La interacció entre el gen del receptor de mineralocorticoides i concentracions elevades de CRH augmenten la vulnerabilitat a la depressió postpart

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Antecedents

Convocatoria PI FIS 2005

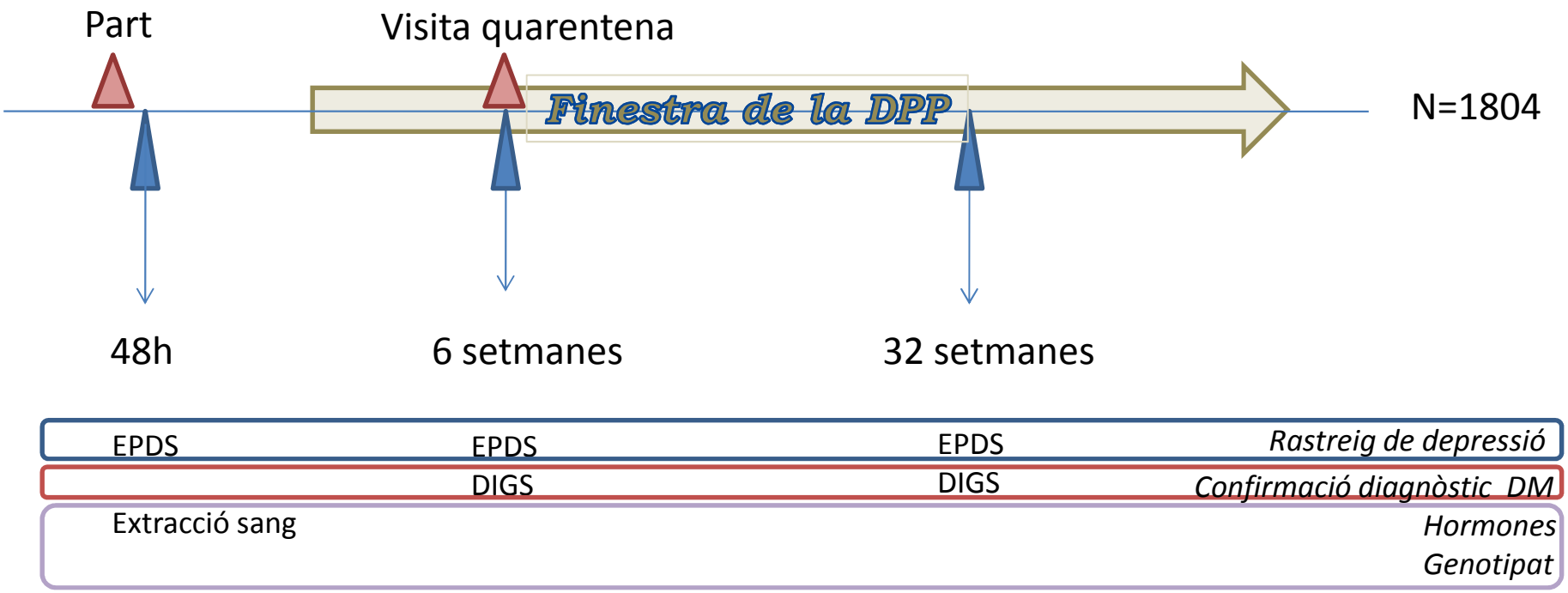
Títol: **“Vulnerabilidad genético-ambiental a la depresión posparto”.**

IP: Julio Sanjuán

S’escull el part com “factor ambiental estressant”

