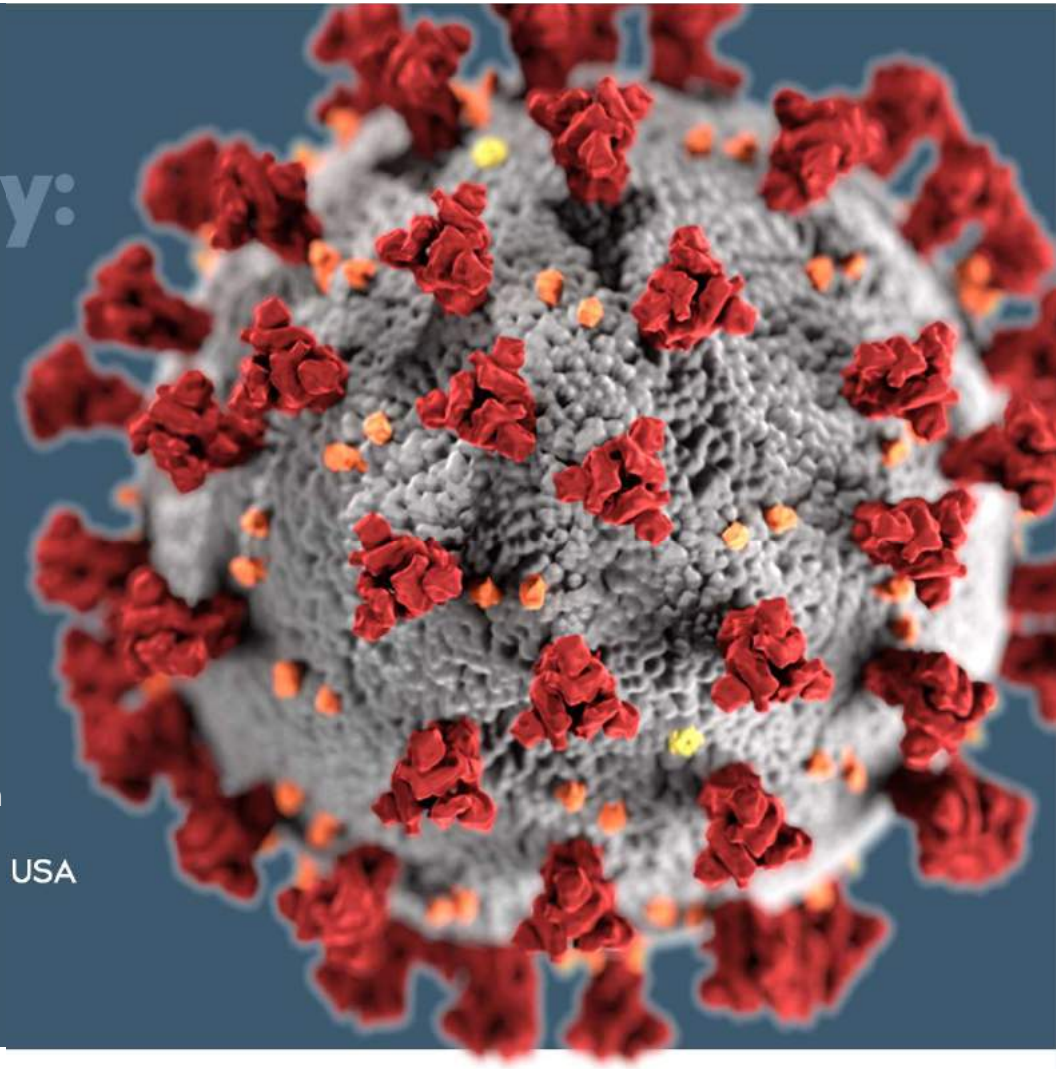
COVID-19 and Pregnancy:

What we need to know now in Reproductive Medicine



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HARVARD MEDICAL SCHOOL

VNIVERSITAT DE VALÈNCIA

Learning Objectives

- ✓ COVID-19 disease and SARS- Cov-2 virus
- ✓ Lessons from previous Coronavirus epidemics
- ✓ COVID-19 and Pregnancy
- ✓ Recommendations from Ob/Gyn professional bodies & Reproductive Medicine Societies
- ✓ Research Task Forces
- ✓ Food for thought

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COVID-19 is the Coronavirus Disease caused by the **SARS-CoV-2 virus**, declared as a new **pandemic** by the World Health Organization (WHO) as of 11th March, 2020.

