Maternal immune system in preeclampsia

Lay summary: Preeclampsia is a syndrome that occurs in women during pregnancy and is diagnosed by having new onset high blood pressure and either protein in the urine or new organ damage. Preeclampsia can have a devastating impact on the health of the mom as well as her growing baby. Although, doctors and researchers have known about preeclampsia for centuries, we still do not yet know exactly what causes preeclampsia and how it develops. Without this knowledge, it makes designing treatments for preeclampsia very hard.

Our research takes a unique approach for studying preeclampsia by focusing on the mom's immune system (the body's defense against infections) which been shown to be different in women with preeclampsia. We studied how the mom's immune cells (specifically, white blood cells) are changed because of preeclampsia and what role they play in activating the lining of blood vessels (specifically endothelial cells) and leading to high blood pressure.

Our results have shown so far that there are important changes in specific type of immune cells, called lymphocytes, in women with preeclampsia. When we extract these immune cells from moms who have preeclampsia, we were able to show directly that these cells act on blood vessel cells and cause strong inflammation. These results may mean that immune cells could be contributing to what is happening in women in pregnancy with preeclampsia.

Overall, our work points to role of mom's immune cells to preeclampsia, which means that these cells could be targeted to reduce the negative impact of preeclampsia in moms and their babies.

Technical summary: We investigated the mechanisms underlying the maternal immune contribution to the etiology of preeclampsia in order to identify new therapeutic targets to minimize the short and long-term impact of maternal health and subsequently on the baby. In our studies, we observed that specific subpopulations of immune cells (especially T lymphocytes) were elevated in the maternal circulation in preeclampsia. Interestingly, changes in immune population were also observed in women with postpartum occurrence of preeclampsia but these were different from women with the classic presentation of the pathology (namely prepartum preeclampsia). Furthermore, placentas from pregnancies that ended up with postpartum preeclampsia presented elevated number of immune cells strongly suggesting a prenatal initiation of the pathology (Brien ME et al., Biol Reprod, 2019). In addition, we investigated the role of immune cells in endothelial activation, hallmark of hypertension and saw that they were potent activator of the endothelium. Overall this work strongly suggest that the maternal immune system is an important contributor to the clinical symptoms of preeclampsia which could be targeted to minimize the impact on maternal health and promote healthier fetal/neonatal development.

Report: Preeclampsia (PE) is an important pregnancy specific pathology characterised primarily by hypertension and being the main cause of maternal mortality and morbidity. Currently used treatment targets mostly the symptoms (i.e. hypertension) and not the cause since the mechanism of the disease is mostly unknown. Aside from the obvious negative impact on the fetus (including fetal growth restriction and often associated preterm birth), PE also has long-term impact on maternal health leading to increased risk of PE in subsequent pregnancies and elevated incidence of cardiovascular diseases later in life. **A better understanding of the mechanisms underlying PE is essential to developed new efficient therapeutic strategies and minimise the long-term impact on maternal health.** Due to the known association

between maternal immune changes and PE, but limited understanding of their involvement in the pathology, we proposed to **(1) investigate the changes in the maternal immune system (both pre and postnatally) in PE as compared to uncomplicated pregnancies** and **(2) determine the involvement of these immune cells in the activation of the vascular endothelium (central component of hypertension).**

For the **first part of the work**, which was under review for publication at the time of the mid-year report, I am happy to say that this work has now been published (**Reference: Brien ME, Boufaied I, Dal Soglio D, Rey E, Leduc L, Girard S. Distinct inflammatory profile in PE and postpartum PE reveal unique disease mechanisms. Biology of Reproduction, 2019; 100(1): 187-194)**. In this work, we published evidence that women with PE had elevated levels of subpopulation of immune cells, especially CD4+ T helper and CD8+ T cytotoxic lymphocytes. Furthermore, we showed that women with postpartum occurrence of PE also had altered immune profile and that their placenta presented with elevated number of immune cells, mostly macrophages strongly suggestive of a prenatal initiation of the pathology. Following up from this, we are now finishing up a retrospective study comparing the perinatal immune profiles of women with uncomplicated pregnancies, PE-complicated pregnancies or women that later developed postpartum PE. We observed significant differences in the maternal immune system prior to delivery in women with seemingly uncomplicated pregnancies that later developed postpartum PE. These changes were specific to women that developed postpartum PE as they were not observed in those with the classical presentation of PE. This work will be submitted for publication in the coming months.