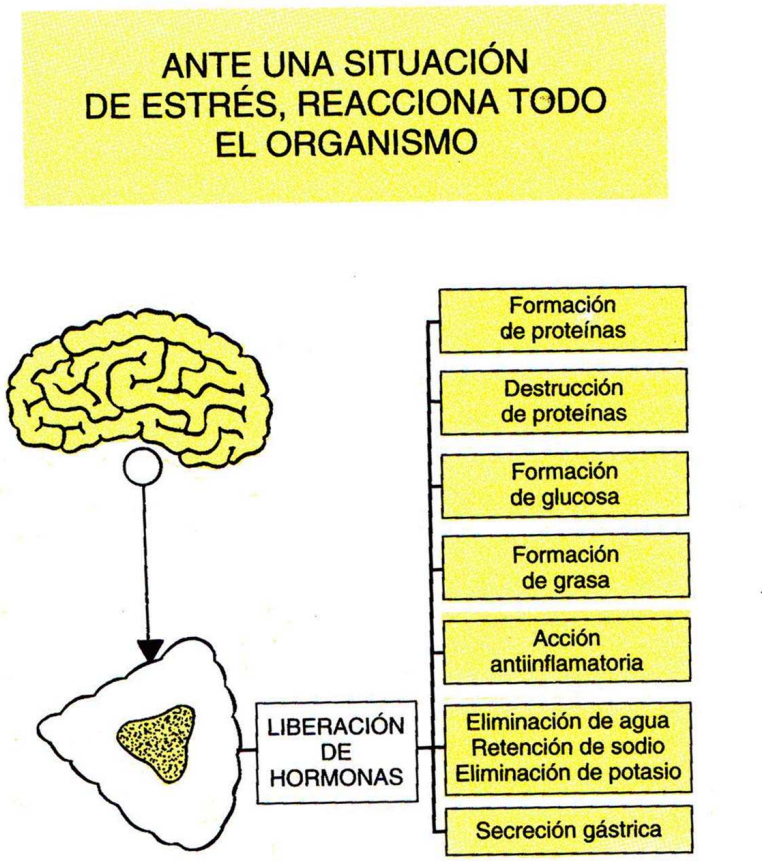
Antecedents

Disseny de l'estudi



Antecedents

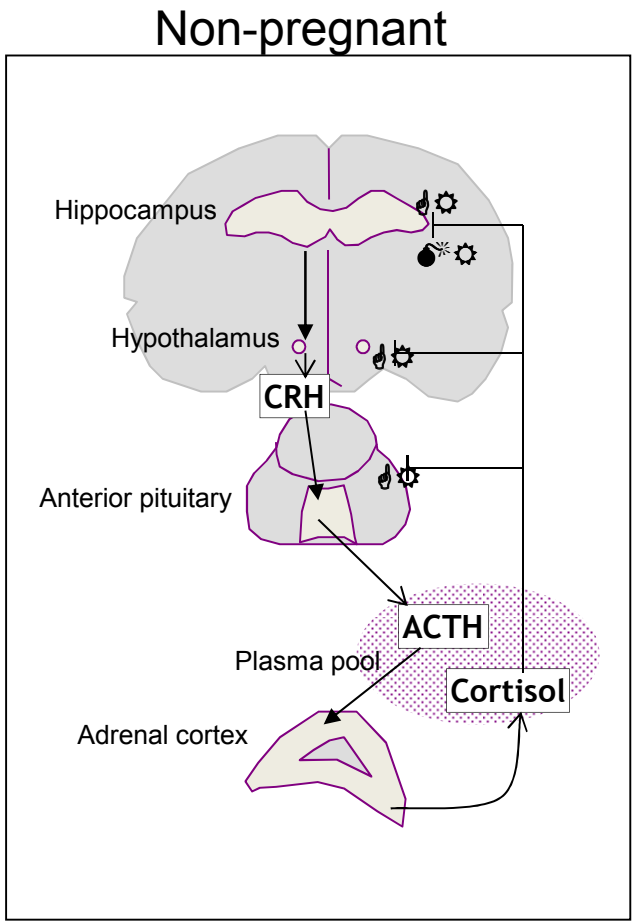
Eix hipotàlem-pituitari-adrenal (HPA): eix de l'estrès



