Other* = sedative, stimulant, opioid, cocaine and hallucinogen abuse.

As shown in Table 2 (which reports the final step in the model BD), women with postpartum onset had significantly more children (OR = 1.38, 95%CI = 1.02–1.86), a lower rate of history of at least one suicide attempt (OR = 0.50, 95%CI = 0.27–0.93) and less lifetime depressive episodes (OR = 0.93, 95%CI = 0.87–0.99) as compared to BD women with a depressive onset outside the postpartum period.

4. Discussion

This study examined the characteristics of parous women who started their BD with a major depressive episode during or outside the postpartum period, in a large French cohort of outpatients. To our knowledge, this is the first study that specifically deals with the “postpartum depressive onset” of BD. Using a large cohort of patients enrolled in the French national FACE-BP network, 12.2% of women started their BD with a major depressive episode in postpartum period. Our main results in multivariate analysis suggest that women starting their BD with postpartum depression have a more favorable course of BD, especially less history of suicide attempts and less lifetime depressive episodes.

Our univariate results indicate that women who started BD with a postpartum depression were more frequently living in couple, had a later age at onset, presented more frequently with a bipolar 2 disorder, had fewer lifetime depressive episodes, and less history of at least one suicide attempt than women for whom BD started in another period.

In our sample, 12.2% of women started their BD with a major depressive episode in postpartum period. This rate is slightly higher than in a combined US and Italian sample, which found that 7.6% of the women had a peripartum onset (Viguera et al., 2011). Our population is comparable for socio-demographic data to samples of women with BD; however Viguera et al. did not include the women with BD NOS whereas we did. In addition, their definition of PP was three months after birth as we used a broader definition up to 6 months postpartum. The prevalence may vary depending on the country, and the clinical profile of the women recruited, and the postpartum onset definition (Tebeka et al.,

Table 2
Multivariable logistic regression analysis using backward selection.

	OR	95% Confidence Limits		p value
Number of lifetime depressive episodes	0.93	0.87	0.99	0.025
Number of children	1.38	1.01	1.86	0.037
Suicide attempt	0.50	0.27	0.93	0.028

Abbreviations: OR, odd ratio.

2018a; Viguera et al., 2011).

Our main results in multivariate analysis indicate that women who started BD with a postpartum depression had more children, less depressive episodes and had less history of suicide attempts than women with depression onset outside postpartum period. Other study showed that women suffering from severe psychiatric disorders have fewer children than women without psychiatric disorders (Power et al., 2013). Combined results of our study suggest that postpartum onset might be a marker of good prognosis among women whose first-episode polarity is depressive. A study of 123 women with BD type I found similar results: a postpartum onset (with a first manic or depressive episode) may predict a more favorable course characterized by a lower recurrence rate (Serretti et al., 2006). We can discuss the hormone dependence hypothesis to explain our results. It can be hypothesized that hormone imbalance during the postpartum period, especially the dysregulation of the allopregnanolone system, may be necessary to trigger BD in some women. Indeed, it has been described that some women are more vulnerable to hormonal fluctuations and present with a better prognosis: women with premenstrual dysphoric syndrome, mood episodes in the postpartum period, or depressions during perimenopause (Freeman, 2010; Graziottin and Serafini, 2009).

In our study, a history of suicide attempt was significantly less common in women who started their disorder with postpartum depression. In the first year of the postpartum period, the incidence of suicide attempts is reported to be less frequent than in some other period of life (Schiff and Grossman, 2006). Furthermore, a long period of untreated BD is associated with an increased risk of suicide (Nery-Fernandes et al., 2012, p.).

Regarding the BD characteristics, in our sample, women with a postpartum onset had a later age at onset and a shorter duration of untreated illness than other, although this result does not remain significant in our multivariable analysis. An early age at onset is known as a factor of poor prognosis for the BD course (Joslyn et al., 2016); it has been associated with a longer duration of untreated illness, a greater number of mood episodes, fewer days with euthymic mood state and a higher suicide risk (Post et al., 2010; Tondo et al., 2016). In the whole sample, age of the first treatment was higher than age of the first mood episode. Our results confirm previous data in the literature concerning the duration of untreated BD, especially when the first episode is of depressive polarity (O'Donovan and Alda, 2020) and begins in postpartum period (Boath et al., 2005; Goodman and Tyer-Viola, 2002). Indeed, after an initial depressive episode, studies found an average of 9 years to convert the diagnosis to BD (Fritz et al., 2017), with a change to BD I in 1% of patients per year and to BD II in about 0.5% of patients per year (Angst et al., 2005). And postpartum depression remains largely underdiagnosed, with less than half of patients being properly diagnosed (Boath et al., 2005; Goodman and Tyer-Viola, 2002). Our study found that a postpartum onset was associated with a shorter duration of untreated illness. A first depressive episode in the postpartum is known to be more likely to change into a BD than a first depressive episode outside the postpartum; in particular, a first depression in the first month after delivery was associated with a 4-times greater risk of change to a BD than a first depression outside the postpartum (Munk-Olsen et al., 2012).

We did not find any significant difference in the family history of BD between women with or without a postpartum depressive onset. Other studies showed that postpartum depression had an increased heritability as compared to depression outside the postpartum period (Bauer et al., 2018; Murphy-Eberenz et al., 2006; Sullivan et al., 2000; Viktorin et al., 2016). Moreover, some studies found clinical markers of familial BD in episodes of psychosis and/or mania in the postpartum period (Jones et al., 2007; Jones and Craddock, 2007). In our sample, we only considered women with a depressive onset, excluding manic and/or psychotic onset, which may explain our negative results on family history of BD.

Treatment is crucial in the course of BD. In our sample, women with a postpartum depressive onset received more mood stabilizers than others

although this difference was not statistically significant in the multivariable analysis. The main hypothesis to explain this result is the more frequent use of lamotrigine in these patients, who mainly suffer from BD II with a depressive onset. Clinicians may also more easily prescribe anticonvulsants such as Valproate or Carbamazepine to women who already had children. There was no difference for the other medications classes between the two groups, including for antidepressants. Adherence to treatment was good in both groups, without significant difference.

The main limitation of the study is the retrospective clinical assessment of postpartum onsets. Prospective studies over several years would overcome the possible memorization bias. Another limitation is that women from the FACE-BD cohort might be not strictly representative of women with BD. Indeed, in general, patients referred to FACE-BD expert centers have a better access to healthcare and a better educational level than other patients with BD. Third, we were unable to assess the impact of BD onset with postpartum depression in women who suffered from postpartum depression throughout their BD because this information was missing. Other studies need to explore this question. Despite these three points, our findings are based on a large, multicentric and homogenous sample of women with BD who had at least one child. In addition, all psychiatric disorders' diagnoses are based on a rigorous clinical assessment using DSM-IV-TR-based criteria, and the assessment of clinical characteristics of BD was thorough.

In our population of women whose bipolar disorder is characterized by a depressive onset, about one in 8 presented with a first episode during the postpartum period. This subgroup of women has a more favorable course of BD, especially less history of at least one suicide attempt and less lifetime depressive episodes. This may reflect that women diagnosed with a BD that began during the postpartum period represent a phenotypically homogenous subgroup, with specific characteristics.

However, given the risk of postpartum depression in women with BD, it is crucial to promote the early diagnosis of BD among pregnant women, in order to offer prevention and specific care as soon as possible. In this context, primary and secondary prevention strategies have recently been proposed to prevent and attenuate the clinical and neurocognitive consequences of BD (Sharma et al., 2019).

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Data availability statement

The data that support the findings of this study are available from FondaMental foundation. Restrictions apply to the availability of these data, which were used under license for this study.

Ethical statement

The assessment protocol, including a letter of information for patients, was approved by the institutional review board (CPP-Ile de France IX, January 18th, 2010), in accordance with French laws for non-interventional studies. Anonymized data are stored in a national database that was approved by the French body overseeing the safety of computerized databases (Commission Nationale de l'Informatique et des Libertés, DR-2011-069).

Declaration of Competing Interest

None of the authors have conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pnpbp.2020.110225>.

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Discussion

I. Résultats principaux

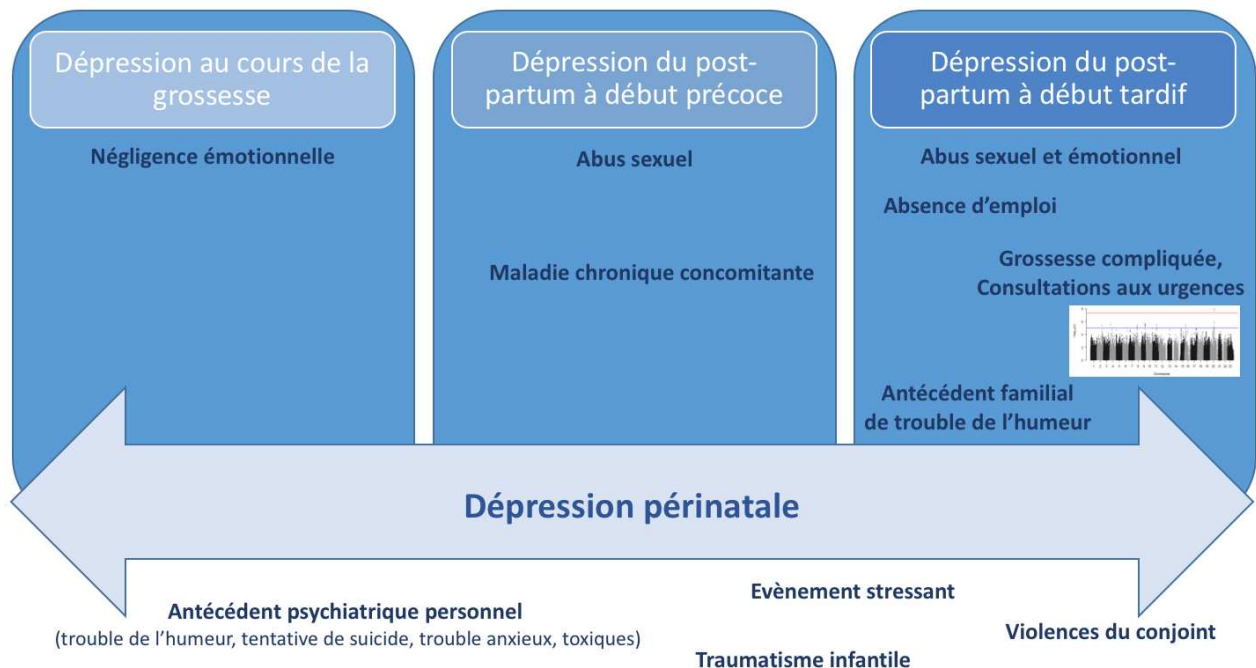
La dépression périnatale est un trouble fréquent en périnatalité. Dans nos travaux, nous avons retrouvé une prévalence de la dépression périnatale à 10,8 % sur une population représentative des femmes américaines. Sur notre cohorte française IGEDEPP, la prévalence de la dépression post-partum à début précoce était à 8,3 % et à 12,9 % pour la dépression du post-partum à début tardif. Ces résultats sont plus précis mais cohérents avec différentes autres études internationales, évaluant la prévalence de la dépression périnatale et du post-partum entre 10 et 20 % au cours de la première année post-partum (L. M. Howard, Molyneaux, et al. 2014; Ko et al. 2012; Shorey et al. 2018; Norhayati et al. 2015). Dans ces deux cohortes, nous avons utilisé un diagnostic basé sur une évaluation clinique avec les critères internationaux de l'épisode dépressif majeur, tandis que la plupart des études reposent uniquement sur un questionnaire de dépistage, par essence moins spécifique, et pouvant induire un biais de mesure.

