Mount Sinai Hospital
Sinai Health System
Joseph & Wolf Lebovic Health Complex

UNIVERSITY OF TORONTO

Routine and experimental medications for pregnant patients with COVID-19

Rohan D'Souza

MD PhD FRCOG MBBS MSc FCPS DNB DGO DFP

Maternal-Fetal Medicine Physician, Mount Sinai Hospital, Toronto, Canada

Clinician-Scientist, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada

Assistant Professor of Obstetrics & Gynaecology, University of Toronto, Canada

Aims and objectives

- Review pharmacologic considerations in pregnant persons with COVID-19
  - Routinely used medications
    - Antenatal corticosteroids
    - Magnesium sulfate
    - Low-dose aspirin
    - Analgesia and Anaesthesia
  - Thromboprophylaxis
  - Experimental medications

Antenatal Corticosteroids

- Obstetric indication
  - Reduces risk of perinatal death, respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, need for respiratory support and neonatal intensive care unit admission
  - Strength of evidence
    - For 24-34 weeks' gestation – Very strong
    - Under 24 and above 34 weeks – Moderate
- Controversy
  - Increased risk of mortality in a systematic review of 30 studies examining their use as adjunctive treatment for influenza *[Lansbury L, et al. Cochrane 2019;2(2):Cd010406]*
    - However, only included one RCT, and the certainty of evidence from observational studies was deemed to be low, because of the potential for confounding by indication
- Recommendations
  - Should be administered if risk for preterm birth between 24 and 34 weeks
  - Caution should be exercised in those under 24 and above 34 weeks of gestation

Magnesium sulfate

- Obstetric indications
  - Seizure prophylaxis in patients with preeclampsia – all gestational ages
  - Fetal neuroprotection – especially under 30 weeks of gestation
- Controversy
  - Increased risk of maternal respiratory muscle weakness but no risk of respiratory failure *[Bain ES, et al. 2013]*
  - Magnesium toxicity in those with renal impairment
- Recommendation
  - Use when indicated, albeit cautiously in those with hypoxia and renal compromise
  - Consider modified dosage regimens, for e.g. single bolus dose and monitoring of magnesium levels

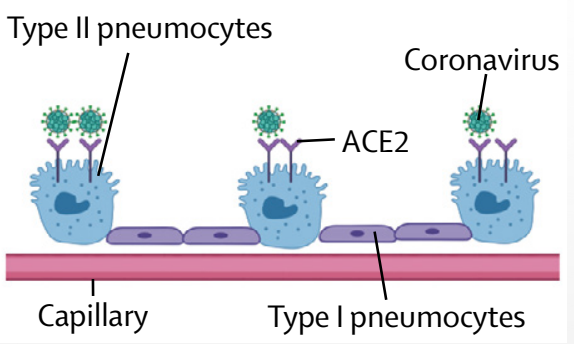
Low-dose aspirin

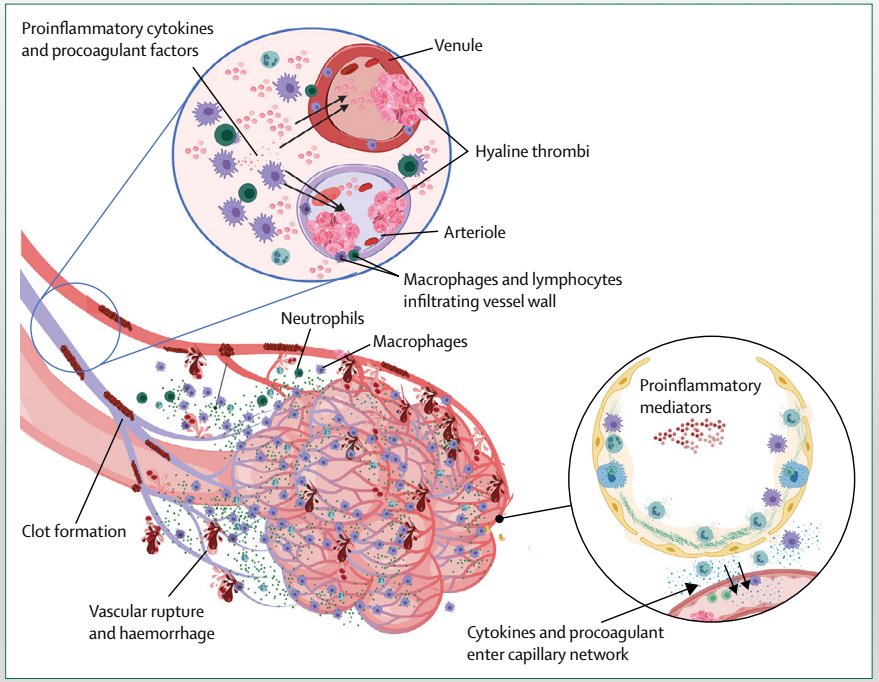
- Obstetric indication
  - From 11 weeks, 75-162mg aspirin – reduces incidence of placentally-mediated pregnancy complications (preeclampsia, fetal growth restriction, preterm birth)
- Controversy
  - Coronaviruses bind to target cells through ACE-2 receptors *[Letko M et al. Nat Microbiol 2020;5(4):562-9]*
  - Given possible increased expression of ACE-2 in patients taking ibuprofen, concerns were initially raised about use of NSAIDs in patients with COVID-19 *[Day M. BMJ. 2020;368:m1086]*.
  - A rapid systematic review showed no association between NSAID use and severe adverse events, increased acute health care utilization, decreased long-term survival, or reduced quality of life in patients with COVID-19 [WHO]
- Recommendation
  - Continue routine administration since benefits outweigh hypothetical risks