Disfunció eix HPA = depressió

pCRH = símptomes depressius postpart

Antecedents

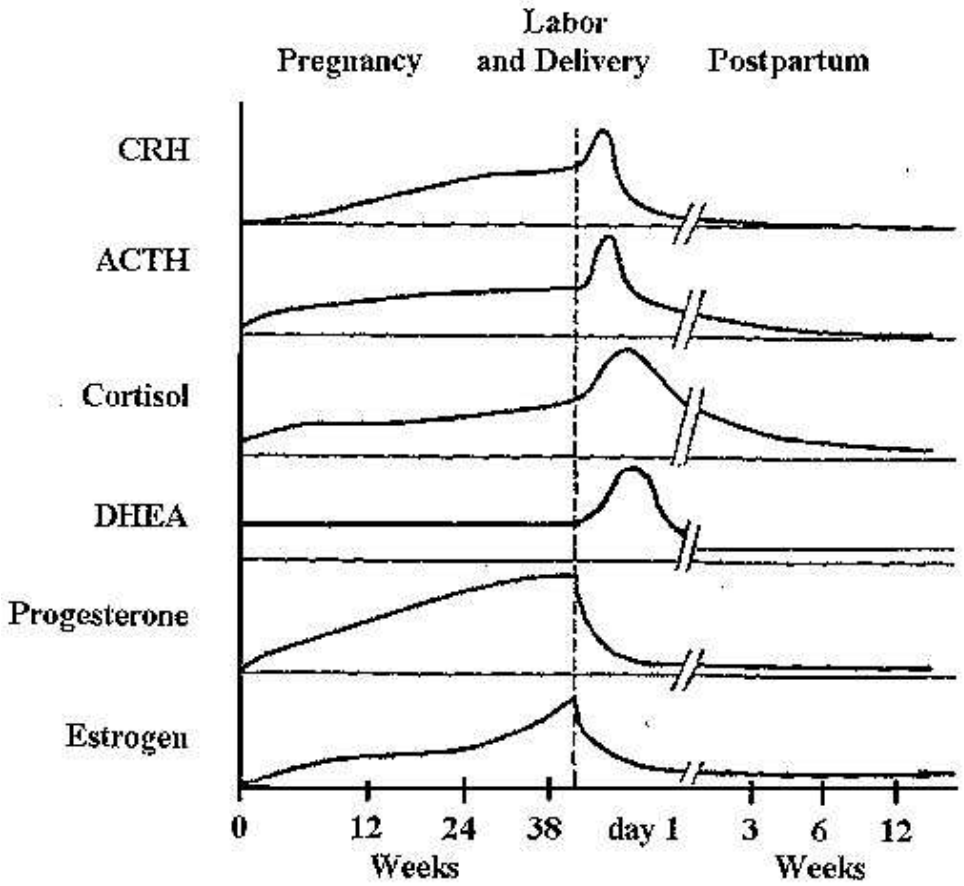


GR, glucocorticoid receptor
MR, mineralocorticoid receptor

Gen GR **NR3C1**
Gen MR **NR3C2**

Antecedents

Eix HPA en l'embaràs i el part



Antecedents

Receptor mineralocorticoide (MR)	Receptor glucocorticoide (GR)
Proteína 984 aa, pm 107 kDa, 2 isoformas: MR-A y MR-B (la B tiene 15 aa en el extremo N terminal por diferente promotor)	Proteína de 777 aa, pm 94 kDa, 2 isoformas: GR-α y GR-β(difieren en exón 9, la β tiene 15 aa menos en el extremo C terminal)*
Gen codificante NR3C2 en 4q31.1	Gen codificante NR3C1 en 5q31-32
Alta afinidad (Kd = 0.5-2 nM)	Baja afinidad (Kd = 10-20 nM)
Ligandos endógenos: Aldosterona, cortisol y corticosterona *Agonista:* Fludrocortisona *Antagonista:* Espironolactona	*Ligandos endógenos:* Cortisol y corticosterona *Agonista:* Dexametasona *Antagonista:* Mifepristona
Ubicación restringida: Tejidos de recuperación de Na+ (TCD, colon, glándulas salivales) SNC (cortezas límbicas e hipotálamo)	Ubicación amplia en todos los tejidos
Ocupado casi todo (90%) a bajas concentraciones	Ocupado al pico matinal (30%) y casi todo (90-95%) bajo estrés

Hipòtesi

- Després del part hi ha una forta devallada de diferents hormones sobretot les produides per la placenta.
- L'eix HPA té una implicació important en l'embaràs i el part.
- El cortisol i la pCRH s'han relacionat amb la depressió.
- Els gens MR i GR d'alta expressió en cervell són importants per la regulació que el propi cortisol fa sobre l'eix i per la funció dels glucocorticoides en el SNC.