Par ailleurs, l'étude IGEDEPP nous a permis d'évaluer, l'incidence cumulée de la dépression du post-partum qui était de 18,1 % sur un an. Comme nous l'avons discuté en introduction, très peu d'étude se sont intéressées à l'incidence. Notre étude, de par son design prospectif, permet d'une part plusieurs évaluations de la prévalence de la dépression à différents temps de la période périnatale, mais également un calcul de son incidence mesurant ainsi le risque pour une femme de développer le trouble à un an ; et considérant la vitesse d'apparition de la maladie au cours de cette année.

Nos travaux sur la dépression périnatale ont été menés avec deux axes parallèles : d'une part l'évaluation de déterminants de la dépression périnatale allant de la petite enfance jusqu'à la grossesse ; d'autre part la mise en évidence de différents facteurs distinguant la dépression du post-partum à début précoce apparaissant dans les premières semaines suivant l'accouchement, de la dépression du post-partum à début tardif débutant après le 2^{ème} mois post-partum. Ces deux aspects de notre travail retrouvent certains facteurs consensuels. Ainsi, quelles que soient les modalités d'évaluation, la dépression périnatale ou du post-partum était associée à des traumatismes dans l'enfance et à des événements de vie stressants

survenant pendant la grossesse et l'accouchement mais également aux antécédents psychiatriques, qu'ils soient personnels ou familiaux.

Figure 15 : Modèle explicatif de la dépression périnatale à partir des travaux originaux présentés



De façon intéressante et originale, nous avons également établi des différences de profil de patientes présentant une dépression du post-partum en fonction du moment du début des troubles, tant sur des corrélats psycho-sociaux, que cliniques et génétiques. Ainsi, la dépression du post-partum à début précoce était indépendamment associée à des antécédents personnels de dépression, d'abus sexuels pendant l'enfance, d'événements de vie stressants pendant la grossesse et de maladies physiques chroniques concomitantes. L'analyse pangénomique ne retrouvait pas de région statistiquement associée à ce phénotype. La dépression du post-partum à début tardif était, elle, indépendamment associée aux abus émotionnels pendant l'enfance, aux événements stressants de la vie pendant la grossesse, au chômage, aux antécédents personnels et familiaux de trouble de l'humeur et aux consultations d'urgence pendant la grossesse. L'analyse génétique renforce également l'idée que les phénotypes « début précoce » et « début tardif » peuvent être distingués, avec une

région du chromosome 20 spécifiquement associé à la dépression du post-partum à début tardif.

Nos travaux se sont particulièrement intéressés aux liens entre traumatismes infantiles et dépression périnatale. Ainsi, le travail en population américaine portant sur la NESARC avait retrouvé une association entre avoir été victime d'un abus sexuel dans l'enfance et dépression périnatale. De même, nous avons montré dans IGEDDEPP le poids des traumatismes infantiles sur la dépression périnatale. Dans un travail spécifique dans de la cohorte française IGEDDEPP, nous avons détaillé le poids de chaque type de traumatismes infantiles en fonction du moment du début de la dépression périnatale. Ainsi, quel que soit le type de traumatisme infantile (abus sexuel, physique ou émotionnel ou négligence physique ou émotionnelle), on retrouvait une association avec la dépression périnatale débutant pendant la grossesse, dans le post-partum précoce ou dans le post-partum tardif. Ces résultats persistaient, après ajustement sur les variables sociodémographiques et les antécédents de dépression. Ces résultats suggèrent que les traumatismes infantiles sont spécifiquement associés à la dépression périnatale, et pas uniquement aux épisodes dépressifs à l'âge adulte. De façon plus spécifique, la négligence émotionnelle est associée à la dépression pendant la grossesse, les abus sexuels étaient associés à la dépression du post-partum, tandis que les abus émotionnels étaient associés à la dépression du post-partum à début tardif. L'association de la négligence émotionnelle avec la dépression pendant la grossesse a été confirmée par d'autres (Lang, Rodgers, et Lebeck 2006; Blalock et al. 2011). D'autres études ont trouvé des associations entre les abus sexuels et physiques et la dépression pendant la grossesse (Robertson-Blackmore et al. 2013; Benedict et al. 1999; Chung et al. 2008), alors que cette association n'était pas significative dans l'IGEDDEPP. Nos résultats pourraient être dû au profil spécifique des participantes à l'IGEDDEPP et à la faible prévalence du traumatisme infantile, le revenu élevé et l'éducation élevée caractérisant notre cohorte, étant négativement associés aux abus sexuels et physiques. Les abus sexuels étaient associés à la fois à la dépression post-partum à début précoce et tardif, tandis que les abus émotionnels étaient spécifiquement associés à la dépression post-partum à début tardif. Dennis et al. ont également trouvé une association entre les abus sexuels et la dépression post-partum précoce (Dennis et Vigod 2013), tandis que d'autres n'ont pas trouvé cette association avec la dépression post-partum précoce et tardive (Robertson-Blackmore et al. 2013). La dépression post-partum à début précoce était également associée aux abus émotionnels dans un échantillon de femmes australiennes à

faible revenu (Edwards et al. 2008). Ces comparaisons avec les données de la littérature doivent être considérées avec prudence, car le traumatisme infantile est souvent évalué comme une dimension unique, ou se limite aux abus sexuels ou physiques, les abus émotionnels et la négligence étant moins souvent évalués. De plus, la majorité des études ont été menées sur de petits échantillons, dans des populations cliniques, principalement en utilisant un auto-questionnaire pour définir la dépression plutôt que les critères diagnostiques internationaux.

Nous avons également observé une relation de type « effet-dose » du nombre de types de traumatismes infantiles sur le risque de dépression périnatale. Ceci est conforme aux études précédentes qui ont trouvé une association entre le nombre de type de traumatisme sur la dépression pendant la grossesse (Robertson-Blackmore et al. 2013) et la dépression post-partum à 6 mois (Grote et al. 2012).

De façon plus générale, les événements de vie stressants pendant la grossesse ont été indépendamment associés à la dépression périnatale dans notre étude en population américaine, et la dépression du post-partum, que son début soit précoce ou tardif, dans notre étude en population française. Ces résultats sont en accord avec les résultats de la littérature (L. M. Howard, Molyneaux, et al. 2014; O'Hara et McCabe 2013). Cependant, notre travail sur IGDEPP révèle que la majorité des femmes vit de tels événements de vie stressants et la plupart ne développe pas de dépression périnatale. Dans notre travail, nous avons pris en compte l'expérience subjective de la femme pour chaque événement stressant et considéré le stress perçu de chaque événement. Il est important de noter que les événements stressants survenant pendant la grossesse influencent le risque de dépression plusieurs mois plus tard, et pas seulement comme une réaction immédiate. Nous avons également révélé un effet cumulatif de ces événements stressants perçus. En effet, il a été démontré qu'un effet cumulatif des événements stressants de la vie au cours de l'année précédant la grossesse avait un impact sur la dépression pendant la grossesse (Rubertsson et al. 2005), mais à notre connaissance, il n'avait pas été testé sur la dépression du post-partum.

L'étude de la NESARC soulignait également l'association spécifique entre deuil en période périnatale, les violences physiques de la part du conjoint et la dépression périnatale.

En ce qui concerne les facteurs obstétricaux avant la grossesse, la NESARC retrouvait une association entre complications au cours de la grossesse et dépression périnatale. La cohorte IGEDEPP a permis une évaluation fine de ces complications avec des résultats plus précis. Seule une maladie physique chronique concomitante était indépendamment associée à une dépression du post-partum à début précoce. L'infertilité et la technologie de procréation assistée n'étaient pas associées à la dépression du post-partum, confirmant des découvertes récentes (Amirchaghmaghi et al. 2020; Furmli et al. 2019). Pendant la grossesse, nous avons souligné que la consultation aux urgences est un facteur important indépendamment associé à une dépression du post-partum à début tardive. Une étude australienne a trouvé des résultats cohérents, avec plus de visites aux urgences pendant la grossesse chez les femmes nécessitant une hospitalisation pour dépression du post-partum (Xu et al. 2017). Dans notre étude, les traumatismes périnéaux et la césarienne n'étaient pas associés à la dépression du post-partum. Les données sur cette thématique sont contrastées. Alors que Dunn et al. ont trouvé une association entre le traumatisme périnéal et la dépression du post-partum à 6 semaines et 3 mois post-partum (Dunn et al. 2015), une étude récente n'a pas trouvé d'association significative (Asif et al. 2020). Dans cette dernière étude, l'association entre un traumatisme périnéal sévère et une dépression du post-partum à début précoce est devenue significative dans le groupe de femmes présentant une faible résilience (Asif et al. 2020). La résilience, considérée comme un modérateur à la fois de la douleur et de la dépression, pourrait moduler le lien entre traumatisme et dépression du post-partum (Southwick et al. 2014). Les données sur la césarienne sont également contradictoires, certaines données suggérant que la césarienne en urgence était spécifiquement associée à la dépression du post-partum (Räisänen et al. 2013; Bahadoran, Oreizi, et Safari 2014; Guintivano et al. 2018).