ACE = angiotensin converting enzyme; NSAIDs = non-steroidal anti-inflammatory drugs; WHO = World Health Organization

Thromboprophylaxis

- Venous thromboembolism
  - All three mechanisms of Virchow's triad are activated in severe COVID-19
    - reduced mobility,
    - a prothrombotic state and
    - endothelial activation
- High rates of deep vein thrombosis and pulmonary embolism in studies from around the world





McGonagle, Lancet Rheumatology 2020; Antoniak S. Res Pract Thrombo Haemost. 2018; Levi. Int J Lab Hematol. 2018

IMMUNOTHROMBOSIS

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STATE OF THE ART REVIEW

AOGS
Acta Obstetricia et Gynecologica Scandinavica

A critical review of the pathophysiology of thrombotic complications and clinical practice recommendations for thromboprophylaxis in pregnant patients with COVID-19

Rohan D'Souza[1,2] | Isabelle Malhamé[3,4] | Lizabeth Teshler[1,5] | Ganesh Acharya[6,7,8] | Beverley J. Hunt[9] | Claire McLintock[10]

- Decisions on thromboprophylaxis should consider:
  - disease severity,
  - timing of delivery in relation to disease onset
  - inpatient versus outpatient status,
  - underlying comorbidities, and
  - contraindications to the use of anticoagulation.

- Anticoagulants (Heparins)
  - Low-molecular weight heparin has distinct advantages over unfractionated heparin
  - Heparins can only reduce risk of VTE, **not immunothrombosis** – increasing the dose of anticoagulants is unlikely to reduce risk of clots, but will increase bleeding complications.

- Other treatments
  - Anti-cytokine therapy
  - Antivirals
  - Correction of hypoxia

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TABLE 3 Clinical recommendations on thromboprophylaxis for pregnant and postpartum women with confirmed or suspected COVID-19

	Isolating at home			Inpatient hospitalized for non-COVID-related reason but asymptomatic or minor symptoms such as anosmia	Inpatient with pneumonia requiring supplementary oxygen but not ventilation	Inpatient with pneumonia requiring mechanical ventilation
	Low risk pregnancy and low risk for VTE	Risk factors for VTE – not receiving thromboprophylaxis	Receiving thromboprophylaxis			
ANTEPARTUM	Encourage hydration and mobilization	Conduct risk assessment & consider thromboprophylaxis on an individual basis	Continue thromboprophylaxis	Conduct risk assessment & consider thromboprophylaxis on an individual basis	Give thromboprophylaxis (LMWH)	Give thromboprophylaxis (LMWH) - dose according to local critical care protocol
PERIPARTUM	NA	Follow local policy for interruption of anticoagulation prior to delivery				
POSTPARUM (while in hospital)	Usual care	Conduct risk assessment & consider thromboprophylaxis on an individual basis	Continue usual thromboprophylaxis	Conduct risk assessment & consider thromboprophylaxis on an individual basis	Give thromboprophylaxis (LMWH)	Give thromboprophylaxis (LMWH) - dose according to local critical care protocol
POSTPARUM (upon discharge)	Usual care Encourage hydration and mobilization	Usual care & consider thromboprophylaxis on an individual basis. Encourage hydration and mobilization	Decision based on primary indication for thromboprophylaxis. Encourage hydration and mobilization	Conduct risk assessment & consider thromboprophylaxis on an individual basis Encourage hydration and mobilization	Conduct risk assessment & consider extended thromboprophylaxis on an individual basis. Encourage hydration and mobilization	Conduct risk assessment & consider extended thromboprophylaxis on an individual basis. Encourage hydration and mobilization

LMWH, low molecular weight heparin; NA, not applicable; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; VTE, venous thromboembolism.