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World Health Organization. Coronavirus disease (COVID-19) outbreak. https://www.who.int/emergencies/diseases/novel-coronavirus-2019
Gorbalenya, et al. Biorxiv. https://www.biorxiv.org/content/10.1101/2020.02.07.937862v1.full.pdf
Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/index-sp.html

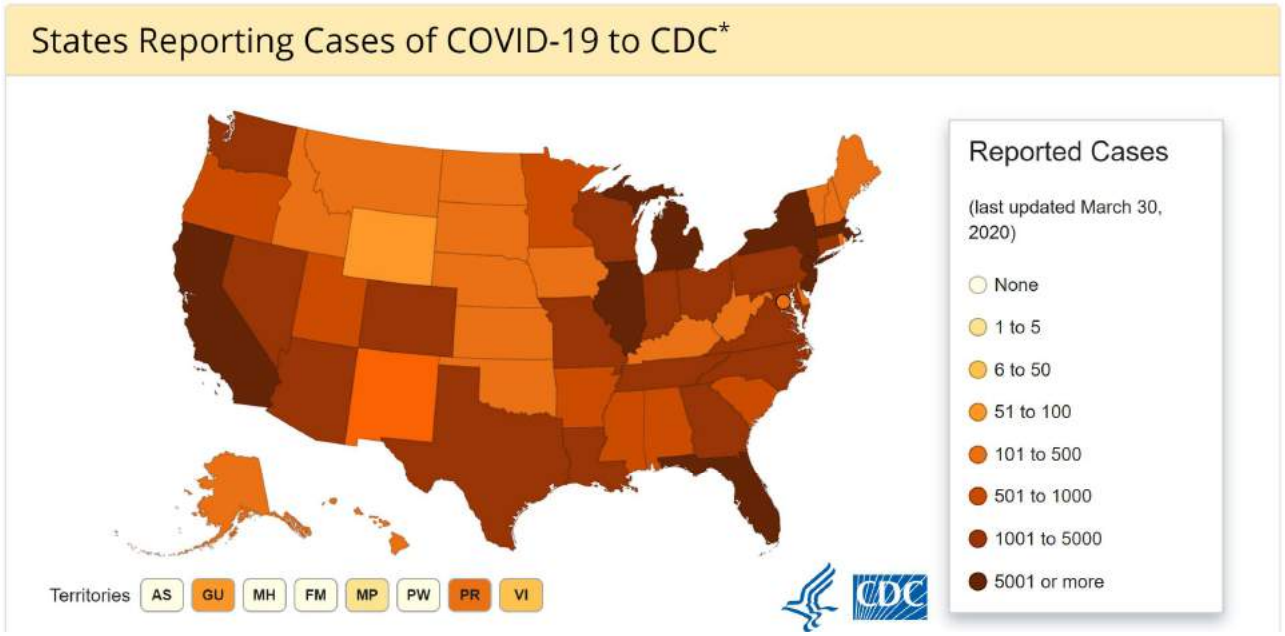
Current situation in the United States (March 31, 2020)

