

PROJECT 2**DoS:** SARA POLETTI

Title: Pregnancy during a pandemic: a deep phenotyping approach exploring the role of inflammation on post-partum cognitive decline and depression.

Link to OSR/UniSR personal page:

<https://research.hsr.it/en/divisions/neuroscience/psychiatry-and-clinical-psychobiology/index.html>

Project description (*Number of characters, including spaces: 2.000 - 3.000*):

A worldwide pandemic with more than 230 million individuals infected and 4.7 million deaths has characterized the last two years. At the outset of the COVID-19 pandemic, the precise extent of the risks in pregnancy was uncertain, recent data, however, showed consistent and substantial increases in severe maternal morbidity and mortality and neonatal complications. Further, CDC report shows that only 23% of pregnant women in the United States had been vaccinated by the end of July for fear of the consequences of the vaccine on the fetus. Pregnancy and the post-partum are a particularly vulnerable period where women may experience cognitive decline and depression. Over 80% of pregnant women experience subjective cognitive decline characterized by poor thinking ability, memory loss, and difficulty concentrating, and this could be worsened by post-partum depression (PPD). PPD affects 10-20% of mothers every year, lasting >6 months in 25-50% of cases. PPD is the most common complication of childbirth affecting the mother, with suicide accounting for approximately 20% of postpartum deaths. An healthy postpartum period is associated with enhanced T cell activity, which is lacking in acute peripartum psychosis, when instead an enhanced pro-inflammatory status ensues. This pattern is similar to that observed in other mood disorders, where a T cell defect associates with higher peripheral markers of inflammation and detrimental effects on brain homeostasis. These immunological alterations may be influenced by COVID-19 infection. Indeed, COVID-19 infection has been associated, by previous research of our group, with symptoms of depression and anxiety and with cognitive decline persisting up to six months after the clearance of the virus, and possibly further on when untreated.

In this project we will apply the same research approach, proven successful in bipolar and unipolar depression, to PPD, which has the unique characteristic of allowing the identification of

the onset of symptoms with the highest precision in mood disorders. This will allow to investigate the possible biological predictors of PPD by studying the immune/inflammatory peripheral biomarkers before and after delivery, and to then explore their changes and their correlation with the clinical status 6 weeks after delivery. Further, the project will specifically focus on cognitive decline both during pregnancy and in the postpartum period in association with the onset of depressive symptoms and taking into account the exposure to COVID-19 infection. The project will also consider the mental status of pregnant women who had vaccination in the pandemic period, the role of anxiety, social status, and education.

The current PhD project is focused on:

- 1) Collecting longitudinal clinical data and information on COVID-19 infection, vaccination, risk perception and use of social media using enabling technologies (online tools, such as internet-based platforms for the administration of questionnaires) through online surveys in Italian general population (sample size: n=500) (1 year); and in patients enrolled at the Department of Obstetrics and Gynecology of IRCCS Ospedale San Raffaele S.R.L.
- 2) Providing an in-deep clinical, behavioral, neurocognitive, neural (structural and functional neuroimaging) and immuno (cytokines, gene expression, and FACS immunophenotyping) phenotyping of women in the post-partum period, in order to better define the biological underpinnings of PPD and neurocognitive deficits. This will be performed in patients enrolled at Department of Obstetrics and Gynecology of IRCCS Ospedale San Raffaele S.R.L. The data collected in the post-partum will be compared with clinical and cognitive data and with immune/inflammatory markers collected during pregnancy. (1-3 years).

We will recruit a sample of 150 pregnant women blood samples will be collected at week 37 of the pregnancy, and 6 weeks after delivery (the DSM 5 “postpartum onset” specifier requires that the onset of symptoms must occur within 4 weeks postpartum). Participants will be tested for cognitive functions and possible presence of depressive psychopathology with MINI structured interview and the Edinburgh Postnatal Depression Scale (EPDS); severity of depression will be rated on the Hamilton Depression Rating Scale (HDRS), the Beck Depression Inventory (BDI), and the Beck Scale for Suicide (BSS). Cognitive functions will be investigated through the Brief Assessment of Cognition in Affective Disorders (BAC-A). For women who screened negative on the 6 week interview, we will repeat a telephone screening at 3 months and 6 months to identify emergent symptoms. The biological samples of these selected participants will then be processed

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for peripheral biomarkers (cytokines), gene expression, and FACS immunophenotyping, to correlate the immune/inflammatory status with the clinical picture before/after delivery.

3) Analyzing cognitive decline both during pregnancy and post-partum, investigating how this is influenced by the emergence of depressive symptomatology. Penalized logistic regression with elastic net will be performed to identify the predictors of cognitive decline;

4) Analyze the contribution of social factors such as the choice to be vaccinated, influence of media, and the fear for the effects of the vaccine on the fetus. Pregnancy is a very vulnerable period also emotionally and women can be easily frightened and influenced by media and social media, understanding the role of social and psychological factors is then of crucial importance to promote new strategies for women wellbeing.

5) Analyzing the impact of COVID-19 infection or vaccination on post-partum mood and cognitive status. Considering the neurotropic effect of the coronavirus, understanding the impact of COVID-19 infection on cognitive decline and depression will enable us to better understand the role of the immune response as a mechanism underlying there behavioral alterations.

6) Multifactorial modelling for disease prediction: A multiple kernel learning (MKL) approach will be used to develop PPD prediction models using multidisciplinary features, while removing the effect of confounding factors. Features will be extracted from neuroimaging, molecular, clinical and cognitive data using advanced quantitative methods.

7) Provide scientific data on the mechanisms underlying post-partum alterations in order to identify preventive strategies and early interventions to promote the wellbeing of mothers and the baby.

Skills to be acquired by the student:

The PhD student will directly participate to the activities performed in Ospedale San Raffaele S.R.L., in a 6 months stage, aimed at defining needs, to implement effective interventions on the clinical processes exploiting key enabling technologies (1-2 years); these will include machine learning algorithms to predict patients' outcomes and internet-based platforms. The candidate will actively participate to all phases of the project: from design of the protocols and surveys, data collection, to the analyses of the data though cutting-edge statistical methods (e.g. MKL) including multimodal neuroimaging analyses (resting state fMRI, including connectivity analyses, structural imaging for grey matter volumes and thickness, and white matter integrity). The performance of

different feature sets will be compared in terms of accuracy and the optimal diagnostic model will be selected for future prediction. (2-3 year) these will include machine learning algorithms to predict disease onset and internet-based platforms

Feasibility:

This project will be carried out within the main research frame of the research unit Psychiatry and Clinical Psychobiology at Ospedale San Raffaele SRL, currently funded for an ongoing research on PPD and neuroinflammation (Italian Ministry of Health RF project grant RF-2019-12371066) and for studying the role of neuroinflammation in mood disorders (European Union H2020 SC1-PM-02-2017 New concepts in patient stratification: "MOODSTRATIFICATION: Immune Signatures for Therapy Stratification in Major Mood Disorders" Grant agreement ID: 754740).

References (max. 3)

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Company:

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