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Reproductive Health

COVID-19 and Miscarriage

Ruth Lath, MD, Professor

Director, Recurrent Pregnancy Loss Program

Stanford University

Disclosures:

- None
- Thank you to Sergio Cabanillas for his help in preparing this presentation

Objectives

Review COVID-19 infection and mechanism of invasion into cells

Review possible mechanisms for COVID-19 to affect early pregnancy and miscarriage

Review available evidence of COVID impacting pregnancy and miscarriage

Future directions

Questions

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Miscarriage

Miscarriage most common complication of early pregnancy

Later miscarriages more often euploid and unexplained.

- Infection, immune mediated, thrombosis, unknown genetic causes

Infectious/inflammation in the endometrium is associated with miscarriage in many studies

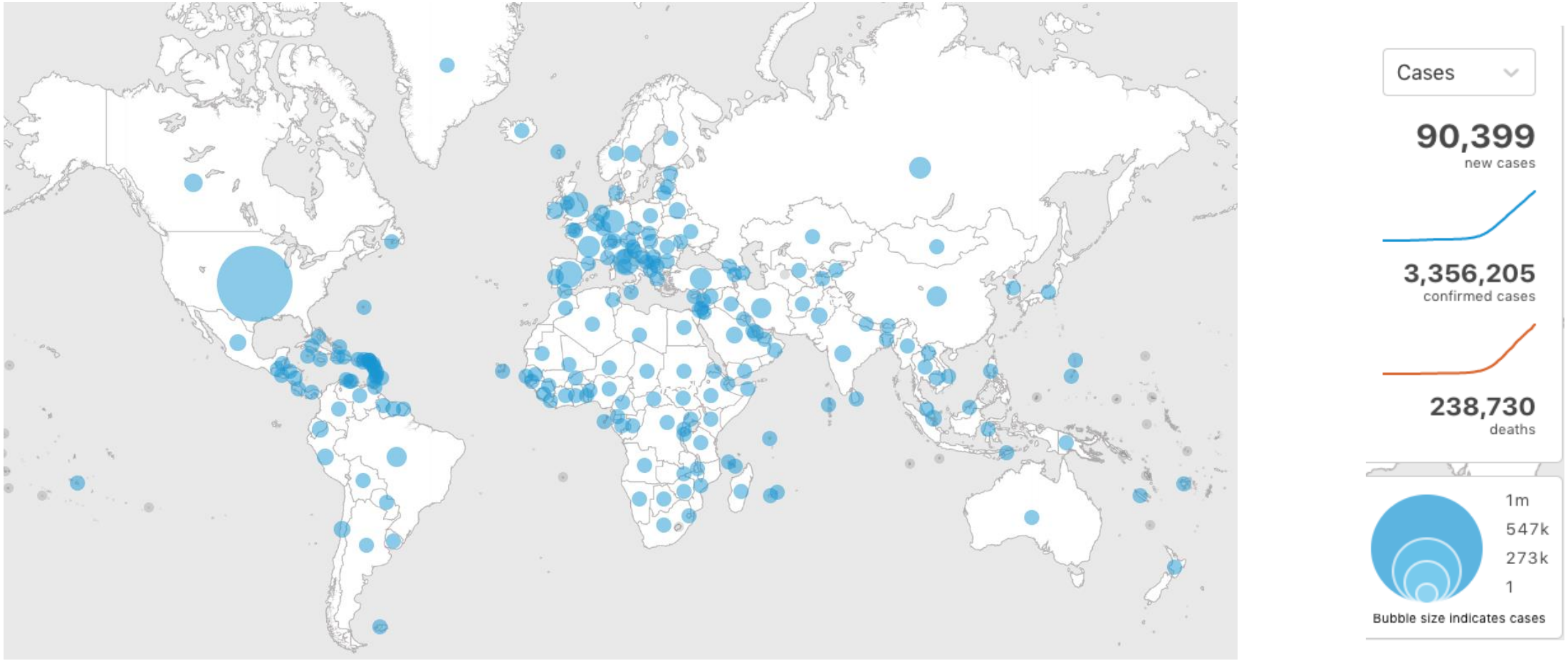
As many as 15% or first trimester and 60% of second trimester miscarriage attributable to infection

Viral infections are associated with miscarriage and still birth

- Parvovirus, zika, CMV, rubella, H1N1,and others

Questions about covid19 and placental and fetal effects remain

Giakoumelou s, et. Al Human Reproduction 2015



WHO data from May 1, 2020

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World since COVD19

> 3 million cases confirmed cases worldwide

True number likely much larger

- Seroprevalence studies in Santa Clara indicate 3% have been infected

Highly contagious

Highly variable presentation

- Flu, fever, cough, GI symptoms, headache, fatigue, etc…
- Women less severe disease then men
- Many asymptomatic or minimally symptomatic