Worldwide
750,890 cases

Europe
423,946 cases

United States
163,539 cases

2,860 deceased



https://www.cdc.gov/coronavirus/2019-nCoV/index.html

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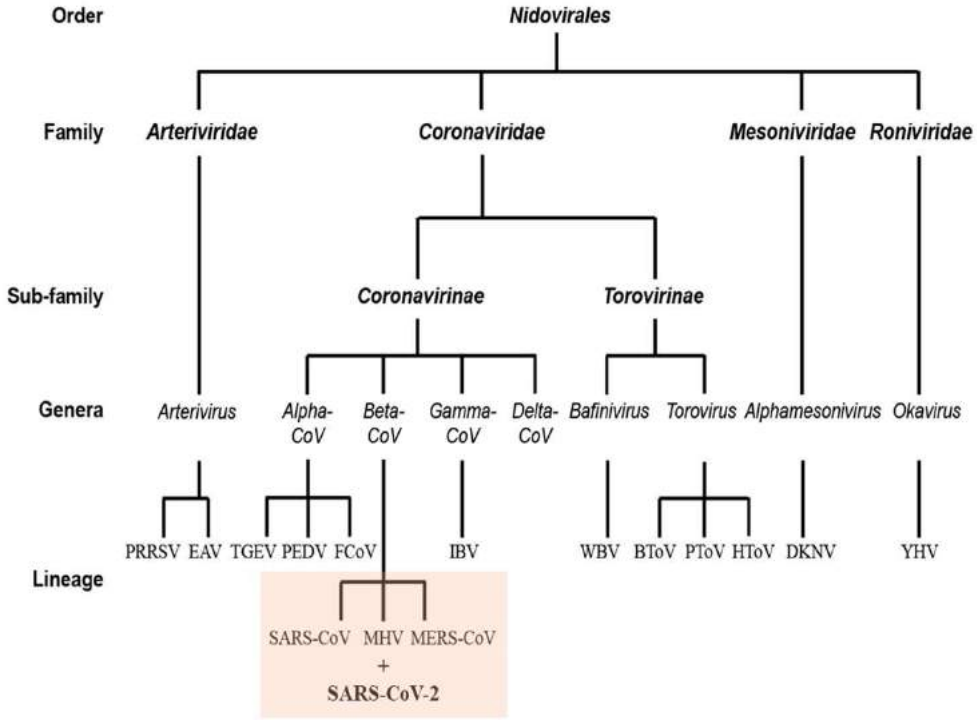
Coronavirus pandemics in the 21st century

Coronaviruses are a group of viruses causing illness ranging in severity from the common flu to fatal outcome.



In the 21st century, three coronaviruses have crossed the species barrier to cause deadly pneumonia in humans:

- Severe acute respiratory syndrome coronavirus (SARS-CoV)
- Middle-east respiratory syndrome coronavirus (MERS-CoV)
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

The recurrent spillovers **suggest that future zoonotic transmission events may continue.**

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Drosten et al. *N Engl J Med*. 2003; Ksiazek et al. *N Engl J Med.* 2003; Li et al. *Science*. 2005; Zaki et al. *N Engl J Med.* 2012; Ge et al. *Nature*. 2013; Menachery et al. *Nat Med*. 2015; Yang et al. *Virus Res*. 2015; Menachery et al. Proc Natl Acad Sci U S A. 2016; Zumla et al. *Nat Rev Drug Discov*. 2016; Anthony et al. *Virus Evol*. 2017; Hu et al. *PLoS Pathog*. 2017; Huang et al. *Lancet*. 2020; Zhou et al. *Nature*. 2020; Zhu et al. *N Engl J Med.* 2020

Comparison of recent coronaviral pandemics

	COVID-19	SARS	MERS
Virus	Betacoronavirus SARS-CoV-2	Betacoronavirus SARS-CoV	Betacoronavirus MERS-CoV
Origin	Wuhan, China	Guandong, China	Saudi Arabia
Onset	December 2019	November 2002 - July 2003	June 2012 – still active
Spread	194 countries	31 countries	27 countries
Cases	750,890 reported	8,422 reported	2,494 reported
Deaths	32,784	916	858
Reproductive no.	≈3	≈2-3	≈1
Age av (range)	59 (10-89) years	40 (1-91) years	50 (1-94) years
Sex ratio (M:F)	56:44	43:57	64.5:35.5%
Mortality	Currently estimated 1%*	9.6%	35-40%

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Rasmussen et al. *Am J Obstet Gynecol.* 2020; de Wit et al. *Nat Rev Microbiol.* 2016.
https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/
https://www.who.int/csr/sars/country/country2003_08_15.pdf?ua=1
https://www.who.int/emergencies/mers-cov/en/