Variacions en els gens dels receptors de glucocorticoides (MR i GR) s'associen amb les concentracions de CRH, ACTH i cortisol després del part i amb la vulnerabilitat a patir una depressió postpart

Objectius

1. Determinar si existeix una relació entre variants dels gens de MR i GR (NR3C1 i NR3C2) i les concentracions de les hormones de l'eix HPA (CRH, ACTH i cortisol) en dones immediatament després del part
2. Determinar si la interacció entre les variants genètiques de NR3C1 i NR3C2 i les concentracions de CRH, ACTH i cortisol s'associen amb la depressió postpart.

Mètode

Evaluació de la depressió

1. Criteris inclusió/exclusió
2. Rastreig de símptomes depressius (EPDS). Basal, 8 setmanes i 32 setmanes
3. Confirmació diagnòstica de Depressió major (DIGS-DSMIV).
4. Variables sociodemogràfiques i mèdiques.
5. Evaluació de la personalitat (EPQ).
6. Evaluació quanti i qualitativa dels factors vitals estressants (St Paul Ramsey)

Característiques submostra

- Inclusió
  - Extracció de sang
    - dejú
    - 8-10 h matí
    - 24-48h postpart
    - Plasma i sèrum obtingut immediatament a l'extracció

N=525

Determinació d'hormones

1. CRH, radioimmunoassaig (Phoenix Pharmaceuticals, Karlsruhe, Germany) en un LKB 1261 Multigamma Counter (LKB, Barcelona, Spain).

2. ACTH, immunoquimoluminiscència (IMMULITE 2000, Siemens, Madrid, Spain).

3. Cortisol, immunoassaig de fluorescencia polaritzada (Axsym System, Abbot Laboratories, Madrid, Spain).

Genotipat

- Es va genotipar amb el sistema SNPlex (Applied Biosystems, Foster City, CA) als nodes de Santiago de Compostela i Barcelona de CEGEN.

Resultats

Table 1a. Characteristics of study participants 48h after delivery grouped according to presence or absence of subsequent postpartum depression

	All N=525	Non-PPD N=483	PPD N=42	P*
Sociodemographic				
Age (years)[a]	32 ± 4.7	32 ± 4.7	32 ± 4.9	0.97
Level of education, graduate school (%)	25.5	25.2	29.5	0.69
Single, widow or divorced (%)	1.86	1.80	1.90	0.10
Employed during pregnancy (%)	71.1	72.0	61.4	0.21
Obstetric				
Primiparous (%)	55.9	55.6	59.1	0.66
Caesarea (%)	17.1	17.0	18.2	0.84
Gestation age at delivery (weeks)[a]	39.3 ± 1.8	39.1 ± 1.8	39.4 ± 1.8	0.24
Offspring birth weight (g)[a]	3207 ± 496	3202 ± 489	3262 ± 568	0.45
Pregnancy complications (%)[b]	39.6	41.1	22.7	0.02
Peripartum complications (%)[b]	43.7	42.7	54.5	0.13

8%

[a]Data presented as means ± SD.
[b]Any medical condition that involved either hospitalization or pharmacological treatment during pregnancy and before, during or after delivery

Resultats

Table 1b. Characteristics of study participants 48h after delivery grouped according to presence or absence of subsequent postpartum depression