Unknown impact on pregnancy and miscarriage

Explosion of literature and research on the topic

Impact of Shelter in Place recommendations unknown

Coronavirus family

- Enveloped RNA virus that has been the source of 3 large epidemics
- Viral pneumonia with risks of developing systemic/multi-organ failure
- Primarily spread by respiratory droplets
- SARS
  - Over 8000 cases with case fatality rate 10.5%
- MERS
  - Over 2500 with case fatality rate of 34%
- COVID-19
  - > 3 million cases, case fatality rate ranging 1-4%
  - Majority of cases mild
  - Unknown number of asymptomatic carriers
  - WHO declared global pandemic March 11, 2020

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Global pandemic of 2009

H1N1

Relatively new virus with low immunity in the general population

Infected > 60 million people worldwide

- 12,000 deaths in US and > 150,000 worldwide
- 80% of deaths were in patients younger than 65
- More severe disease course in pregnant women
- Little data published on miscarriage before 2013

https://doi.org/10.1007/s10654-020-00680-2

PERINATAL EPIDEMIOLOGY

Seasonal and pandemic influenza during pregnancy and risk of fetal death: A Norwegian registry-based cohort study

Nina Gunnes[1,2] · Håkon Kristian Gjessing[3,4] · Inger Johanne Bakken[3] · Sara Ghaderi[4] · Jon Michael Gran[5] · Olav Hungnes[1] · Per Magnus[3] · Sven Ove Samuelsen[1,6] · Anders Skrondal[3,7,8] · Camilla Stoltenberg[1,4] · Lill Trogstad[1] · Allen J. Wilcox[9] · Siri Eldevik Håberg[3]

Norwegian surveillance system for communicable diseases

Influenza like syndromes (ILI) and Fetal death (>12 week)

During normal flu seasons no increase in fetal death, based on ILI

During pandemic influenza season 2009/2010 (H1N1), increase in fetal death

Strongest effect if exposure (ILI) in first trimester (HR 2.28, 95% CI 1.45-.59)

April 2020. European Journal of Epidemiology

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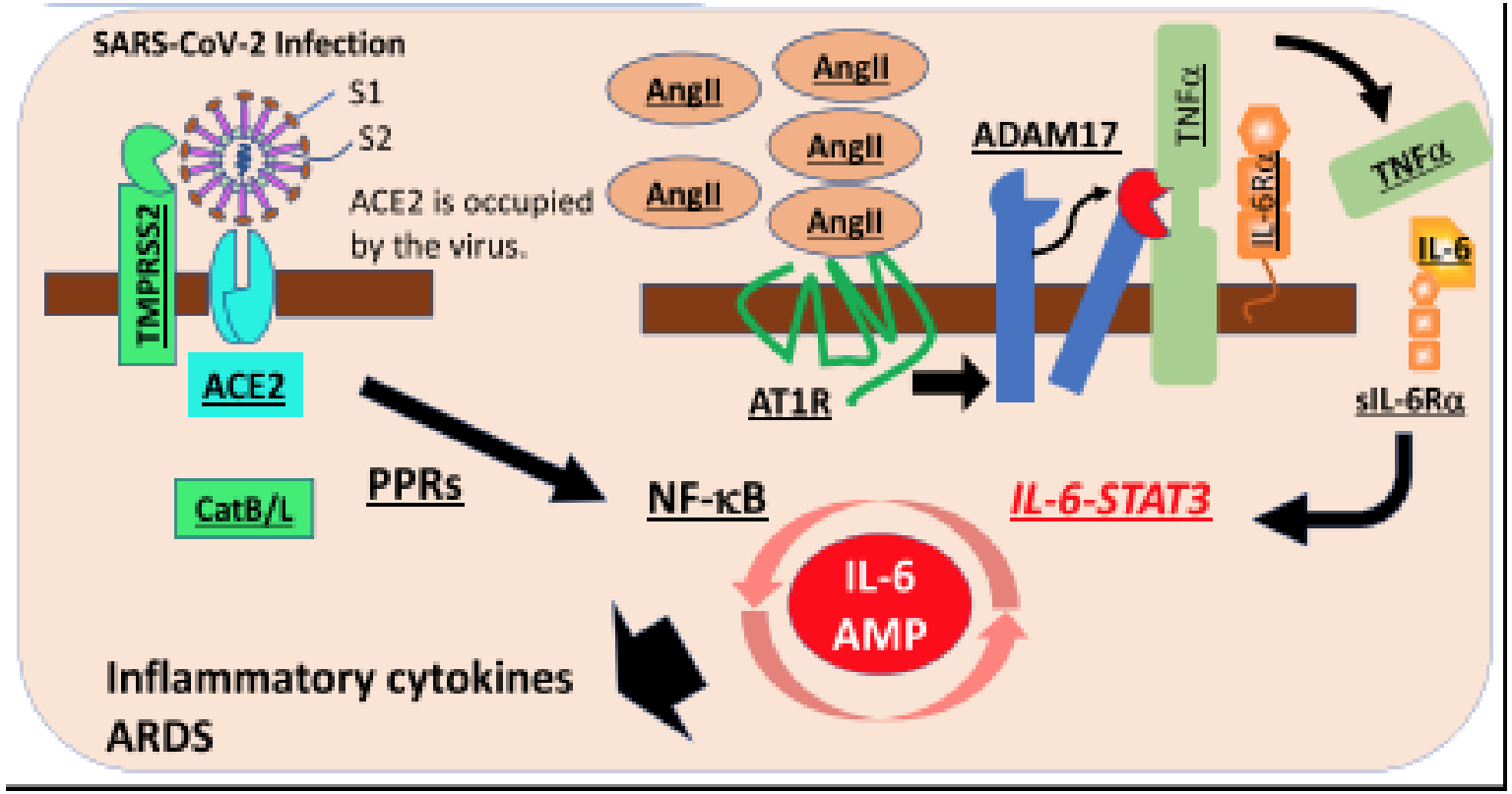
COVID-19

