

Inflammatory biomarkers in the plasma and cerebrospinal fluid of patients with persistent pain and postpartum depression after elective cesarean delivery: an exploratory study

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- Severe acute pain after cesarean delivery increases risk of developing persistent pain (23% incidence)¹ and perinatal depression (15% incidence)²
- Neuroinflammation has emerged as a mediator of persistent pain and depression in non-obstetric population
- Inflammatory markers may play a role in peripheral and central sensitization of pain
- Relationship between peripheral and central inflammatory markers is unclear

1. *Rev Bras Anesthesiol* 2012; **62**: 775-87.

2. *JAMA Psychiatry* 2013; **70**: 490-8.

Methods

- Term singleton pregnancies undergoing scheduled cesarean delivery under spinal or combined spinal epidural anesthesia recruited
- 10 ml of blood (plasma) collected preoperatively and 48 hours post-cesarean delivery
- 10 ml CSF collected prior to administration of standard neuraxial anesthetic
- Primary Outcome: composite outcome of persistent pain (pain score ≥ 3) or perinatal depression (EPDS ≥ 10) versus neither outcome at 3 months postpartum
- Multiplex analyses using MSD custom Uplex assay (MesoScale, Rockville, MD) on 12 candidate biomarkers assessed for association with primary outcome
 - CRP, TGF β 1, IFN γ , TNF α , IL-1 β , IL-6, IL-8, IL-10, IL-12p70, IL-13, IL-18, and IL-21
- Using $\alpha=0.05$ and a two-sided Mann-Whitney test, a sample size of 70 would provide >80% power to detect a 15% difference in our candidate inflammatory marker levels between patients with vs. without primary outcome

Results

Preoperative plasma inflammatory marker levels in patients with or without persistent pain and/or PPD

Cytokine	No persistent pain or PPD (N=40)	Persistent pain and /or PPD (N=21)	Mann-Whitney P-value
CRP	5172.61 [2936.70, 8838.80]	5445.42 [2198.05, 7019.55]	>0.999
TGFβ1	2292.13 [1675.64, 2960.46]	2878.62 [2240.55, 5493.65]	0.043
INFγ	10.17 [8.09, 15.39]	10.88 [8.82, 17.03]	0.529
IL-10	0.56 [0.43, 0.70]	0.55 [0.42, 0.80]	0.958
IL-18	769.88 [623.30, 1015.03]	916.70 [710.44, 1039.89]	0.216
IL-6	2.20 [1.96, 2.88]	2.10 [1.97, 2.56]	0.585
IL-8	4.42 [3.36, 6.07]	3.58 [2.99, 9.16]	0.676
TNFα	0.89 [0.69, 1.06]	0.98 [0.79, 1.18]	0.246
Detectable IL-12p70*	11 (27.5%)	4 (19.0%)	0.466
Detectable IL-13*	13 (32.5%)	3 (14.3%)	0.124
Detectable IL-1β*	15 (37.5%)	8 (38.1%)	0.964
Detectable IL-21*	11 (27.5%)	4 (19.0%)	0.466

Values are in median [Q1, Q3] and count (%) and pg/ml unless otherwise indicated. *count (%) of patients with detectable analytes > LLOD (lower limit of detection) PPD: Postpartum Depression.

- 80 patients enrolled, 63 completed clinical follow-up at 3-months via phone call
- CSF obtained from all 63 patients who completed follow-up
- Preop plasma obtained from 61 of 63 who completed clinical follow-up

Preoperative cerebrospinal fluid inflammatory marker levels in patients with or without persistent pain and/or PPD

Analyte	No persistent pain or PPD (N=40)	Persistent pain and/ or PPD (N= 23)	Mann-Whitney P-value
CRP	8594.82 [4142.60, 14881.07]	8826.08 [2531.91, 13441.23]	0.881
TGFβ1	35.51 [26.05, 48.04]	46.13 [27.55, 63.16]	0.262
Detectable IFNγ*	6 (15.0%)	4 (17.4%)	0.803
IL-18	8.47 [7.06, 10.63]	7.64 [7.02, 10.48]	0.994
IL-1β	0.30 [0.25, 0.35]	0.36 [0.29, 0.39]	0.033
IL-6	1.48 [1.20, 1.76]	1.38 [1.14, 1.87]	0.617
IL-8	58.79 [51.78, 68.21]	64.39 [56.23, 71.72]	0.096

Values are in median [Q1, Q3] and count (%) and pg/ml unless otherwise indicated. >95% of samples had non-detectable levels IL-10, IL-12p70, IL-13, IL-21, and TNFα *count (%) of patients with detectable analytes > LLOD (lower limit of detection) PPD: Postpartum Depression.