	All N=525	Non-PPD N=483	PPD N=42	P*
Psychopatological				
EPDS score	6.15 ± 4.1	5.9 ± 4.0	8.7 ± 4.9	<0.001
Family history of psychiatric treatment (%)	32.4	31.2	45.5	0.054
Personality traits-Neuroticism[c]	41.2 ± 8.2	40.8 ± 7.9	45.72 ± 10.1	<0.001
Stressful life events	1.02 ± 0.98	0.97 ± 0.98	1.50 ± 0.93	0.001
HPA-axis Hormones[a]				
Cortisol (nmol/L)	832.9 ± 227.8	834.9 ± 230	810.6 ± 189	0.51
ACTH (pmol/L)	4.64 ± 2.86	4.69 ± 2.90	4.14 ± 2.27	0.22
pCRH (pg/mL)	141.1 ± 54.04	141.3 ± 54.4	138.6 ± 49.2	0.76
Correlation Cortisol-ACTH (rho, P)[d]	0.345 (0.01)	0.342 (0.01)	0.440 (0.01)	-

[c]Extraversion and psychoticism did not differ between PPD and Non-PPD groups and are not shown.
[d]Other correlations between hormone parameters were not statistically significant and are not shown.

Resultats

Table 2. Significant results in the analysis of association between SNPs at NR3C2 and NR3C1 and PPD, adjusted by hormonal concentration

Hormone	SNP	Gene	Chr Position	Exon/Intron[a]	LRT χ^2	P value[b]
cortisol	rs7695118	NR3C2	149012794	Intron 1	8.412	0.0149
cortisol	rs2883929	NR3C2	149084112	Intron 1	6.303	0.0428
ACTH	rs6810951	NR3C2	149126915	Intron 1	8.254	0.0161
CRH	rs3910052	NR3C2	149221110	Intron 1	6.513	0.0385
CRH	rs4635799	NR3C2	149350527	Intron 1	15.49	0.0004[c]
CRH	rs11099695	NR3C2	149354139	Intron 1	10.18	0.0062

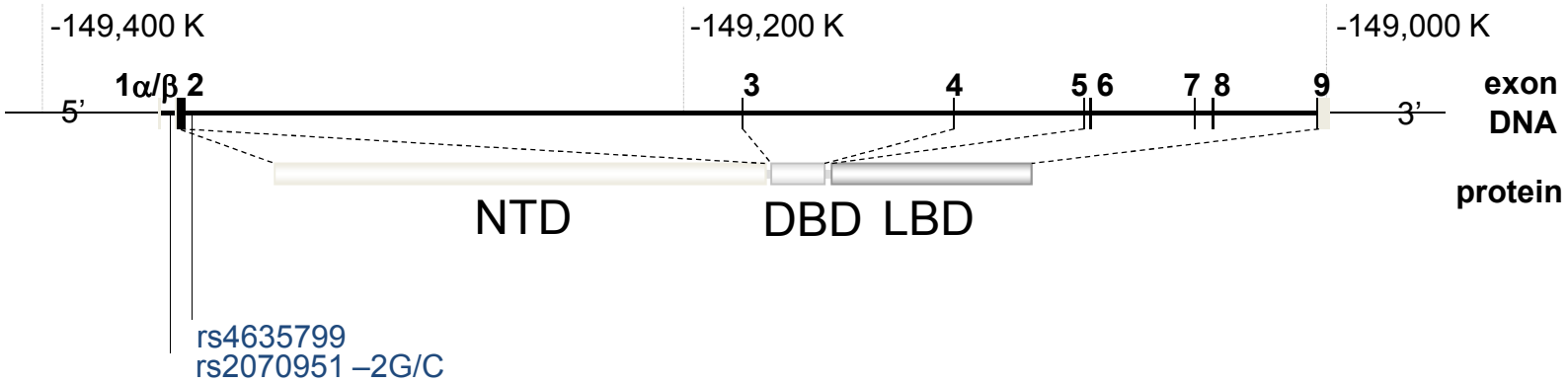
[a]Based on genome version NCBI 37.1
[b]P value of the likelihood ratio test for overall association, as implemented in UNPHASED v3.01
[c]Significant after Bonferroni correction
LRT, Likelihood ratio test

Resultats

Table 1c. Characteristics of study participants 48h after delivery grouped according to presence or absence of subsequent postpartum depression	All N=525	Non-PPD N=483	PPD N=42	P*
Relevant polymorphisms				
NR3C2 rs4635799[e]				
CC	0.260	0.233	0.286	ns
CT	0.511	0.523	0.500	
TT	0.229	0.244	0.214	

[e] C is the ancestral and most frequent allele.