Nos travaux confirment l'importance des antécédents psychiatriques, personnels comme familiaux dans le risque de développer une dépression en période périnatale. La NESARC retrouvait en particulier, l'association entre un premier épisode dépressif au cours de l'adolescence et la dépression périnatale. Il est établi qu'une entrée précoce dans un trouble unipolaire signe la sévérité de la pathologie – avec un risque de récurrence à l'âge adulte important (Pelkonen et al. 2008). Globalement, le facteur prédictif principal retrouvé dans nos travaux est l'existence d'un antécédent personnel de pathologie psychiatrique, quelle qu'elle soit – ce qui est conforme à la littérature (Räisänen et al. 2013). Ainsi, dans notre étude en

population américaine, un antécédent de dépression au cours de la vie était le facteur de risque le plus important avec un OR ajusté dépassant 4. Notre étude sur la cohorte française IGEDEPP retenait également un antécédent personnel de dépression dans le modèle final pour la dépression du post-partum, que son début soit précoce ou tardif. Ces résultats sont conformes aux données publiées précédemment (L. M. Howard, Molyneaux, et al. 2014; Tebeka, Le Strat, et Dubertret 2016; Rich-Edwards et al. 2006). Ceci peut s'expliquer en partie par une vulnérabilité préexistante, mais également par l'arrêt fréquent des traitements au cours de la grossesse et du post-partum ce qui augmente le risque de rechute dépressive (Bennett et al. 2004).

Un antécédent de trouble anxieux était associé à un risque de dépression périnatale multiplié par plus de 3 en population américaine. Des travaux antérieurs retrouvent cette association (Guintivano et al. 2017; Dindo et al. 2017; Le Strat, Dubertret, et Le Foll 2011). Notre étude en population française trouvait elle que les antécédents de trouble anxieux étaient également associés à une dépression du post-partum, quel qu'en soit le début précoce ou tardif, après ajustement sur les données sociodémographiques, bien que le modèle final ne l'ait pas retenu. Une explication est la possible colinéarité existant entre les troubles anxieux et les épisodes dépressifs majeurs, très souvent comorbides (Huang et al. 2019; Moscati, Flint, et Kendler 2016).

Les tentatives de suicide étaient également fortement associées à la dépression périnatale en population américaine. Là encore, ce paramètre était également associé à la dépression du post-partum à début précoce ou tardif, après ajustement sur les données sociodémographiques dans IGEDEPP, sans que le modèle final n'ait retenu les antécédents de tentative de suicide. Le manque de puissance pourrait expliquer ce résultat (les antécédents de tentative de suicide concernaient 14 femmes avec PPD précoce, 13 avec PPD tardive, et 44 témoins).

Sur la population américaine, le fait d'avoir un antécédent familial au premier degré de dépression était associé à un risque près de 5 fois plus important de dépression périnatale. Dans la cohorte IGEDEPP, les femmes présentant une dépression du post-partum, de début précoce ou tardif déclaraient davantage d'antécédents familiaux de trouble de l'humeur que les contrôles (53 % et 60 % contre 47 % respectivement), avec une différence significative après ajustement sur les données sociodémographiques. Notre modèle final a retenu les antécédents familiaux de troubles de l'humeur uniquement pour la dépression du post-

partum à début tardif, suggérant un effet moindre des antécédents familiaux sur la dépression du post-partum à début précoce. Une étude récente basée sur des registres danois a révélé que les antécédents psychiatriques parentaux de dépression, de trouble bipolaire ou de schizophrénie étaient associés à des troubles psychiatriques post-partum, en particulier chez les femmes ayant des antécédents psychiatriques personnels (Bauer et al. 2019). Ces résultats sont renforcés par l'analyse pangénomique qui identifie une région du chromosomes 20 spécifiquement associée à la dépression du post-partum à début tardif ; soulignant le poids génétique dans l'apparition de ce phénotype.

Pour les femmes ayant des antécédents psychiatriques, la période post-partum semble donc être une période de vulnérabilité à la dépression, ce qui suggère que des facteurs génétiques peuvent jouer un rôle dans le développement de la dépression en période périnatale.

Nous avons également étudié la dépression du post-partum comme mode d'entrée dans le trouble bipolaire. Tout d'abord, nous confirmons les données préexistantes sur la fréquence de ce début dans la maladie puisqu'elle concernait près d'une patiente ayant débuté leur trouble bipolaire par une dépression sur 8 (12,2 % parmi les femmes débutant un trouble bipolaire par un épisode dépressif caractérisé). Une autre étude associant une population américaine et italienne retrouvait une fréquence de début dans les 3 mois post-partum de 7,6 % (Viguera et al. 2011).

De façon intéressante, nos résultats montrent que ce sous-groupe de patientes à début en post-partum présente moins d'épisodes dépressifs, et moins de tentative de suicide au cours de leur vie. Une étude de 123 femmes atteintes de trouble bipolaire de type I a trouvé des résultats similaires : un début des troubles dans le post-partum, quel qu'en soit la polarité, semble prédire une évolution plus favorable, en particulier marquée par un taux de récurrence plus faible (Serretti, Olgiati, et Colombo 2006). Il a été par ailleurs décrit que les femmes plus vulnérables aux fluctuations hormonales, présentant un syndrome dysphorique prémenstruel, des épisodes d'humeur en période périnatale ou des dépressions lors de la péri-ménopause, présentent un meilleur pronostic (Graziottin et Serafini 2009; E. W. Freeman 2010).

Ainsi, il semble que débuter un trouble de l'humeur bipolaire par une dépression du post-partum est associé à des marqueurs de bon pronostic. D'autres études prospectives restent nécessaires pour confirmer ces données.

Les données de la littérature convergent vers un taux de fécondité moins important chez les patientes souffrant d'un trouble bipolaire, par rapport à la population générale (Power et al. 2013; Grover, Nehra, et Thakur 2017; Tondo, Lepri, et Baldessarini 2011; Mansour et al. 2011). De façon intéressante, cette différence restait significative après ajustement sur le statut marital ($p=0,001$) (Mansour et al. 2011). Ainsi, plusieurs études retrouvent un continuum de sévérité : les femmes souffrant de trouble bipolaire de type I avaient un taux de fécondité inférieur aux femmes souffrant de trouble bipolaire de type II, elles même ayant plutôt moins d'enfants que les femmes présentant un trouble dépressif caractérisé (Power et al. 2013; Grover, Nehra, et Thakur 2017; Tondo, Lepri, et Baldessarini 2011). En revanche, les marqueurs de sévérité du trouble, tels que le nombre d'épisodes, les hospitalisations, les tentatives de suicide ou la prévalence de comorbidités psychiatriques et addictologies, ne sont pas associés au taux de fécondité (Tondo, Lepri, et Baldessarini 2011). Plusieurs freins peuvent expliquer ce moindre taux de fécondité. Tout d'abord, l'inquiétude des patientes face au risque de décompensation au cours de cette période périnatale, au risque de tératogénicité mais également au risque de transmission génétique de la maladie (Dolman, Jones, et Howard 2016; Anke et al. 2019; Stevens et al. 2018; Pope, Sharma, et Mazmanian 2014). Par ailleurs, l'accès à une information précise pour éclairer la prise de décision d'avoir un enfant est souvent insuffisant : les professionnels sont décrits comme n'ayant pas toujours les connaissances spécialisées nécessaires pour répondre aux questions de manière adéquate (Dolman, Jones, et Howard 2016; Megnin-Viggars et al. 2015). De plus, plusieurs études mettent en avant une stigmatisation vis-à-vis des femmes souffrant de trouble psychiatriques, et en particulier de trouble bipolaire en période périnatale (Dolman, Jones, et Howard 2016; 2013). Une étude qualitative a mis en évidence 3 niveaux de stigmatisation : de la part de l'entourage qui s'inquiète du projet de grossesse, de la part de la société via les médias entre autres, enfin de la part des professionnels de santé qui peuvent avoir des attitudes perçues par les patientes comme discriminatoires (Dolman, Jones, et Howard 2016).

Nos travaux concernant l'impact de la parité sur l'évolution du trouble bipolaire permettent de répondre à certaines inquiétudes et de limiter la stigmatisation. Les résultats sont rassurants. En effet, bien qu'avoir deux enfants ou plus est associé au trouble bipolaire de type I et à un risque accru d'épisodes hypomaniaque dans le suivi à 3 ans, le trouble bipolaire ne semble pas pour autant plus sévère : en particulier, il n'y a pas plus d'épisodes dépressif ou maniaque, d'hospitalisation ou de risque suicidaire. De plus, nous avons montré que ces

femmes recevaient davantage de traitement thymorégulateur que les celles n'ayant pas d'enfant.

En revanche, près d'un tiers des femmes de l'échantillon américain de la NESARC souffrant de trouble bipolaire n'était pas traité pour cette maladie. Or, le trouble bipolaire est une maladie sévère, en particulier chez les femmes qui, à chaque évènement en lien avec le cycle de reproduction, qu'il s'agisse de la période prémenstruel, de la grossesse ou de la ménopause, sont à risque de présenter des symptômes thymiques, voir des épisodes caractérisés (Perich et al. 2017; Slyepchenko et al. 2017; Truong et Marsh 2019; Perich et al. 2021). Il est donc indispensable de mieux repérer, suivre, orienter ces femmes afin qu'elles puissent bénéficier d'un traitement adapté.

II. Forces et limites

Nos travaux reposent sur trois cohortes importantes. A notre connaissance, IGEDEPP est la plus grande cohorte européenne prospective multicentrique de 3310 femmes enceintes suivies pendant 1 an pour déterminer la prévalence et l'incidence de la dépression post-partum, distinguant un début précoce d'un début tardif. Très peu de participants ont été perdus de vue au cours de l'étude. Nous avons 91 % de données disponibles à 8 semaines d'évaluation post-partum, et 71 % à 1 an, augmentant la validité externe de ces résultats. Cependant, comme nous n'avons pas de données sur ceux qui refusent de participer à cette cohorte, nous ne pouvons pas éviter un biais d'inclusion des sujets atteints de dépression du post-partum qui pourrait modifier nos résultats. Les différents temps d'évaluation à la maternité, à 8 semaines puis à 1 an post-partum permettent de distinguer la dépression périnatale en fonction du moment de survenue du trouble.

La NESARC est un large échantillon de plus de 1000 femmes, en période périnatale, représentatif de la population américaine. A notre connaissance, il représente la plus grande base de données représentatives des femmes enceintes et dans le post-partum aux États-Unis. Les travaux portant sur IGEDEPP et la NESARC nous ont permis de comparer les femmes présentant une dépression périnatale à des femmes également non déprimées en période périnatale. La majorité des études utilisent des femmes en population générale ou des femmes en âge de procréer – ce qui peut mésestimer les risques associés à la période périnatale (L. M. Howard, Molyneaux, et al. 2014). La cohorte FACE-BD est une large étude, multicentrique et homogène comprenant 1912 femmes atteintes de trouble bipolaire qui ont

eu au moins un enfant. Pour les trois cohortes, les diagnostics psychiatriques posés reposent sur des évaluations cliniques, basés sur les critères internationaux du DSM. Comme nous l'avons vu, cela limite les biais, et permet le diagnostic le plus fiable. De plus, les évaluations psychiatriques permettaient d'avoir une vue d'ensemble des troubles psychiatriques au cours de la vie, y compris les troubles de l'humeur, les troubles anxieux, les troubles liés à l'usage de substance et les tentatives de suicide, avec une caractérisation phénotypique importante. Enfin, IGEDEPP et la NESARC fournissent une évaluation approfondie d'un large éventail de déterminants, comprenant les caractéristiques sociodémographiques, les antécédents personnels et familiaux de troubles psychiatriques, les traumatismes dans l'enfance, ainsi que les événements stressants de la vie pendant la grossesse et le post-partum, qu'ils soient liés ou non à la grossesse. Cela permettait de retracer le parcours de vie des femmes.