- SARS-Corona virus
- 80% sequence identity with SARS-1
- 50% identity with MERS
- Spike proteins bind ACE2 receptor
- TMPRSS2 digest spike proteins allowing virus to enter cells



Hirano and Murakami, Immunity May 2020

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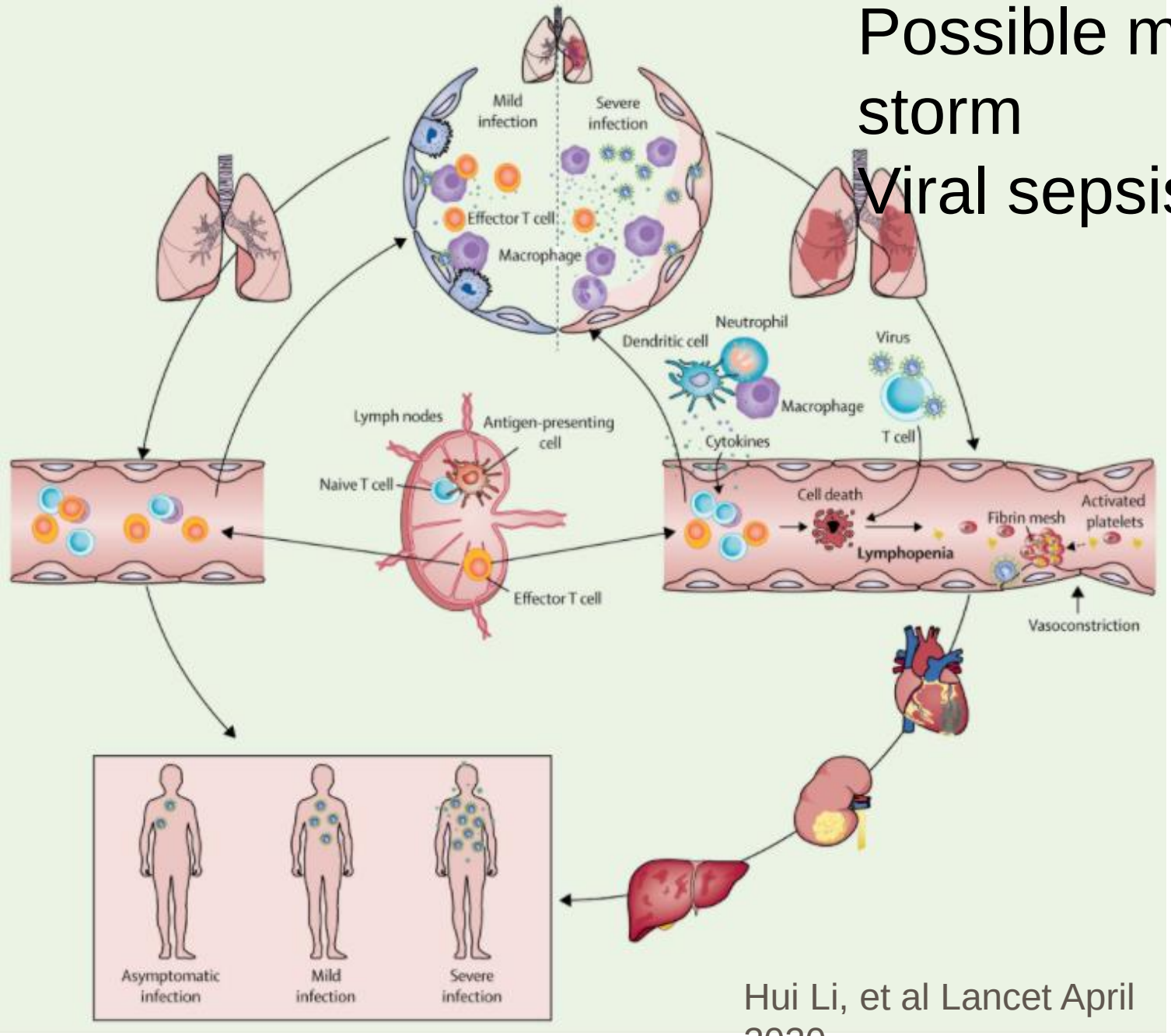
Possible mechanism of cytokine storm
Viral sepsis