For the **second part of the work**, which was to determine the involvement of maternal immune cells in the activation of the vascular endothelium (central component of hypertension), we obtained strong preliminary evidence that immune cells from women with PE were potent activator of the endothelium, as seen by elevated secretion of markers of activation (ICAM-1, VCAM-1, e-selectin) and that both cell-contact (between immune and endothelial cells) and soluble inflammatory mediators being released by maternal immune cells, are involved in vascular endothelium activation. This work is of high importance as it is the beginning to the understanding of the mechanisms linking immune changes and the clinical symptoms of PE, which could potentially be targeted therapeutically. In order to pursue this work, additional funding is required and we recently submitted a grant proposal to the Canadian Institutes of Health Research (CIHR), thanks to the results we obtained supported by Preeclampsia Foundation Canada.

Please see (in the next page) the list of presentation which highlighted the support from the foundation and we would like to thank Preeclampsia Foundation Canada for the grant which allowed us to pursue this important work and acquire the needed preliminary data to apply for additional funding.

List of presentations highlighting the support from Preeclampsia Foundation Canada

· **Brien ME**, Piché J, Boufaied I, Rey E, Girard S., Perinatal immune changes to identify women at high-risk of postpartum preeclampsia. American Society for Reproductive Immunology, Michigan, USA, June 2019

· Piché J, **Brien ME**, Boufaied I, Rey E, Girard S., Perinatal immune changes to identify women at high-risk of postpartum preeclampsia. Congrès provincial de la recherche mère-enfant, Montréal, Quebec, Canada, May 2019

· Piché J, **Brien ME**, Boufaied I, Rey E, Girard S., Perinatal immune changes to identify women at high-risk of postpartum preeclampsia. Congrès de la recherche des étudiants des cycles supérieurs et des postdoctorants, Montréal, Canada, May 2019

· **Duval C,** Boufaied I, Girard S. Endothelial activation by peripheral immune cells from women with PE-complicated pregnancies. (Poster) The Canadian National Perinatal Research Meeting 2019 (CNPRM), February 2019

· Piché J, **Brien ME**, Boufaied I, Rey E, Girard S., Perinatal immune changes to identify women at high-risk of postpartum preeclampsia. Journée du département d'obstétrique et gynécologie de l'université de Montréal, Montréal, February 2019 (Oral)

· Piché J, **Brien ME**, Boufaied I, Rey E, Girard S., Perinatal immune changes to identify women at high-risk of postpartum preeclampsia. Canadian National Perinatal Research Meeting, Québec, Tremblant, Quebec, Canada, February 2019 (Prize for best poster presentation)

· **Duval C,** Boufaied I, Girard S. Endothelial activation by peripheral immune cells from women with PE-complicated pregnancies. (Poster) Meeting of the International Federation of Placenta Associations, Tokyo, Japan, September 2018

· **Duval C,** Boufaied I, Girard S. Endothelial activation by peripheral immune cells from women with PE-complicated pregnancies. (Oral) XXIIIe Colloque annuel d'Immuno-Inflammation, Eastman, Québec, Canada, June 2018

· **Duval C,** Boufaied I, Girard S. Endothelial activation by peripheral immune cells from women with PE-complicated pregnancies. (Poster) Journée du Centre de Recherche du CHU Sainte-Justine, Montréal, Québec, Canada, June 2018

· **Duval C,** Boufaied I, Girard S. Endothelial activation by peripheral immune cells from women with PE-complicated pregnancies. (Oral) Congrès Provincial Mère-Enfant, Montréal, Québec, Canada, May 2018

· **Duval C,** Boufaied I, Girard S. Endothelial activation by peripheral immune cells from women with PE-complicated pregnancies. (Poster) Journée de la recherche du Département de Pharmacologie et de Physiologie de l'Université de Montréal (Journée Gabriel L. Plaa), Montréal, Québec, Canada, May 2018

· **Duval C,** Boufaied I, Girard S. Endothelial activation by peripheral immune cells from women with PE-complicated pregnancies. (Oral) Journée du Département d'Obstétrique et de Gynécologie de l'Université de Montréal, Montréal, Québec, Canada, February 2018