COVID-19 and Miscarriage

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Disclosures:

• None
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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
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% of 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

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
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
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)
COVID-19

SARS-CoV-2 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
Infection of T cells leads to:
- Lymphopenia
- Hypercoagulation
- Vasoconstriction
- Damage to non-infected organs – PCR negative
  - Heart
  - Kidney

Possible mechanism of cytokine storm
Viral sepsis

Hui Li, et al Lancet April 2020
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
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
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

PLOS ONE April 2020 Li, et al
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
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

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
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
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

<table>
<thead>
<tr>
<th>RT-PCR positive tissues</th>
<th>RT-PCR negative tissues</th>
</tr>
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<tbody>
<tr>
<td>Nasopharyngeal swabs mother at presentation and delivery</td>
<td>Vaginal swab at presentation and at delivery</td>
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<tr>
<td>Placental submembrane</td>
<td>Maternal blood</td>
</tr>
<tr>
<td>Placental cotyledon</td>
<td>Amniotic fluid</td>
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<tr>
<td></td>
<td>Umbilical cord</td>
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<td></td>
<td>Fetal mouth, armpit, anus, liver, lung</td>
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Fetal Autopsy: No malformations
Fetal blood and tissue: negative for bacteria by both PCR and culture
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
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.
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
Thank you

Stay healthy!

Any Questions?