Certaines limites doivent être prises en compte dans l'interprétation de ces résultats. Bien que nous travaillions sur des cohortes importantes, notre pouvoir de détection de différence dans la prévalence d'événements rares est limité. Ce manque de puissance statistique explique peut-être certains des résultats – parfois en contradiction avec la littérature.

De plus, le design de nos études ne permet pas de conclure à des liens de causalité. Nous évoquons uniquement des associations.

Enfin, les deux cohortes françaises, IGEDEPP et FACE-BD, ne sont pas représentatives de la population générale ; ce qui limite la généralisation de nos résultats. Ainsi, les participantes à l'étude IGEDEPP ont rapporté des niveaux d'étude plus élevés que dans la population générale (INSEE 2018), un constat qui a également été associé à la participation à la recherche génétique (Hensley Alford et al. 2011; McQuillan et al. 2003). Les huit centres de recrutement étaient à Paris ou en proche banlieue parisienne. De plus, conformément à la conception de l'étude IGEDEPP qui comprend une composante génétique, l'échantillon est composé uniquement de femmes caucasiennes. Notre étude n'a pas inclus les femmes françaises d'origine non caucasienne ou les femmes migrantes. Or, la migration est un facteur de risque connu de dépression post-partum (Ahmed et al. 2008; Falah-Hassani et al. 2015), nous avons peut-être sous-estimé la prévalence de dépression du post-partum dans la population française générale et perdu des informations sur les facteurs de risque dans ce sous-groupe vulnérable. Concernant les patientes incluses dans FACE-BD, il s'agit de femmes ayant un meilleur accès aux soins et un meilleur niveau d'éducation.

III. Perspectives

III.A. Améliorer les connaissances sur la dépression périnatale

Bien que la dépression périnatale soit largement étudiée depuis 20 ans, elle reste largement sous-diagnostiquée et sous-traitée (Vesga-López et al. 2008), ce qui suggère l'importance d'une compréhension globale de la dépression périnatale.

III.A.1. Par une caractérisation phénotypique de la dépression périnatale

Une caractérisation précise du phénotype, tant sur les types de symptômes présentés, que sur leur date d'apparition est nécessaire. Un travail préliminaire sur la cohorte IGEDEPP a ainsi révélé des différences significatives portant sur le type de symptômes dépressifs recueillis pour le diagnostic DSM-5 présentées par les patientes selon qu'elles présentent une dépression du post-partum à début précoce ou à début tardif. Ainsi les femmes souffrant précocement d'une dépression du post-partum vont présenter davantage de modifications de poids, un retentissement psychomoteur plus important et une asthénie ou une perte d'énergie plus importante que les femmes présentant un épisode dépressif à début tardif (cf. tableau 3). Ces résultats méritent d'être publiés et d'autres travaux permettant une description phénotypique la plus précise possible des différentes formes de dépression périnatale seront nécessaires à partir d'autres cohortes.

Tableau 3 : Analyse phénotypique des dépressions du post-partum, selon le moment d'apparition du trouble, à partir de la cohorte IGEDEPP.

Critères DSM	Dépression du post-partum à début précoce	Dépression du post-partum à début tardif	p
	N (%) (N=250)	N (%) (N=235)	
Humeur dépressive	222 (88.8)	220 (93.6)	0.088
Diminution de l'intérêt ou du plaisir	203 (81.2)	190 (80.9)	1
Perte ou gain de poids	140 (56.0)	106 (45.1)	0.021
Insomnie ou hypersomnie	143 (57.2)	141 (60.0)	0.59
Agitation ou ralentissement psychomoteur	207 (82.8)	174 (74.0)	0.025
Fatigue ou perte d'énergie	244 (97.6)	214 (91.1)	0.0033
Dévalorisation ou culpabilité excessive	182 (72.8)	155 (66.0)	0.12
Trouble de la concentration	189 (75.6)	163 (69.4)	0.15
Pensée de mort	18 (7.2)	29 (12.3)	0.079

III.A.2. Par une meilleure compréhension des données génétiques

Nos résultats sur les données génétiques relèvent une piste intéressante. Au sein de la région du chromosome 20 associée à la dépression du post-partum à début tardif, le génotypage de deux des 10 SNPs significatifs au seuil de 5×10^{-8} est en cours au Centre National de Recherche en Génomique Humaine. Cela nous permettra de confirmer nos résultats issus de l'imputation. En cas de confirmation de nos résultats issus de l'imputation, il faudra évaluer s'il existe des éléments de régulation dans cette région afin de comprendre le rôle physiopathologique de cette région.

Par ailleurs, une cohorte de réplication est en cours de constitution dans trois maternités d'île de France : Saint Joseph, Port Royal et Louis Mourier. Dans le cadre de l'ANR RA-COVID 19, le projet PsyCOVIDUM a été financé afin d'inclure 2180 femmes afin d'estimer la prévalence des manifestations dépressives périnatale en contexte de pandémie COVID-19. Une étude ancillaire permet de recueillir l'ADN des femmes qui ont donné leur accord. Cela nous permettra d'avoir une deuxième cohorte française afin de répliquer nos résultats.

De plus, notre cohorte IGEDEPP est incluse dans une méta-analyse portant sur les données génétiques de la dépression du post-partum, coordonnée par le Dr Jerry Guintivano et l'équipe du Pr Patrick Sullivan, fondateur du Psychiatric Genomics Consortium. A ce jour, aucun GWAS n'a été publié spécifiquement sur la dépression périnatale, mais plusieurs GWAS sur la dépression renseignent le caractère périnatal de celle-ci, permettant de reconstruire le phénotype « dépression périnatale ». Ces futurs résultats de méta-analyse permettront d'avoir une puissance plus importante, révélant possiblement d'autres régions.

III.A.3. Par une évaluation de l'interaction gène-environnement dans la dépression périnatale

La cohorte IGEDEPP permet par son design une étude d'interaction gène-environnement : avec à la fois une évaluation génétique pangénomique, mais également de nombreux facteurs environnementaux évalués. Ainsi, l'analyse d'interaction gène-environnement va permettre d'évaluer si l'impact de certains polymorphismes associés au risque de dépression du post-partum est augmenté en présence de facteurs environnementaux de stress. Cette analyse permettrait d'améliorer la prévention ou la détection et la prise en charge des dépressions du post-partum.

III.B. Améliorer le dépistage de la dépression périnatale

La prévention et l'identification précoce sont des stratégies indispensables pour limiter l'incidence et les conséquences des troubles de l'humeur en période périnatale (Pereira et al. 2014; Milgrom et Gemmill 2014). Actuellement, la dépression périnatale est encore largement sous-diagnostiquée, moins de la moitié des patients étant diagnostiqués en partie à cause de symptômes atypiques, de la réticence des patients à demander de l'aide, et aussi en raison du manque de dépistage systématique de cette maladie en post-partum (Boath, Bradley, et Henshaw 2005; Goodman et Tyer-Viola 2010). La période périnatale est une période d'intervention privilégiée du fait des nombreux contacts avec les services de santé pour la plupart des femmes. Ainsi, les programmes de dépistage de la dépression périnatale peuvent avoir une place centrale, reposant sur des professionnels formés et des outils appropriés (Pereira et al. 2014; Milgrom et Gemmill 2014).

Pourtant, une méta-analyse montre que le dépistage de la dépression en population générale permet une réduction significative du risque de dépression persistante (risque relatif 0,87 ; IC à 95 % 0,79 à 0,95), par rapport aux soins usuels (Pignone et al. 2002). Sur cette base, le US Preventive Services Task Force (USPSTF) a recommandé un dépistage systématique de la dépression chez les adultes lorsque des dispositifs de soins sont disponibles (U.S. Preventive Services Task Force 2009). Depuis, ces recommandations ont été mises à jour, incluant la pertinence du dépistage systématique pour les femmes dans un contexte de périnatalité (Siu et al. 2016). Cependant, la faisabilité de ce dépistage en période périnatale n'est pas encore entièrement connue (Milgrom et Gemmill 2014; The Lancet - Editorial 2016).

En France, le premier contact avec les sages-femmes ou obstétriciennes pendant la grossesse se situe classiquement vers le 4ème mois de grossesse. La Haute Autorité de Santé (HAS) recommande l'évaluation des facteurs de risque de dépression lors de cette première consultation depuis 2005 (HAS 2005). L'entretien prénatal précoce fait donc parti du parcours de soins et s'adresse à tous les futurs parents. En revanche, seules 29 % des mères en bénéficient réellement, probablement en raison de l'évaluation de la dépression, pouvant être considérée comme difficile et chronophage (Blondel et al. 2017; French Ministry of Solidarities and Health 2017). La loi n° 2019-1446 du 24 décembre 2019 de financement de la sécurité sociale rend l'entretien prénatal précoce obligatoire depuis le mois de mai 2020 (Assemblée Nationale 2019).

Dans ce contexte, les recommandations nationale et internationale préconisent d'utiliser un outil de dépistage tel que l'EPDS. Il est recommandé par la directive NICE et l'Autorité nationale de la santé des femmes en contexte périnatale (Haute Autorité de Santé 2005; L. M. Howard, Megnin-Viggars, et al. 2014; Eastwood et al. 2017). Un score seuil de 10 ou plus est recommandé pour dépister les femmes qui pourraient être en détresse et potentiellement à risque de dépression (Chaudron et al. 2010; Littlewood et al. 2018; Eastwood et al. 2017). Il a été montré que la prise de conscience des symptômes dépressifs d'une femme enceinte par l'équipe soignante (sages-femmes ou obstétriciens) permet un soutien plus efficace et une amélioration (Wickberg, Tjus, et Hwang 2005). De plus, l'acceptabilité de l'EPDS pour la femme et pour les praticiens qui conduisent l'évaluation est bonne (Littlewood et al. 2018; Buist 1997).

