Should we stop aspirin prophylaxis in pregnant women when diagnosed with COVID-19?

Gavillet Mathilde[1], MD PhD; Daniel L. Rolnik [2], MD PhD; Matthew K. Hoffman[3], MD MPH; Alice Panchaud, Pharm PhD[4,5]; David Baud[6], MD PhD

[1] Service and Central Laboratory of Hematology, Department of Oncology and Department of Laboratories and Pathology, Lausanne University Hospital (CHUV), Lausanne, Switzerland

[2] Department of Obstetrics and Gynaecology, Monash University, Melbourne, Australia

[3] Department of Obstetrics and Gynecology, Christiana Care, Delaware, USA

[4] Center for Research and Innovation in Clinical Pharmaceutical Sciences, Institute of Pharmaceutical Sciences of Western Switzerland, Lausanne University Hospital and University of Lausanne, University of Geneva, Switzerland.

[5] Service of Pharmacy Service, Lausanne University Hospital and University of Lausanne, Switzerland.

[6] Materno-fetal and Obstetrics Research Unit, Department Woman-Mother-Child, Lausanne University Hospital, Lausanne, Switzerland

***Corresponding author:** David Baud, MD PhD

Materno-fetal & Obstetrics Research Unit

Department of Obstetrics and Gynecology

Centre Hospitalier Universitaire Vaudois (CHUV)

1011 Lausanne - SWITZERLAND

Email: david.baud@chuv.ch

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COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can progress to critical illness with acute respiratory distress and disseminated intravascular coagulation (DIC). Biomarkers of DIC (elevated D-dimer and thrombocytopenia) are detectable early in the course of the disease and correlate with a dismal prognosis [1, 2]. In the first SARS outbreak, thrombocytopenia was reported in 20-55% of patients [2]. Data for the current SARS-CoV-2 are less mature and vary between 5-41.7% [2]. Multiple phenomena underpin the SARS-CoV-2 associated thrombocytopenia: decreased production in infected hematopoietic marrow as well as increased consumption by DIC and in damaged lung tissue and capillaries [3]. The natural course of COVID-19 that shows mild symptoms for days before clinical deterioration, including those who will subsequently present with a severe form or a fatal outcome, is not different in pregnant women [4]. Furthermore, as children with COVID-19 have mild or asymptomatic disease; children in the household are highly contagious to future mothers.

Prophylactic administration of low-dose aspirin to pregnant women is common. It is currently indicated in those at moderate to high-risk of preeclampsia [5], a group which represents 10-15% of all pregnancies. In the "Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE)" trial, daily administration of aspirin at 150 mg, initiated between 11 and 14 weeks of gestation, resulted in a 62% reduction in the incidence of preterm preeclampsia when compared to placebo in women at high risk identified by means of a predictive algorithm that combines maternal characteristics, medical history and biomarkers (1.6% with aspirin therapy versus 4.3% in the placebo group, odds ratio 0.38, 95% CI 0.20–0.74, P=0.004) [5]. Low-dose aspirin is also indicated in pregnant women with antiphospholipid syndrome (APS), and with mechanical heart valves or prescribed for the prevention of early pregnancy loss, fetal growth restriction, or stillbirth (Table 1) [6].

During the current COVID-19 pandemic, systematic screening of any suspected SARS-CoV-2 infection in pregnancy is recommended [4]. Positive cases should have careful evaluation of the risk/benefit ratio of low-dose aspirin therapy is advised (taking into account the indication, the gestational age and platelet counts) (Table 1). Aspirin belongs to the group of nonsteroidal anti-inflammatory drugs (NSAID), the use of which is controversial in COVID-19 patients. As it irreversibly inhibits platelet cyclooxygenase, aspirin effect persists for the circulating life of platelets (7-10 days). Thus, the delay between SARS-CoV-2 test positivity and clinical deterioration is similar to the delay between the last aspirin intake and the end of its clinical effect. Furthermore, aspirin is not indicated for the treatment of DIC, or other venous thrombo-embolic complication that might be associated with severe COVID-19, and may increase the bleeding risk in severely thrombocytopenic patients.

While supporting the continuous use of prophylactic aspirin in pregnant women during the COVID-19 pandemic, thus along the lines of the paper by Kwiatkowski *et al.* [7] published recently in this journal, our view is more nuanced. We recommend immediate cessation of aspirin prescribed for preeclampsia prophylaxis upon diagnosis of a SARS-CoV-2 infection, avoidance of aspirin for the duration of the disease, and restarting the medication after full recovery (Table 1); especially for women in the third trimester of pregnancy, as the benefit is minimal and aspirin could contribute to severe bleeding in thrombocytopenic COVID-19 patients or if emergency delivery (cesarean section) is indicated by maternal condition. The above listed propositions should help tailoring individualized therapeutic decisions for pregnant women during the COVID-19 pandemic.

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Table 1

Indication	Percent affected pregnancies	Therapy	Benefit	Attitude if positive SARS-CoV-2 testing
Moderate to high-risk for preeclampsia	10-15%, depending on screening method used	Low-dose aspirin <14 weeks of gestation until 36 weeks (or delivery)	Preterm preeclampsia occurred in 1.6% under aspirin, as compared 4.3% in the placebo group (odds ratio 0.38; P=0.004)	Immediate cessation in pregnant women, who test positive for COVID-19, avoidance of aspirin for the duration of the disease, and consider restarting the medication after full recovery
Intrauterine growth restriction (IUGR)	Varies with local practice	Low-dose aspirin	Not demonstrated in the absence of risk factors for preeclampsia	Immediate cessation in pregnant women, who test positive for COVID-19, and consider **not** restarting
Past history of preterm birth	Varies with local practice	Low-dose aspirin	Not demonstrated in the absence of risk factors for preeclampsia	Immediate cessation in pregnant women, who test positive for COVID-19, and consider **not** restarting
Past history of stillbirth	Varies with local practice	Low-dose aspirin	Not demonstrated in the absence of risk factors for preeclampsia	Immediate cessation in pregnant women, who test positive for COVID-19, and consider **not** restarting
Past history of recurrent pregnancy loss (without APS)	Varies with local practice	Low-dose aspirin	Not demonstrated in the absence of APS	Immediate cessation in pregnant women, who test positive for COVID-19, and consider **not** restarting
All nulliparous singleton pregnancies (in low-income countries)	Up to 100% in certain areas	Low-dose aspirin	Significant reductions in preterm birth, and reduced perinatal morbidity	Immediate cessation in pregnant women that test positive for SARS-CoV-2, avoidance of aspirin for the duration of the COVID-19 disease, and restarting the medication after full recovery
Antiphospholipid syndrome (APS)	Approx. 0.05%	Low-dose aspirin +/- LMWH	Reduction in the risk of thrombosis (>10% if untreated, to <1%) Significantly increased live births	Continue therapy. **Monitor** platelet count and coagulation parameters closely during the course of the disease.
Mechanical heart valve	Approx. 0.02%	Low-dose aspirin + anticoagulation	Significant reduction of valve thrombosis and thromboembolic events	Continue therapy. **Monitor** platelet count and coagulation parameters closely during the course of the disease.