Hui Li, et al Lancet April 2020

Infection of T cells

Leads to lymphopenia

Hypercoagulation

Vasoconstriction

Damage to non-infected organs – PCR negative

- Heart
- Kidney

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Severe infection and miscarriage: mechanisms

- Hypoxia and ventilator use
- Fever
- Medications
- Cytokine storm – impacting early implantation and placental function
- Hypercoagulable state- placental infarction
- Direct infection of placenta/fetus with virus?

Hypercoagulable state

COVID-19 patients admitted to hospital appear to have altered coagulation profiles

Case series in NEJM of young patients presenting with ischemic strokes

Hyperfibrinogenemia

Higher D-dimer

Shorter clot formation time

Higher maximum clot firmness

We will need studies in pregnancy

- *Possible need for more aggressive anticoagulation, or lower threshold for starting*

Spiezia L et. Al. Thromb Haemost April 2020
Tang N J Thromb Haemost April 2020
Okley NEJM April 2020

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Endometrium/ reproductive tract

- ACE2 receptors are present in ovary and endometrium and trophoblasts, and testes
- No data on PCR proven Covid19 in Endometrium
- Renin angiotensin pathway active in endometrial decidualization and menstruation
- ACE2 receptors relatively low in non-pregnant endometrium
  - higher in epithelial cells
  - higher secretory phase

Vaz-silva Repro sci 2009

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Gene expression studies for maternal-fetal interface

Single cell RNA sequencing data from publicly available cell specific data on ACE2 and TMPRSS2 at maternal-fetal interface and multiple fetal organs

ACE2 receptors widely expressed at maternal fetal interface

ACE2 and TMPRSS2 co-expressed

- Extra villous trophoblast
- Increasing expression > 24 weeks

Mechanism for vertical transmission or placental dysfunction

Call for further studies on miscarriage and placental dysfunction

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PLOS ONE April 2020 Li, et al

Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis

Daniele Di Mascio, MD; Asma Khalil, PhD; Gabriele Saccone, MD; Giuseppe Rizzo, MD; Danilo Bi
Marco Liberati, MD; Jacopo Vecchiet, MD; Luigi Nappi, MD; Giovanni Scambia, PhD; Vincenzo B
Francesco D'Antonio, PhD

Review of all 3 COVID virus epidemics

19 studies – 79 women (41 women with COVID 19)

92% had pneumonia

39% miscarriage

7% perinatal death

No vertical transmission

Published March 25th, included reports through March 13

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March Meta-analysis

Hospitalized women, with > 90% pneumonia

Case reports/retrospective studies and case series

79 pregnancies included

- 41 with COVID-19
- 12 with MERS
- 26 with SARS

26% in the ICU

12% maternal deaths

COVID 19 patients had lower rates of ICU admission (9.3%) and no deaths

Di Mascio, D, et al AJOG-MFM

Miscarriage risk in AJOG article

39% Miscarriage (8/21) noted in abstract

- Only 2/19 studies included miscarriage as an outcome. (SARS only)