III.B.1. L'étude PREVIDEPP (PREvention de la DEpression Perinatale)

Dans ce contexte, nous avons obtenu un financement dans le cadre des Programmes Hospitaliers de Recherche Clinique (PHRC) Nationaux 2019 afin de mettre en place une étude permettant d'évaluer l'impact d'un dépistage systématique de la dépression par EPDS lors d'une consultation précoce en comparaison avec les pratiques habituelles, sur le risque de dépression périnatale. Il s'agit d'un essai clinique, prospectif, en aveugle, randomisé par cluster. Notre hypothèse est que l'identification précoce de la vulnérabilité / dépression chez les femmes enceintes permettrait à l'équipe clinique d'offrir des soins psychologiques et psychosociaux adéquats pendant la grossesse, réduisant ainsi la survenue ou la persistance d'une dépression périnatale chez ces femmes.

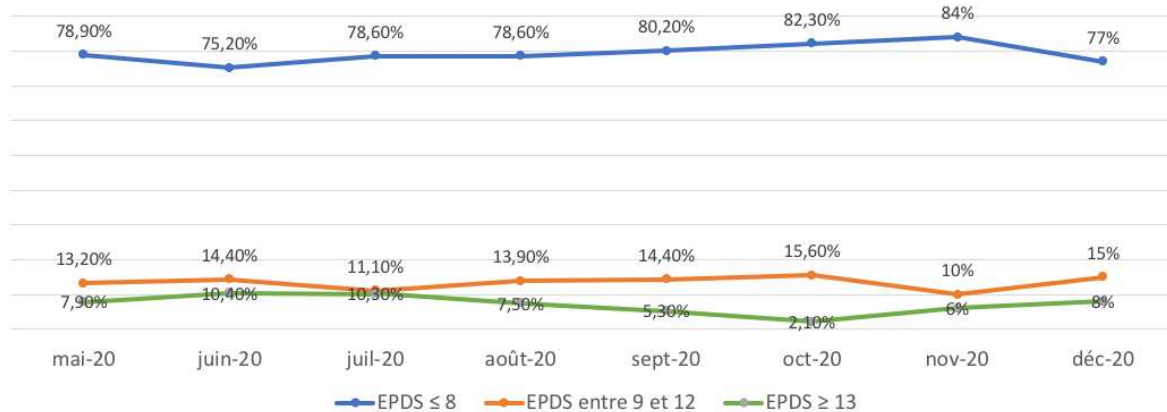
III.B.2. Soins courants à la maternité de l'hôpital Louis Mourier

Parallèlement à cette étude, nous avons mis en place dans la maternité de l'hôpital Louis Mourier, APHP, Colombes, un dépistage systématique de la dépression périnatale en suite de couche depuis le 2 mai 2020. L'EPDS a été validé dans ce contexte de post-partum immédiat (Jardri et al. 2006). Le questionnaire, remis par les sages-femmes entre J0 et la sortie permet d'une part une évaluation systématique par l'EPDS, et d'autre part une information systématique des patientes sur les symptômes et les signes d'appel d'une dépression. Les sages-femmes ont ensuite un protocole de soins : en fonction du score obtenu elles peuvent proposer une simple information des femmes, une consultation avec un psychologue de la

maternité ou encore un entretien psychiatrique qui pourront avoir lieu avant la sortie de la patiente en cas de signes cliniques ou après la sortie (cf. protocole en annexe 2, p. 130).

En 8 mois (début mai à fin décembre 2020), 2271 femmes ont accouché à la maternité de l'hôpital Louis Mourier, dont 79,7 % (N=1811) ont bénéficié de ce dépistage. Parmi elles, 7,0 % ont eu un score EPDS supérieur à 12 (N=128), soit en faveur d'un épisode dépressif et 13,4 % un score EPDS entre 9 et 12 soit à risque (N=242), de façon stable au cours des 10 derniers mois (cf. figure 16). Les premières analyses effectuées comparant les patientes ayant un score supérieur ou égal à 9 (soit à risque de dépression périnatales) aux femmes ayant un score inférieur à 9 retrouvaient des facteurs connus : ainsi le fait d'être primipare, d'avoir des antécédents personnels psychiatriques, d'avoir eu une grossesse compliquée ou un accouchement prématuré ou encore une souffrance néonatale nécessitant une hospitalisation étaient des facteurs significativement plus fréquents chez les femmes à risque de dépression du post-partum. Il s'agit de résultats préliminaires qui devront être ajustés par la suite et mis en valeur par une publication.

Figure 16 : Évolution des scores EPDS à la maternité de Louis Mourier, chez des femmes en post-partum immédiat.



III.B.3. Formations des équipes soignantes

Enfin, un autre défi important est d'améliorer la sensibilisation des professionnels de la santé à la dépression périnatale, car ils peuvent participer au dépistage, aider à soutenir les femmes présentant des symptômes d'apparition précoce et les orienter précocement vers des soins adaptés (Bina 2020). Ainsi, former les sages-femmes ou les médecins généralistes peut

permettre d'améliorer le dépistage et la prise en charge précoce de ces patientes (Jardri, Maron, Pelta, et al. 2010; Ford, Shakespeare, et al. 2017). Dans ce contexte, le réseau de soins périnatal est un moyen de diffuser de l'information.

Ce dépistage, qu'il soit dans une approche de soins courants ou une approche scientifique d'évaluation de sa pertinence, semble une pierre angulaire dans les soins à proposer en psychiatrie périnatale.

Conclusion

La dépression périnatale touche plus d'une femme sur 10 selon nos travaux en population américaine et française. Afin de mieux comprendre la dépression périnatale et de développer des pratiques de prévention ciblées, plusieurs études ont tenté de définir des sous-types de dépression périnatale en fonction de la date d'apparition, de la gravité ou des symptômes prédominants (Putnam et al. 2017; Baron et al. 2017; Santos, Tan, et Salomon 2017; Fisher et al. 2019). Dans nos travaux, nous avons choisi de distinguer la dépression périnatale en fonction de l'apparition des symptômes, avec un seuil à 8 semaines dans le post-partum, correspondant au pic de dépression observé dans les premières semaines post-partum, ainsi qu'aux critères internationaux (Norhayati et al. 2015; American Psychiatric Association 2013, 5). La dépression périnatale, qu'elle débute au cours de la grossesse, dans le post-partum précoce ou tardif, présentent certains facteurs associés, tels que des traumatismes infantiles, des antécédents personnels de trouble dépressif ou des événements de vie stressants pendant la grossesse. Cependant, et de façon intéressante, les dépressions du post-partum à début précoce et tardif peuvent être distinguées par des corrélats socio-économiques, des événements de la vie et des troubles psychiatriques associés ; mais également par leur profil génétique.

Par ailleurs, nous avons montré que dans un échantillon de femmes souffrant de trouble bipolaire, une sur 8 débute ce trouble par une dépression du post-partum. Ce sous-groupe de femmes présentait des caractéristiques de bon pronostic du trouble bipolaire.

Enfin, concernant les liens entre parité et évolution du trouble bipolaire, il semble que la parité n'est pas associée à une évolution défavorable du trouble bipolaire. Cependant, les femmes souffrant d'un trouble bipolaire sont insuffisamment traitées pour celui-ci. Il apparaît indispensable d'améliorer le dépistage et la période périnatale est un moment privilégié pour cela.

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Annexes

Annexe 1: Changes in alcohol use and heavy episodic drinking in U.S. women of childbearing-age and peripartum between 2001-2002 and 2012-2013

ARTICLE 7



Changes in alcohol use and heavy episodic drinking in U.S. women of childbearing-age and peripartum between 2001-2002 and 2012-2013

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Changes in alcohol use and heavy episodic drinking in U.S. Women of childbearing-age and peripartum between 2001–2002 and 2012–2013

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HIGHLIGHTS

- Prevalence of at least one alcohol drink increased in childbearing-aged women.
- Prevalence of heavy episodic drinking increased in childbearing-aged women.
- Alcohol use have even dramatically increased in U.S. pregnant and postpartum women.

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ABSTRACT

Background: Heavy episodic drinking (HED) is a frequent pattern of alcohol use in women of childbearing age with severe consequences for both women and child, making it a major public health issue. Some states in the US have reported laws that target the use of alcohol during pregnancy. Our aim was to examine the evolution of 12-month alcohol use and 12-month HED prevalence in childbearing age, pregnant and postpartum women between 2001 and 2002 and 2012–2013.

Methods: Our data were drawn from the National Epidemiologic Study of Alcohol and Related Conditions (NESARC) conducted in 2001–2002 and NESARC-III conducted in 2012–2013, two independent, representative samples of U.S. population. Past-year alcohol use and HED was evaluated according face-to-face interview for all participants.

Results: Our sample consisted of 24,536 women of childbearing age, including 2846 pregnant and postpartum women. Prevalence of 12-month alcohol use increased from 2001 to 2002 to 2012–2013, in both childbearing-aged women (66.14% to 75.48%; aOR = 1.62, 95%CI = 1.46–1.80) and pregnant and postpartum women (57.81% to 66.19%; aOR = 1.56, 95%CI = 1.25–1.94). Prevalence of 12-month HED increased from 2001 to 2002 to 2012–2013, in both childbearing-aged women (22.57% to 36.34%; aOR = 1.97, 95%CI = 1.79–2.16) and pregnant and postpartum women (17.85% to 28.21%; aOR = 1.84, 95%CI = 1.47–2.30).

Conclusions: Alcohol use and HED increased in last 10 years in both childbearing age and pregnant and postpartum US women. That questions the impact of implemented laws, policies and alcohol guidelines in this population within the last 10 years.

1. Introduction

Heavy episodic drinking (HED) is a frequent pattern of alcohol use in women of childbearing age, between 18 and 50 years old, associated with adverse consequences for women, including unintended pregnancies, later recognition of pregnancy, unintentional injuries, suicide

attempts and sexually transmitted infection (Poulin & Graham, 2001; Naimi, Lipscomb, Brewer, & Gilbert, 2003; Seiler, 2016; Kittel, Bishop, & Ashrafioun, 2019). In 2017, 59% of U.S women of childbearing age reported alcohol use in the past 30 days, and 31% at least one episode of binge drinking (Substance Abuse and Mental Health Services Administration, 2018). Between 8.7 and 21% of U.S pregnant women

Abbreviations: CI, Confidence Interval; FAS, Fetal Alcohol Syndrome; FASD, Fetal Alcohol Spectrum Disorder; HED, Heavy episodic drinking; NESARC, National Epidemiologic Study of Alcohol and Related Conditions; aOR, Adjusted Odds Ratio; SE, Standard Error

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Table 1

Prevalence and sociodemographic correlates of alcohol use in last 12-months in women of childbearing age and pregnant and postpartum women in the 2001–2002 NESARC and the 2012–2013 NESARC-III.