Gen del Receptor Mineralocorticoide , NR3C2



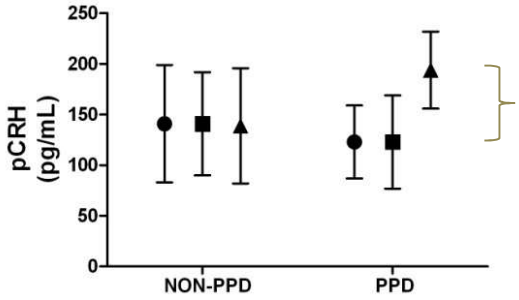
Resultats

Valors normals

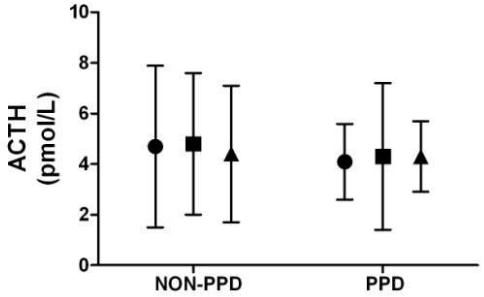
indetectable

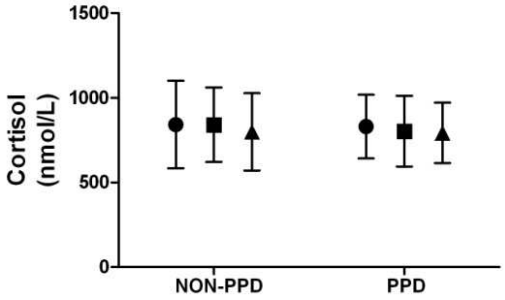
<10.12 pmol/L

115.9-1059.8 nmol/L



71 pg/mL, P<0.0001





NR3C2 rs4635799

- ● **CC**
- ■ **CT**
- ▲ **TT**

Resultats

Table 3. Multivariate logistic regression analysis

Step/method	Variable/s in equation	B	Wald Statistic	P	OR	95% CI
1/Enter	rs4635799TT	-0.183	0.219	0.640	0.833	0.387-1.793
2/Enter	rs4635799TT	-0.180	0.211	0.646	0.835	0.388-1.799
	pCRH	-0.001	0.046	0.830	0.999	0.993-1.005
3/Enter	rs4635799TT	-3.551	8.232	0.004	0.029	0.003-0.325
	pCRH	-0.007	3.295	0.069	0.993	0.993-1.001
	rs4635799TT by pCRH	0.022	9.835	0.002	1.022	1.008-1.036
4/Stepwise[a]	rs4635799TT	-3.610	8.000	0.005	0.027	0.002-0.330
	pCRH	-0.008	3.214	0.073	0.992	0.984-1.001
	rs4635799TT by pCRH	0.022	9.206	0.002	1.022	1.008-1.037
5/Stepforward[b]	neuroticism	0.062	11.231	0.001	1.064	1.026-1.103
	pregnancy complications	-1.137	5.298	0.021	0.321	0.122-0.845
	peripartum complications	-0.345	0.643	0.423	0.708	0.304-1.647
	stressful life events	0.496	9.025	0.003	1.642	1.188-2.268

[a,b]Variables not in the equation: CRH by neuroticism, CRH by stressful life events, neuroticism by stressful life events, rs4635799TT by neuroticism, rs4635799TT by stressful life events

Resultats-discussió

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Elevated Corticotropin-Releasing Hormone in Human Pregnancy Increases the Risk of Postpartum Depressive Symptoms

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Abstract

Context—Postpartum depression (PPD) is common and has serious implications for the mother and her newborn. A possible link between placental corticotropin-releasing hormone (pCRH) and PPD incidence has been discussed, but there is a lack of empirical evidence.

Objective—To determine whether accelerated pCRH increases throughout pregnancy are associated with PPD symptoms.