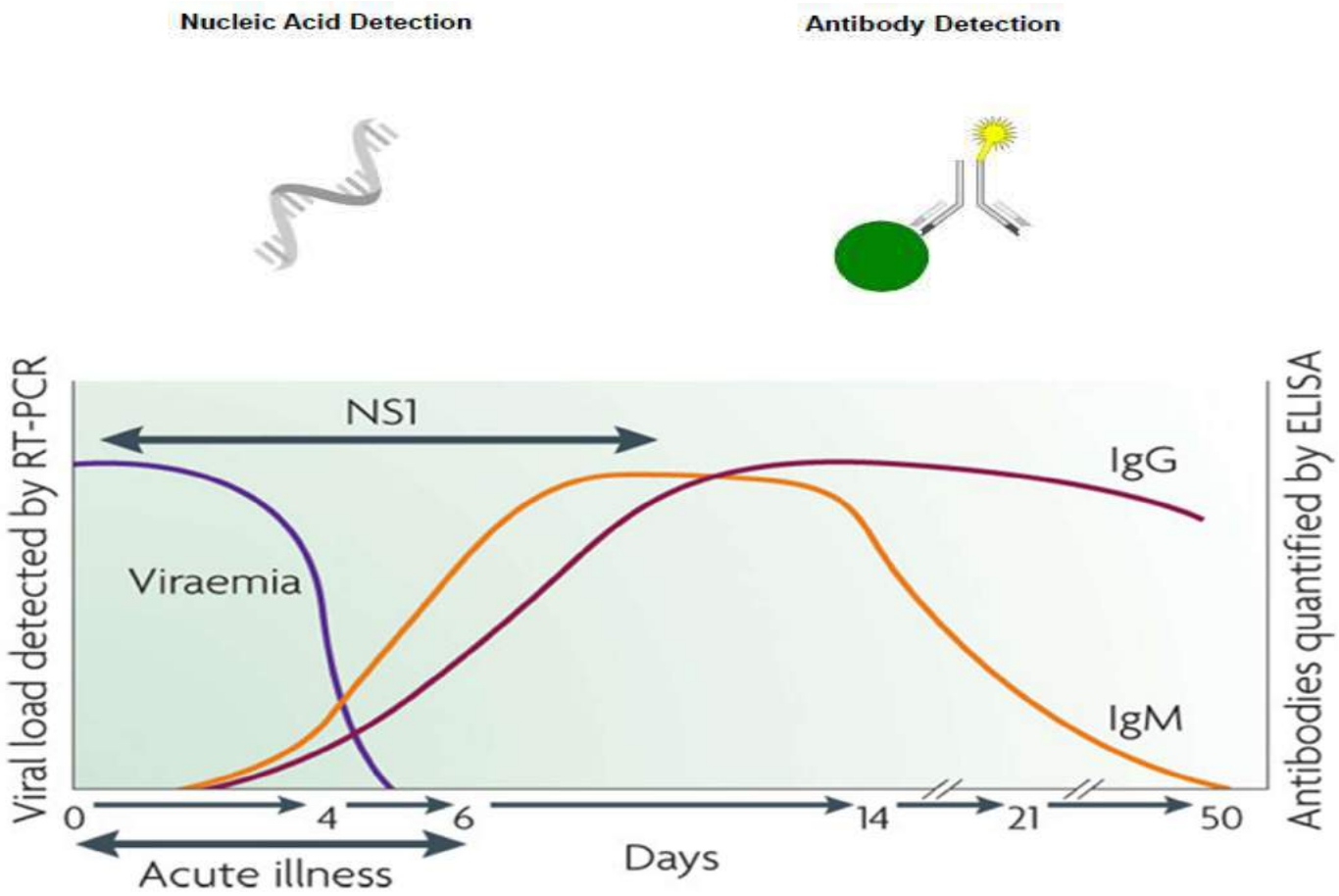
Epidemiology of SARS-CoV-2

- Incubation period – average of 5 days (range of 2-14 days).
- Hospitalized patients (49-56 years).
- Population at risk: elderly, chronic respiratory syndrome, immunosuppressed, pregnant women.
- Underlying illness – no symptoms, fever, cough, myalgia, headache, diarrhea, disnea.

Transmission

- Person-to-person – between people who are in close contact with one another (within ~6 feet) via respiratory droplets produced when an infected person coughs or sneezes.
- Other forms of transmission (e.g., from infected surfaces or objects) might be possible.
- Hospital-associated transmission playing a key role.