Characteristic	Women of childbearing age			Women who were pregnant last year		
	2001–2002 N = 13,371	2012–2013 N = 11,165	Logistic regression	2001–2002 N = 1524	2012–2013 N = 1322	Logistic regression
	% (SE)	% (SE)	aOR 95% CI	% (SE)	% (SE)	aOR 95% CI
All Sample	N = 884366.14%	N = 842775.48%	1.62; 1.46–1.80	N = 88157.81%	N = 87566.19%	1.56; 1.25–1.94
Race/ethnicity						
White	75.46 (0.87)	81.77 (0.92)	ref	69.88 (2.13)	77.38 (2.19)	Ref
Black	53.24 (1.21)	71.29 (1.71)	0.64 0.50–0.82	51.46 (3.79)	63.03 (3.23)	1.05 0.78–1.42
American Indian/Alaska Native	57.62 (4.51)	80.24 (3.03)	1.17 0.81–1.67	73.26 (9.94)	87.90 (7.03)	0.71 0.35–1.45
Asian/Native Hawaiian/Pacific Islander	44.45 (2.98)	60.57 (2.32)	1.17 0.91–1.50	24.12 (4.85)	51.38 (6.70)	1.18 0.72–1.93
Hispanic/ latino	55.42 (1.63)	70.41 (1.08)	1.08 0.86–1.36	41.89 (4.00)	58.60 (3.04)	1.38 0.97–1.95
US born						
Yes	72.44 (0.79)	80.32 (0.78)	Ref	66.53 (1.63)	75.23 (1.86)	Ref
No	44.44 (1.62)	60.15 (1.32)	0.68 0.57–0.81	29.32 (2.75)	44.34 (4.11)	0.79 0.57–1.08
Age (years old)						
18–24	68.58 (1.75)	77.09 (1.21)	ref	58.07 (2.47)	76.41 (2.68)	Ref
25–50	67.96 (0.91)	76.68 (0.79)	0.93 0.83–1.04	59.51 (2.02)	67.43 (1.94)	1.11 0.87–1.41
Education						
Less than high school	48.12 (1.95)	59.93 (1.75)	Ref	40.95 (4.66)	60.63 (3.94)	Ref
High school graduate	62.10 (1.29)	70.14 (1.33)	0.95 0.80–1.13	59.91 (2.70)	65.20 (3.52)	1.02 0.79–1.31
Some college or higher	74.31 (0.79)	81.75 (0.69)	1.09 0.91–1.30	64.08 (1.97)	73.49 (1.99)	1.33 0.99–1.77
Income (\$)						
0–19,999	61.40 (1.05)	71.65 (1.00)	ref	53.59 (2.24)	64.41 (2.49)	Ref
20,000–34,999	73.70 (1.19)	79.53 (1.11)	0.87 0.79–0.96	65.70 (3.54)	76.22 (2.52)	1.20 0.92–1.56
35,000–69,999	78.14 (1.33)	84.74 (0.96)	1.03 0.89–1.19	78.37 (4.16)	78.28 (3.23)	1.61 1.17–2.22
≥70,000	87.65 (1.69)	86.52 (1.79)	1.60 1.28–2.00	81.99 (6.81)	86.86 (4.27)	2.19 1.28–3.74
Marital status						
Married	67.33 (1.08)	75.95 (0.86)	Ref	56.98 (2.07)	69.61 (2.05)	ref
Widowed, divorced or separated	69.66 (1.39)	79.03 (1.25)	1.05 0.93–1.20	69.97 (5.87)	72.36 (5.64)	1.30 0.89–1.91
Never married	68.92 (1.22)	77.05 (1.08)	0.99 0.88–1.11	64.53 (3.45)	70.74 (3.08)	1.34 0.99–1.82
Region						
Northeast	72.67 (2.57)	81.23 (1.90)	Ref	62.02 (3.89)	70.24 (3.64)	Ref
Midwest	75.33 (1.16)	81.66 (1.28)	1.12 0.56–2.21	69.25 (3.48)	75.96 (2.90)	1.06 0.55–2.04
South	61.68 (1.09)	72.74 (1.22)	1.48 0.79–2.75	54.98 (2.82)	64.58 (3.07)	1.22 0.68–2.20
West	66.70 (2.49)	75.50 (1.36)	0.96 0.46–1.99	52.69 (3.40)	73.08 (3.64)	1.00 0.50–2.00

Numbers are unweighted, percentages are weighted values. Significant differences are in bold.

Abbreviations: aOR, odds ratio adjusted; CI, confidence interval; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; SE, standard error. Odds ratios were adjusted for all sociodemographic characteristics (race, nativity, age, education, income, marital status, and region, and estimated through logistic regression.

reported having consumed alcohol in the past 30 days, and 3 to 5% reported past-month binge drinking (Lange, Probst, Rehm, & Popova, 2017; Oh, Reingle Gonzalez, Salas-Wright, Vaughn, & DiNitto, 2017; Substance Abuse and Mental Health Services Administration, 2018). In pregnant women, the majority of consumption takes place before the recognition of pregnancy (O’Keeffe, Kearney, & McCarthy, 2015; Tan, Denny, Cheal, Sniezek, & Kanny, 2015).

Alcohol consumption is associated with poor health outcomes and reduced life expectancy. Alcohol is responsible for more than 200 types of injuries and around 6% of deaths worldwide (Bardach, Alcaraz, & Ciapponi, 2019). Alcohol consumption also generates major costs for society (Rehm et al., 2009). In the UK, it has been estimated that the costs related to alcohol misuse over the next five years would amount to £ 17 billions (\$ 22 billions) (Williams, Alexander, & Armstrong, 2018). The health consequences of alcohol use during pregnancy can be also severe for the fetus, including stillbirth, prematurity, low birth weight or Fetal Alcohol Spectrum Disorder (FASD) (Sokol, Delaney-Black, & Nordstrom, 2003; Popova, Stade, Bekmuradov, Lange, & Rehm, 2011; Hoyme, Kalberg, & Elliott, 2016). In the United States, an estimation of the total lifetime cost of FASD is more than \$2.0 million per individual case, with an annual total cost of \$4 billion (Lupton, Burd, & Harwood, 2004). It is therefore important to do primary prevention to avoid these pathologies. As there is no known safe level of alcohol use during pregnancy, many alcohol guidelines worldwide recommend abstinence for pregnant women. In the United States, the

Surgeon General reissued recommendations in 2005 advising pregnant women, women planning to become pregnant, or women at risk of becoming pregnant to abstain from alcohol consumption (FDA, 2005). The recent recommendations of the World Federation of Societies of Biological Psychiatry and the International Association for Women’s Mental Health advocate the same (Thibaut et al., 2019). The American College of Obstetricians and Gynecologists recommend a systematic screening of alcohol use every year in women of childbearing age as well as during the first trimester of pregnancy for all pregnant women (Obstetric and Gynecologic Implications - ACOG, 2011). In the United States, to promote information and early intervention, a federal law requires warning labels on all alcoholic beverages. In some states, laws have facilitated the execution of these recommendations (Seiler, 2016). Twenty four states have voted laws that requires that warning signs about the risks of drinking during pregnancy should be placed where alcoholic beverages are sold and in healthcare facilities treating pregnant women (Alcohol Policy Information System, 2016). Some states promote treatment and services for pregnant women, including prioritizing admission for treatment of substance use disorders (Grella, 2008; National Institut on Alcohol Abuse and Alcoholism, 2017). Other states have a coercive approach, including civil commitment of pregnant women with alcohol related behaviors.

Alcohol use and HED prior to pregnancy are among the most consistently reported factors associated with alcohol use and HED during pregnancy (Ethen, Ramadhani, & Scheuerle, 2009; Skagerström,

Table 2

Prevalence and sociodemographic correlates of heavy episodic drinking in last 12-months in women of childbearing age and pregnant and postpartum women in the 2001–2002 NESARC and the 2012–2013 NESARC-III.

Characteristic	Women of childbearing age		Logistic regression		Women who were pregnant last year		Logistic regression	
	2001–2002 N = 13,371 % (SE)	2012–2013 N = 11,165 % (SE)	aOR	95% CI	2001–2002 N = 1524 % (SE)	2012–2013 N = 1322 % (SE)	aOR	95% CI
All Sample% of heavy episodic drinking	N = 301722.57%	N = 405736.34%	1.97	1.79–2.16	N = 27217.85%	N = 37328.21%	1.84	1.47–2.30
Race/ethnicity								
White	28.68 (0.76)	43.22 (1.06)	ref		24.15 (1.90)	37.69 (2.41)	ref	
Black	12.96 (0.81)	26.96 (1.16)	1.14	0.93–1.39	12.28 (2.25)	24.20 (2.74)	1.05	0.78–1.45
American Indian/Alaska Native	29.19 (4.21)	51.01 (3.77)	1.21	0.89–1.65	41.92 (10.97)	22.60 (8.78)	0.71	0.35–
Asian/Native Hawaiian/Pacific Islander	11.41 (1.76)	21.24 (2.13)	1.74	1.35–2.24	3.61 (1.82)	8.80 (4.23)	1.18	0.72–1.93
Hispanic/ latino	17.18 (0.97)	33.94 (1.17)	1.82	1.45–2.28	13.03 (1.91)	23.26 (2.19)	1.38	0.97–1.95
US born								
Yes	27.00 (0.67)	41.77 (0.83)	Ref		22.87 (1.50)	34.34 (1.71)	ref	
No	9.64 (0.72)	20.02 (1.04)	0.89	0.75–1.05	6.18 (1.41)	12.73 (2.45)	0.79	0.57–1.08
Age (years old)								
18–24	35.15 (1.59)	48.13 (1.59)	ref		23.69 (2.24)	36.57 (3.16)	ref	
25–50	21.83 (0.68)	35.21 (0.76)	0.88	0.80–0.97	17.45 (1.53)	28.32 (1.86)	1.11	0.87–1.41
Education								
Less than high school	17.13 (1.50)	28.72 (1.62)	Ref		14.43 (2.72)	31.96 (3.54)	ref	
High school graduate	22.71 (0.96)	33.21 (1.29)	0.91	0.79–1.05	22.12 (2.29)	32.74 (3.32)	1.02	0.79–1.31
Some college or higher	26.28 (0.79)	41.02 (0.86)	1.18	1.02–1.38	19.83 (1.71)	29.76 (1.82)	1.33	0.99–1.77
Income (\$)								
0–19,999	22.27 (0.84)	35.87 (0.93)	ref		17.82 (1.54)	28.66 (1.86)	ref	
20,000–34,999	27.44 (1.21)	39.24 (1.47)	0.96	0.87–1.06	19.52 (2.80)	37.81 (3.54)	1.20	0.92–1.56
35,000–69,999	25.14 (1.20)	42.03 (1.46)	1.20	1.06–1.35	27.14 (4.53)	24.71 (4.02)	1.61	1.17–2.22
≥70,000	31.73 (2.65)	38.65 (2.55)	1.94	1.59–2.37	32.63 (9.49)	45.00 (8.38)	2.19	1.28–3.74
Marital status								
Married	19.74 (0.76)	33.24 (0.85)	ref		17.06 (1.45)	28.60 (1.84)	ref	
Widowed, divorced or separated	27.35 (1.44)	37.70 (1.42)	1.27	1.15–1.40	22.45 (4.94)	44.00 (6.17)	1.30	0.89–1.91
Never married	32.66 (1.17)	45.77 (1.33)	1.28	1.15–1.42	28.54 (3.34)	34.36 (3.29)	1.34	0.99–1.82
Region								
Northeast	24.22 (1.55)	41.90 (1.96)	ref		19.55 (2.92)	28.61 (2.98)	ref	
Midwest	31.33 (2.19)	45.36 (1.43)	1.07	0.62–1.86	24.92 (3.00)	41.22 (3.99)	1.06	0.55–2.04
South	19.97 (0.87)	32.33 (1.28)	1.22	0.75–1.97	18.03 (2.26)	28.31 (2.62)	1.22	0.68–2.20
West	23.95 (1.69)	37.32 (1.36)	1.09	0.60–1.96	16.38 (2.30)	26.06 (2.71)	1.00	0.50–2.00