No data on COVID-19 and miscarriage

No first or early second trimester cases in papers described in COVID-19 reports

7% Perinatal death in COVID-19

Limitations

- Only represents outcome of sickest patients
- Unable to comment on impact of mild cases on pregnancy outcome
- No reports of early pregnancy exposure in COVID-19 patients
- Authors recommend data need to be frequently updated

Di Mascio, D, et al AJOG-MFM

Case series –China experience COVID19

116 pregnant women with COVID19 pneumonia

January –March 24, 2020

No neonatal infections- vertical transmission

-amniotic fluid and neonatal nasopharyngeal swabs

No Maternal deaths

Concluded no increased risk of miscarriage

Only 8 patients presented in first or second trimester

one miscarried

Yan Ji, et al. AJOG April 17, 2020

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Systematic Review COVID-19 – Elshafeey, et al

International Journal of Gynecology and Obstetrics –April 24, 2020

Epub ahead of print

Review of 33 studies- as of April 19, 2020

16 Case series, 16 case reports and one case control study out of china

385 women

Gestational age 6 weeks to 41 weeks

Majority of cases beyond 24 weeks gestation (276/285)

No clear evidence of vertical (transplacental) transmission

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Clinical presentation of COVID 19 and pregnancy

Ages 21-42

Severity of symptoms

- Mild or asymptomatic – 95.6%
- Severe - 3.6%
- Critical – 0.8% (3 women, one death)

Similar presentation breakdown to age matched non-pregnant controls

2 still births (both in critically ill women)

1 neonatal death due to prematurity

109 prior to 24 weeks, 3 miscarriages

El-Shafeey, et al April 2020

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Limitations of current evidence

No systematic way to collect early pregnancy outcomes

No systematic way to collect asymptomatic carriers, or even outpatients care

No control group

Follow up relatively short.

Difficult to connect early exposure to later outcomes

Small number of miscarriages, and no tissue analysis

Larger population based studies not available for COVID19

Case Report- Switzerland

28 yo presents at 19 weeks with fever, cough, fatigue, myalgias x 2 d

Nasopharyngeal swab + COVID 19

Sent home with acetaminophen for fever

2 days later presents with persistent symptoms + contractions and cervical dilation (5cm)

- Fetal tachycardia, normal anatomy

Patient given antibiotics and allowed to labor and deliver stillborn

Placental pathology

- Mixed inflammatory infiltrate in placenta
- Funisitis
- Gram stain, PCR and culture negative for bacteria

Baud JAMA April 30

SARS-COVID 19 PCR in 19 week miscarriage

RT- PCR positive tissues	RT-PCR negative tissues
Nasophanygeal swabs mother at presentation and delivery	Vaginal swab at presentation and at delivery
Placental submembrane	Maternal blood
Placental cotylendon	Amniotic fluid
	Umbilical cord
	Fetal mouth, armpit, anus, liver, lung

Fetal Autopsy: No malformations
Fetal blood and tissue: negative for bacteria by both PCR and culture

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Conclusions from Case report

Testing supports viral infection of placenta

No evidence of vertical transmission

Contamination unlikely- given neg vaginal PCR

Findings similar to MERS

- Maternal side infection of the placenta
- Placental insufficiency
- IUGR (40%)
- Miscarriage (4/7 infected in first trimester)

Need more studies

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Any Conclusions on miscarriage

Difficult to say given case series has few early exposures

Stillborn cases both occurred in critically ill patients

One case report of a mildly symptomatic woman developing placental infection and 19 week pregnancy loss

Need large scale prospective studies

True impact will likely not be known for several months to a year

COVID19 seems less severe/different than SARS and MERS, but that does not mean no risk.

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Challenges in miscarriage research

- Not always linked to hospital encounters
- Multifactorial- yet final common pathway
- Delay in diagnosis of miscarriage, due to missed miscarriages
- Many women may not report COVID 19 symptoms or receive testing
- Making sequence of events harder to track
- Depending on hospital reports and patient recall introduces bias
- Studies linking prenatal and early pregnancy exposure to miscarriage and ultimate pregnancy outcome are rare. And extremely difficult

Future Directions- research

Systematic approach to capture as many exposed as possible

Routine testing of asymptomatic pregnant patients to identify cohort of women who are not selected by severity of symptoms

When adverse outcomes occur, even in the absence of symptoms, consider serology and RT-PCR for Covid19

Registries are already started, encourage patients to participate

- UCSF –PRIORITY. https://priority.ucsf.edu

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Thank you

Stay healthy!

Any Questions?

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