Design—Pregnant women were recruited into this longitudinal cohort study. Blood samples were obtained at 15, 19, 25, 31 and 37 weeks gestational age (GA) for assessment of pCRH, cortisol and ACTH. Depressive symptoms were assessed with a standardized questionnaire at the last four pregnancy visits and postpartum.

Setting—Subjects were recruited from two Southern California Medical Centers, and visits were conducted in university research laboratories.

Participants—100 adult women with a singleton pregnancy.

Main Outcome Measure—PPD symptoms were assessed 8.7 weeks (SD = 2.94 wks) after delivery with the Edinburgh Postnatal Depression Scale.

Results—Sixteen women developed PPD symptoms. At 25 weeks GA, pCRH was a strong predictor of PPD symptoms (R^2 = .21, β = .46, p < .001), an effect that remained significant after controlling for prenatal depressive symptoms. No significant associations were found for cortisol and ACTH. Receiver Operating Characteristic curve analyses revealed that pCRH at 25 weeks GA is a useful diagnostic test (area under the curve = .78, p = .001). Sensitivity (.75) and specificity (.74) at the ideal cut-off point (56.86 pg/ml pCRH) were high. Growth curve analyses indicated that pCRH trajectories in women with PPD symptoms are significantly accelerated between 23 and 26 weeks GA.

Conclusion—There is a critical period in mid-pregnancy during which pCRH is a sensitive and specific early diagnostic test for PPD symptoms. If replicated, these results have implications for identification and treatment of pregnant women at risk of PPD.

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Elevated Corticotropin Releasing Hormone (CRH) during Pregnancy and Risk of Postpartum Depression (PPD)

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Abstract

Context: Perinatal depression has a prevalence of 10% with devastating consequences for mother and baby. The prospective identification of those at risk for postpartum (PPD) or prenatal (PND) depression has led to biomarker searches in pregnancy. There are conflicting reports of associations between midpregnancy placental CRH (pCRH) and PPD or PND.

Objective: The objective of the study was to quantify the association of maternal pCRH with PPD and PND.

Design: This was a prospective cohort study (the Pregnancy, Infection, and Nutrition Study).

Setting: The study was conducted at a prenatal clinics at the University of North Carolina at Chapel Hill.