Numbers are unweighted, percentages are weighted values. Significant differences are in bold.

Abbreviations: aOR, odds ratio adjusted; CI, confidence interval; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; SE, standard error. Odds ratios were adjusted for all sociodemographic characteristics (race, nativity, age, education, income, marital status, and region, and estimated through logistic regression.

Alehagen, Häggström-Nordin, Årestedt, & Nilsen, 2013; McCormack, Hutchinson, & Burns, 2017). Other factors, such as a history of any psychiatric disorder, tobacco use, significant conflicts with the partner or a traumatic history of sexual abuse or exposure to violence, are also associated with alcohol consumption during pregnancy (Skagerström et al., 2013; O’Keeffe et al., 2015; Lamy, Houivet, & Marret, 2019).

The purpose of our study was to examine the evolution of the prevalence of 12-month alcohol use and 12-month HED over a 10-year period in a large, representative sample of women, considering (i) childbearing age women and (ii) pregnant and postpartum women. To give a better understanding of the decennial evolution of alcohol use and HED in this population, we examine these trends overall and among sociodemographic subgroups between 2001 and 2002 and 2012–2013.

2. Methods

2.1. Sample

National Epidemiologic Study of Alcohol and Related Conditions (NESARC) and National Epidemiologic Study of Alcohol and Related Conditions III (NESARC-III) are two independent, nationally representative surveys of U.S. civilian population 18 years and older residing in households and group quarters. NESARC and NESARC-III respectively included 43,093 in 2001–2002 and 36,309 participants in 2012–2013. Reponses rates were 81.0% in NESARC and 60.1% in

NESARC-III (Grant, Kaplan, Shepard, & Moore, 2003, Grant, Amsbary, Chu, & Moore 2014). Members of the US Census Bureau (NESARC) and West, Inc. (NESARC III) conducted face-to-face interviews by trained interviewers. Both surveys used similar procedures.

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) sponsored the two surveys. Unlike the NESARC, a financial incentive (\$90.00) for participation was offered for the NESARC-III. Both surveys used the same multistage sampling designs with oversampling for Hispanic, black, and (in NESARC-III) Asian individuals. The NESARC involved the U.S. Census for sample design and field work, including a sample of > 40,000 from counties selected from the American Community Survey across the 50 states. Age and marital status variables were imputed using both assignment and allocation. All other variables imputed used only the allocation method. More details on sampling and weighting procedures can be found elsewhere (Grant, Goldstein, & Saha, 2015; National Institut on Alcohol Abuse and Alcoholism, 2017).

The research protocol, including informed consent procedures, received ethical approval from the US Census Bureau and the Office of Management and Budget for NESARC and from the institutional review boards of West at and the National Institutes of Health for NESARC-III.

For this study, the sample consisted of all women of childbearing age (18 to 50 years old) in NESARC and NESARC-III. The women who answered “yes” to the question “have you been pregnant in the last 12 months?” defined the “pregnant and postpartum women” group, which therefore included both currently pregnant and postpartum

Table 3

Prevalence and sociodemographic correlates of heavy episodic drinking among alcohol user in last 12-months in women of childbearing age and pregnant and postpartum women in the 2001–2002 NESARC and the 2012–2013 NESARC-III.

Characteristic	Women of childbearing age		Logistic regression		Women who were pregnant last year		Logistic regression	
	2001–2002 % (SE)	2012–2013 % (SE)	aOR	95% CI	2001–2002 % (SE)	2012–2013 % (SE)	aOR	95% CI
All Sample% of heavy episodic drinking among alcohol user	N = 301734.12%	N = 405748.14%	1.85	1.68–2.04	N = 27230.87%	N = 37342.63%	1.70	1.33–2.17
Race/ethnicity								
White	38.00 (0.92)	52.85 (1.08)	ref		34.56 (2.38)	48.71 (3.11)	ref	
Black	24.33 (1.48)	37.82 (1.35)	1.39	1.13–1.71	23.86 (3.90)	38.39 (4.33)	1.22	0.87–1.71
American Indian/Alaska Native	50.66 (5.13)	63.57 (4.24)	1.52	1.06–2.17	57.22 (12.76)	25.71 (10.08)	0.73	0.34–1.57
Asian/Native Hawaiian/Pacific Islander	25.66 (3.33)	35.07 (3.23)	1.88	1.43–2.49	14.95 (7.29)	17.12 (8.21)	1.82	0.92–3.61
Hispanic/ latino	31.00 (1.59)	48.20 (1.41)	1.91	1.51–2.41	31.12 (4.82)	39.70 (3.63)	1.43	0.94–2.18
US born								
Yes	37.27 (0.84)	52.00 (0.85)	Ref		34.37 (2.00)	45.65 (2.25)	Ref	
No	21.69 (1.59)	33.27 (1.48)	1.05	0.86–1.28	21.10 (4.50)	28.70 (4.78)	0.91	0.56–1.47
Age (years old)								
18–24	51.25 (1.69)	62.43 (1.77)	ref		40.79 (3.30)	47.86 (3.97)	Ref	
25–50	32.12 (0.84)	45.92 (0.78)	0.88	0.78–0.98	29.32 (2.30)	42.00 (2.51)	0.89	0.65–1.22
Education								
Less than high school	35.59 (2.58)	47.91 (2.01)	Ref		35.24 (5.76)	52.71 (4.97)	Ref	
High school graduate	36.57 (1.31)	47.35 (1.61)	0.87	0.74–1.03	36.92 (3.26)	50.22 (3.96)	0.78	0.53–1.14
Some college or higher	35.37 (0.93)	50.17 (0.93)	1.13	0.95–1.33	30.94 (2.53)	40.50 (2.41)	1.11	0.75–1.64
Income (\$)								
0–19,999	36.28 (1.11)	50.06 (1.00)	Ref		33.25 (2.52)	44.49 (2.49)	Ref	
20,000–34,999	37.24 (1.48)	49.34 (1.66)	0.89	0.79–0.99	29.70 (4.18)	49.61 (4.77)	1.22	0.90–1.65
35,000–69,999	32.18 (1.35)	49.60 (1.53)	1.12	0.99–1.28	34.63 (5.65)	31.56 (4.98)	1.47	0.99–2.15
≥70,000	36.20 (2.93)	44.67 (2.80)	1.67	1.36–2.04	39.80 (10.62)	51.81 (8.76)	2.02	1.10–3.72
Marital status								
Married	29.31 (0.99)	43.77 (0.99)	ref		29.93 (2.13)	41.09 (2.50)	ref	
Widowed, divorced or separated	39.27 (1.64)	47.70 (1.59)	1.25	1.12–1.40	32.09 (6.45)	60.81 (7.09)	1.13	0.72–1.75
Never married	47.38 (1.36)	59.40 (1.34)	1.21	1.07–1.37	44.23 (5.02)	48.57 (3.91)	1.10	0.74–1.63
Region								
Northeast	33.34 (1.49)	51.58 (1.72)	Ref		31.53 (3.94)	40.73 (5.05)	Ref	
Midwest	41.59 (2.56)	55.55 (1.71)	1.05	0.61–1.80	35.98 (3.53)	54.27 (4.56)	1.04	0.56–1.92
South	32.38 (1.29)	44.45 (1.39)	1.24	0.77–1.98	32.79 (3.50)	43.84 (3.19)	1.30	0.73–2.29
West	35.91 (1.71)	49.44 (1.57)	1.08	0.62–1.90	31.09 (4.09)	35.65 (4.23)	1.19	0.61–2.32

Numbers are unweighted, percentages are weighted values. Significant differences are in bold.

Abbreviations: aOR, odds ratio adjusted; CI, confidence interval; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; SE, standard error. Odds ratios were adjusted for all sociodemographic characteristics (race, nativity, age, education, income, marital status, and region, and estimated through logistic regression.

women.

2.2. Measures

2.2.1. Sociodemographic measures

Sociodemographic characteristics were assessed identically across the two surveys. Race/ethnicity was categorized into: (i) White, (ii) Black, (iii) American Indian/Alaska Native, (iv) Asian/Native Hawaiian/Pacific Islander and (v) Hispanic/Latino. Age at interview was categorized into: (i) 18–24, and (ii) 25–50 years old. Educational level was classified into: (i) less than high school, (ii) high school graduate and (iii) some college or higher. Personal income during a year was classified into: (i) \$0–19,999, (ii) \$20,000–34,999, (iii) \$35,000–69,999, and (iv) \$70,000 or greater. Marital status was classified into (i) married, (ii) widowed/separated/divorced and (iii) never married. Region of residence was classified into: (i) Northeast, (ii) Midwest, (iii) South, and (iv) West.

We present change in alcohol use over the study period for each of the 23 subgroups according to this sociodemographic data.

Alcohol consumption drinker status was defined by one question: “Are you a current drinker, an ex-drinker or a lifetime abstainer?” (yes/no).