Peripartum analgesia and anaesthesia

- **Nitrous oxide** may be administered for labour analgesia while using appropriate personal protective equipment
- Intravenous **remifentanil** patient-controlled analgesia should be used with caution in patients with respiratory depression
- Liberal use of **neuraxial labour analgesia** may reduce the need for emergency general anaesthesia which results in aerosolization.
- Short courses of **non-steroidal anti-inflammatory drugs** can be administered for postpartum analgesia, but opioids should be used cautiously due to risks of respiratory depression.

Experimental drugs - corticosteroids

- RECOVERY Trial
  - Hospitalized patients with COVID-19
    - 2014 participants: Dexamethasone 6mg orally or IV for up to 10 days
    - 4321 participants: routine care
  - 22.9% vs. 25.7% died within 28 days
  - Difference most pronounced in those on mechanical ventilation or needing oxygen
  - Six pregnant patients
- Recommendations
  - Corticosteroids may be administered in pregnant patients needing oxygen or on mechanical ventilation [NIH]

Other experimental medications

- Although hydroxycholoroquine, lopinavir/ritonavir and remdesivir may be used during pregnancy and lactation within the context of clinical trials, data from non-pregnant populations have not shown benefit
- The role of monoclonal antibodies (tocilizumab), immunomodulators (tacrolimus), interferon, inhaled nitric oxide and convalescent plasma in pregnancy and lactation needs further evaluation

ULTRASOUND
in Obstetrics & Gynecology

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Pregnancy and COVID-19: Pharmacologic Considerations

Rohan D'Souza MD PhD FRCOG[1,2], **Rizwana Ashraf** MBBS[1], **Hilary Rowe** BSc(Pharm) PharmD ACPR [3,4], **Jonathan Zipursky** MD PhD(c)[5,6], **Lauren Clarfield** BSc[7], **Cynthia Maxwell** MD FRCSC[1], **Cristian Arzola** MD MSc[8], **Stephen Lapinsky** MD[9], **Katryn Paquette** MDCM SM FRCPC FAAP[10,11], **Srinivas Murthy** MD MHSc FRCP(C) FAAP[12,13], **Matthew P. Cheng** MDCM FRCP(C) FACP(D) ABMM[14,15,16], **Isabelle Malhamé** MD MSc FRCP(C)[16,17]

AVAILABLE EVIDENCE FOR THE USE OF EXPERIMENTAL MEDICATIONS IN PREGNANCY AND BREASTFEEDING

MEDICATION	Pregnancy Risk		Breastfeeding
	Teratogenicity	Other toxicity	
ANTIMALARIALS			
Chloroquine			
Hydroxychloroquine			
ANTIVIRALS			
Lopinavir/Ritonavir [protease inhibitors/ booster drug			
Tenofovir [Nucleoside reverse transcriptase inhibitor]			
Remdesivir [Adenosine nucleotide analogue]			
Ribavirin [Guanosine nucleotide analogue and inhibits RNA polymerase]			
Emtricitabine [Nucleoside reverse transcriptase inhibitor]			
Favipiravir [RNA polymerase inhibitor]			
Nitazoxanide [First-in-class broad spectrum antiviral]			
BIOLOGICS (Monoclonal antibodies)			
Tocilizumab [Humanized monoclonal anti-IL-6 antibody]			
Eculizumab [Humanized monoclonal anti-C5 (terminal complement) antibody]			
Sarilumab [Humanized monoclonal anti-IL-6 antibody]			
Bevacizumab [Humanized monoclonal anti-VEGF-A antibody			
Emapalumab [Humanized monoclonal anti-interferon-ɣ antibody]			
Siltuximab [Chimeric monoclonal anti-IL-6 antibody]			
Nivolumab [Humanized monoclonal anti-IgG4 antibody against PD-1 receptor]			
IMMUNOMODULATORS			
Anakinra			
Tacrolimus [Calcineurin inhibitor]			
Sirolimus [Inhibitor of mTORC1]			
Thalidomide			
Fingolimod [Sphingosine-1-phosphate receptor modulator]			
Baricitinib [Janus Kinase inhibitor]			
Tofacitinib [Janus Kinase inhibitor]			
Ruxolitinib [Janus Kinase inhibitor]			
Recombinant human interferon α1b and α2b			
Angiotensin Converting Enzyme inhibitors/ Angiotensin receptor blockers			
Camostat Mesylate and Nafamostat			
Bromhexine hydrochloride [Inhibits serine protease TMPRSS2]			
Convalescent Plasma			
Corticosteroids			
Colchicine			
Azithromycin [Macrolide antibiotic]			

Legend	Compatible; Benefits>Risk	Limited data; probably compatible	Weigh risks vs. benefits	Limited data; potential risk	Contraindicated	No human data

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Annals of Internal Medicine

IDEAS AND OPINIONS

The Moral Imperative to Include Pregnant Women in Clinical Trials of Interventions for COVID-19

Isabelle Malhamé, MD, MSc; Rohan D'Souza, MD, PhD; and Matthew P. Cheng, MDCM

Acknowledgements

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