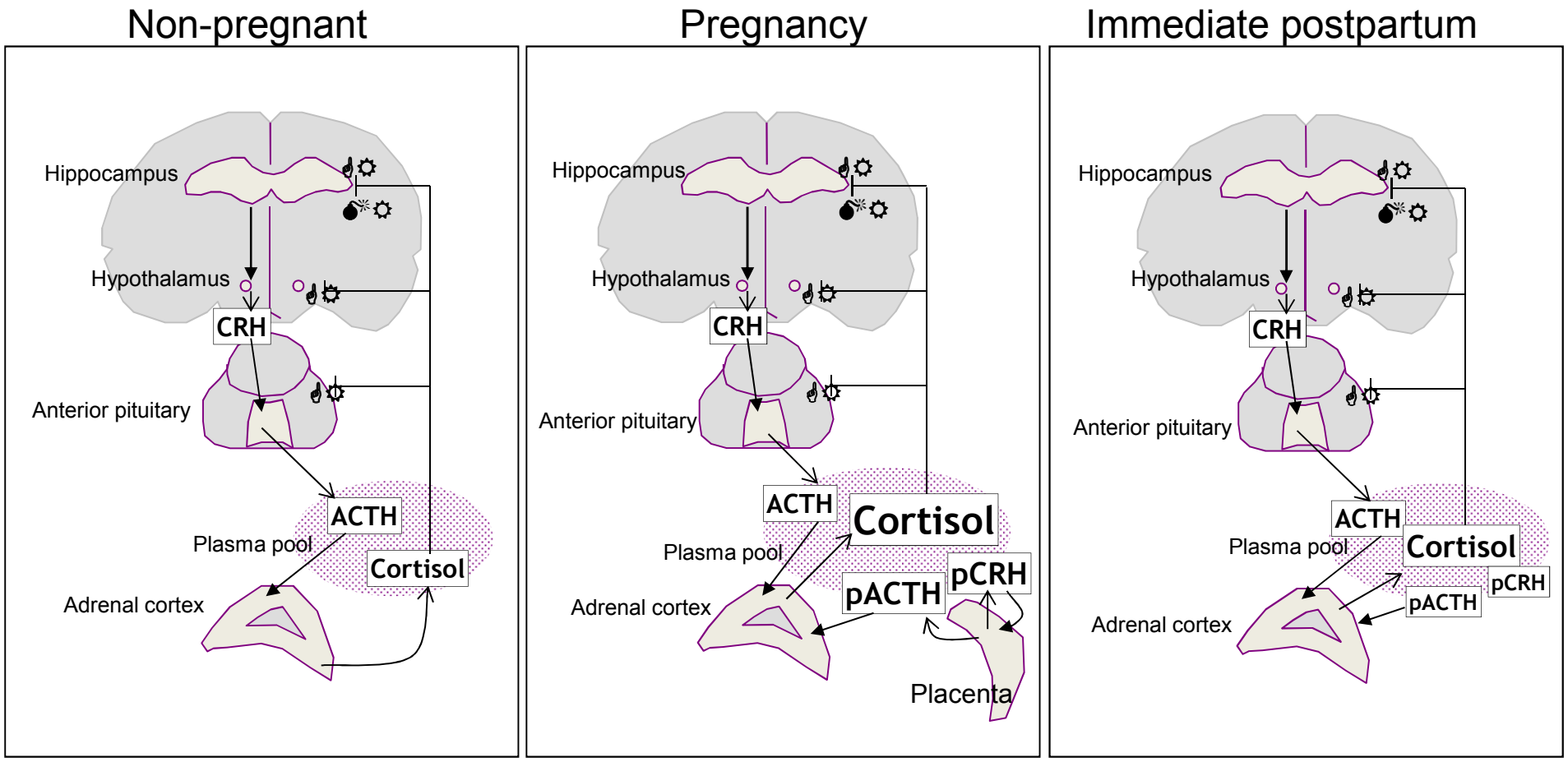
Patients: Patients included 1230 pregnant women.

Main Outcome Measures: The relationship between pCRH at less than 20 wk and 24–29 wk and maternal depression assessed in pregnancy [Center for Epidemiologic Studies Depression Scale (CES-D)] and postpartum (12 wk and 1 yr) with the Edinburgh Postnatal Depression Scale (EPDS).

Results: At 24–29 wk, 24.8% of women had CES-D score of 17 or greater, and 9.7% had a CES-D score of 25 or greater. At 12 wk postpartum, 18.2% of women had an EPDS score of 10 or greater and 7.6% had an EPDS score of 13 or greater. CRH measures at less than 20 wk and 24–29 wk were inversely correlated with a CES-D score at 24–29 wk (n = 1080, $P < 0.05$ and $P < 0.01$, respectively). Pregnancy pCRH was not correlated with the EPDS score at 12 wk (n = 484) or 1 yr postpartum (n = 391). In covariate-adjusted models, higher pCRH was not associated with a CES-D of 17 or greater at 24–29 wk (odds ratio 0.88 per SD change in pCRH at 24–29 wk, 95% confidence interval 0.76–1.03). There was no association between log CRH at 24–29 wk and PPD (covariate-adjusted odds ratio per SD 0.99, 95% confidence interval 0.69–1.42).

Conclusion: Higher midpregnancy pCRH was not associated with an increased risk of PND or PPD.

Resultats-discussió



GR, glucocorticoid receptor
MR, mineralocorticoid receptor
CRH, cortisol releasing hormone
pCRH, placental CRH
pACTH, placental ACTH

Conclusió

- Trobem una intereacció important entre la pCRH 48 hores després del part i el genotip NR3C2 rs4635799TT.
- Aquesta interacció augmenta d'una manera moderada el risk de desenvolupar DPP.
- Aquests resultats, si es reprodueixen en altres estudis, poden ajudar a identificar els factors de risc i les estrategies terapèutiques de la DPP.

L'equip investigador …

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Moltes gràcies