Alcohol use and HED were defined by the answer in “yes or no” to separate questions. Alcohol use was defined by the question “During the last 12 months, did you have at least 1 drink of any kind of alcohol?” (a drink equals 14 g of pure alcohol). HED was defined as drinking 4 or more standard drinks in a single day during the past 12 months, with the question “During the last 12 months, about how often did you drink

four or more drinks in a single day?”

2.3. Statistical analyses

We pooled NESARC and NESARC-III data to conduct repeated cross-sectional analyses, as was done previously (Dawson, Goldstein, Saha, & Grant, 2015; Martins et al., 2017; Kerridge, Chou, & Pickering, 2019). We added a dummy variable for study period.

Weighted percentages and standard-errors (SEs) were computed for full samples and by subgroups using SUDAAN, version 11.01 (Research Triangle Park, NC). Because of the weighting and clustering used in the NESARC and NESARC-III design, SUDAAN implements a Taylor linearization method. Multivariable logistic regressions were conducted with simultaneous entry of sociodemographic characteristics. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were derived to reflect the strength and significations of the associations.

We first estimate prevalence of (i) alcohol use, (ii) HED in two different populations: women of childbearing age and women who were pregnant or in postpartum. We then tested associations between sociodemographic variables and alcohol use or HED between NESARC and NESARC-III with a multivariable logistic regression model, adjusted for all other sociodemographic variables, in order to measure the evolution of alcohol consumption in each of the subgroups. The variable of interest was survey period effect with the 2001–2002 survey serving as reference.

3. Results

The full sample consisted of 24,536 women of childbearing age (13,371 in 2001–2002 and 11,165 in 2012–2013), including 2846 pregnant and postpartum women (1524 in 2001–2002 and 1322 in 2012–2013).

3.1. Lifetime alcohol use

Lifetime abstainers were 18.67% (SE 0.96) among childbearing-aged women in 2001–2002, and 12.40% (SE 0.56) in 2012–2013. We found the same trend in pregnant and postpartum women with a decrease in lifetime abstainers (respectively 22.25% and 12.20% in 2001–2002 and 2012–2013). The former drinkers among women of childbearing age were 13.25% (SE 0.44) in 2001–2002, and 10.83% (SE 0.45) 10 years later. Among pregnant or postpartum women, 18.72% (SE 1.08) were ex-drinkers in 2001–2002 while they were 17.50% (SE 1.25) in 2012–2013.

3.2. 12-Month alcohol use (Table 1)

Prevalence of at least one alcohol drink in last 12 months increased from 2001 to 2002 to 2012–2013, in both childbearing-aged women (66.14% to 75.48%; aOR = 1.62, 95%CI = 1.46–1.80) and pregnant and postpartum women (57.81% to 66.19%; aOR = 1.56, 95%CI = 1.25–1.94). In both childbearing-aged women and pregnant and postpartum women, this increase was found in 22 of the 23 subgroups according to the sociodemographic categories. Table 1

In childbearing-aged women, the increase was higher in two subgroups: US born compared to non-US born, and very high income (more than 70,000\$) compared to the lowest income level (less than 20,000\$); and smaller in black women compared to the white ones. In pregnant and postpartum women, the increase was higher in women with high and very high incomes (between 35,000 and 69,999\$ and more than 70,000\$) compared to the lowest income levels (less than 20,000\$).

3.3. 12-month heavy episodic drinking (Table 2)

Prevalence of HED in the last 12 months increased from 2001 to 2002 to 2012–2013, in both childbearing-aged women (22.57% to 36.34%; aOR = 1.97, 95%CI = 1.79–2.16) and pregnant and postpartum women (17.85% to 28.21%; aOR = 1.84, 95%CI = 1.47–2.30). Concerning childbearing-aged women, all sociodemographic subgroups were affected by this increase. Concerning pregnant and postpartum women, this increase was found in 21 of the 23 subgroups according to the sociodemographic categories: only the prevalence of HED in American Indian/Alaska native and medium-income (between 35,000 and 69,999\$) subgroups decreased (41.92% to 22.60% and 27.14% to 24.71% respectively). Table 2

In both childbearing-aged women and pregnant and postpartum women, the increase was higher in two subgroups of women: high and very high incomes (between 35,000 and 69,999\$ and more than 70,000\$) compared to the lowest income's levels (less than 20,000\$). In childbearing-aged women, the increase was higher in Asian, native Hawaiian, Pacific Islander and in Hispanic, Latino women, and in young women (less than 24), and lower in married women in comparison to widowed, divorced or separated and to never married.

3.4. Heavy episodic drinking in women with alcohol use (Table 3)

Prevalence of HED in women who used at least one alcohol drink in last 12 months increased from 2001 to 2002 to 2012–2013, in both childbearing-aged women (34.12% to 48.14%; aOR = 1.85, 95%CI = 1.68–2.04) and pregnant and postpartum women (30.87% to 42.63%; aOR = 1.70, 95%CI = 1.33–2.17). Table 3

4. Discussion

Alcohol use and HED increased between 2001 and 2002 and 2012–2013 in both women of childbearing age and pregnant and postpartum women. In women of childbearing age, the use of alcohol raised from two-thirds to three-quarters, corresponding to an increased risk of 51%. This increase was also observed in pregnant and postpartum women, with more than half (57.81%) of pregnant and postpartum women using alcohol in the past year in 2001–2002, and more than two-thirds (66.19%) 10 years later, corresponding to an increased risk of 35%.

HED increased from almost 80% (from 22.57% to 36.34%) between 2001 and 2002 and 2012–2013 in women of childbearing age. This very significant increase in HED was also observed in pregnant and postpartum women (17.85% in 2001–2002 and 28.21% in 2012–2013, corresponding to a 70% increase).

The results of this study were consistent with previous national studies showing that the use of alcohol increased in young women (Grucza, Norberg, & Bierut, 2009; Hasin, Shmulewitz, & Keyes, 2019). A recent report from the Centers for Disease Control and Prevention in the United State (CDC) in 2011–2013 estimated that 53.6% of women of childbearing age have consumed alcohol in the last month and that 18.2% have engaged in HED during the same timeframe (Tan et al., 2015). In this CDC analysis, 10.2% of women reported the use of alcohol during pregnancy, and 3.1% have engaged in HED in the last month (Tan et al., 2015). The lower prevalence of alcohol use and HED in both women of childbearing age and pregnant in the CDC report compared to the present report could be partially explained with the different timeframes considered for alcohol use assessment (last month in the CDC versus past-12 month in the NESARC).

Our results were also consistent with previous national studies showing that the use of alcohol increased in the U.S. general population. Considering both genders in the NESARC, the 12-month prevalence of alcohol use has increased by 11.2% between 2001 and 2002 and 2012–2013, while high-risk drinking has increased by almost 30%, and DSM-IV alcohol use disorder has increased by 49.4% (Grant, Chou, & Saha, 2017). Another study conducted on the same cohort compared this increase according to sex and found that it was greater both in quantity and in frequency in women than in men (Dawson et al., 2015).

Non-U.S. studies suggest a highly variable prevalence of alcohol use in pregnancy, ranging from 5.5% to 52.2% (de Chazeron, Llorca, & Ughetto, 2008; Skagerström et al., 2013). Further studies should assess the generalizability of our findings in non-U.S. populations.

Some limitations should be considered when interpreting these results. The main limit is that our work does not discriminate between pregnancy and postpartum period as the women in NESARC who answered “yes” to the question “have you been pregnant in the last 12 months?” make up this group et that we have no information about the beginning of pregnancy or the date of delivery. With this limit, the prevalence of alcohol consumption during pregnancy could be over-estimated. However, alcohol consumption study during postpartum is interesting as 74.2% of women breastfed their children between 2008 and 2010; and alcohol concentrations in breast milk closely resemble those in maternal blood (Haastруп, Pottegård, & Damkier, 2014) and that exposing infants to alcohol through breastmilk may reduce their cognitive abilities (Gibson & Porter, 2018). World Health Organization recommends avoiding alcohol while breastfeeding (World Health Organization, 2014, 2014).

Moreover, the prevalence of alcohol use in pregnant women was assessed regardless of pregnancy recognition by participants. However, since most pregnancies in the United States are unplanned and most pregnancies are recognized after weeks of gestation, alcohol consumption before pregnancy is often a reflection of consumption in the first weeks of pregnancy (Naimi et al., 2003; Anderson et al., 2014; Pryor, Patrick, Sundermann, Wu, & Hartmann, 2017).

To stop alcohol consumption during pregnancy, federal policies

have been implemented by States in both supportive and punitive interpretations, which have increased significantly in the past decade. The most common policy interventions are laws related to mandated reporting of alcohol consumption during pregnancy (Drabble, Thomas, O'Connor, & Roberts, 2014). This policy intervention has increased during the 10-year frame of the study (26 states in 2003 to 35 states in 2013). Between 2001 and 2013, national recommendations recommending abstinence during pregnancy have been reissued. Other studies specifically studying the link between policies and alcohol use during pregnancy have found no effect on the number or the type of policies (supportive, punitive or mixed) and effective reduction in alcohol use during pregnancy (Roberts, Thomas, Treffers, & Drabble, 2017, Roberts et al., 2019). Policies, interventions and alcohol consequences have an important financial cost for society (Popova et al., 2011), and there is little or scarce data to support a population benefit from these strategies. In parallel with policies, many screening and early intervention programs have been developed (Fergie et al., 2019). Thus, various brief interventions have shown effectiveness in reducing alcohol consumption among women of reproductive age such as technology-based interventions (Hai, Hammock, & Velasquez, 2019) or motivational interview (Delrahim-Howlett, Chambers, & Clapp, 2011; Ceperich & Ingersoll, 2011; Montag, Brodine, & Alcaraz, 2015; Hai et al., 2019). Tools to reduce consumption targeting pregnant women have also shown effectiveness, whether based on behavioral contracts, social support or information (Fergie et al., 2019).

Our study suggests that alcohol use and HED have dramatically increased in U.S. women, including in pregnant and postpartum women. Further examinations of current policies, interventions and societal drinking norms that have emerged within the past decade are warranted.

Author contribution

Sarah Tebeka drafted the initial manuscript and approved the final manuscript as submitted. Alix de Premorel Higgons drafted the initial manuscript and approved the final manuscript as submitted. Yann Le Strat carried out the initial analyses, revised the manuscript, and approved the final manuscript as submitted. Caroline Dubertret revised the manuscript, and approved the final manuscript as submitted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.addbeh.2020.106389>.

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Annexe 2 : Protocole du dépistage systématique de la dépression périnatale en suite de couche à la maternité de l'hôpital Louis Mourier.

Dépistage systématique en suite de couche de la dépression périnatale