Identification Methods



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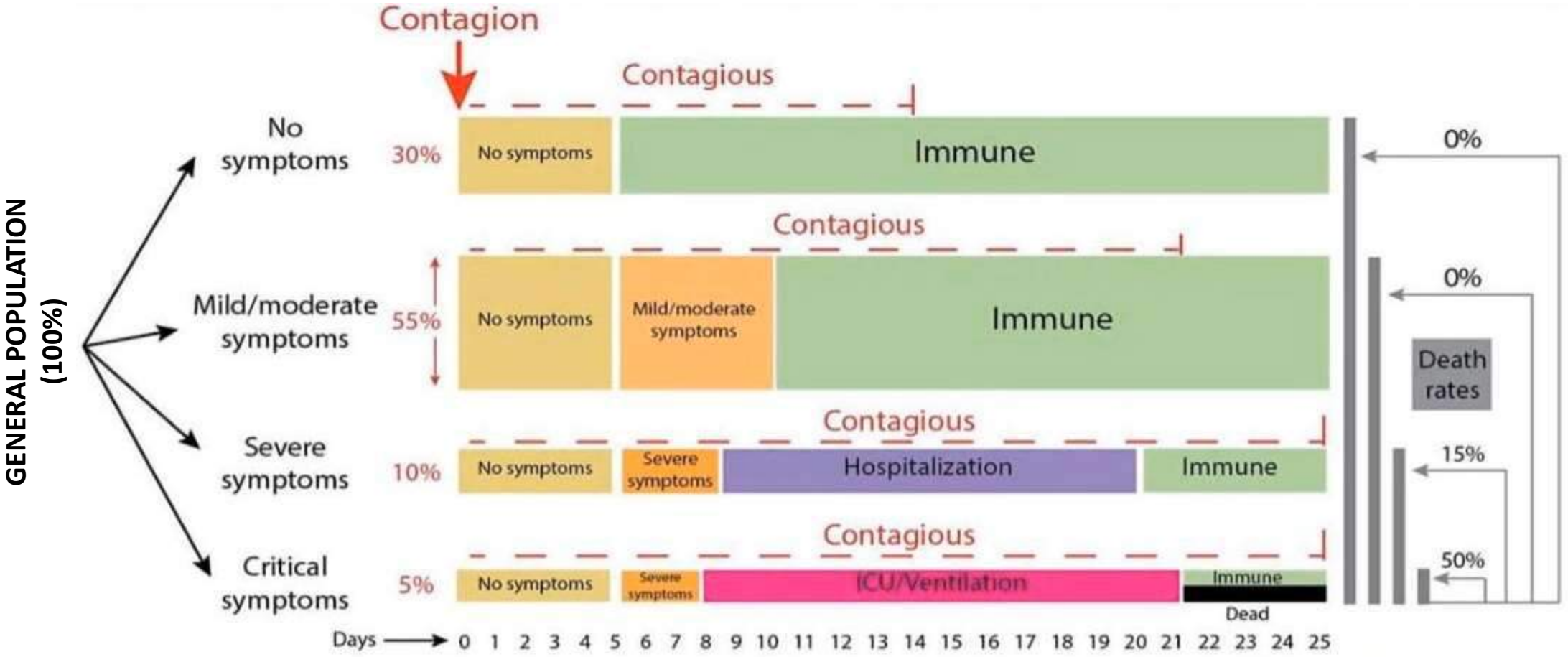
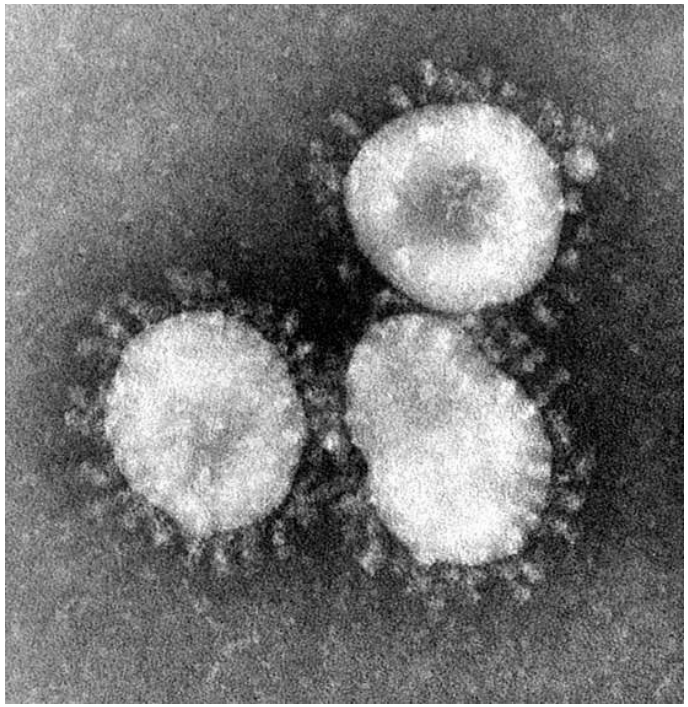
Covid-19 infection timeline

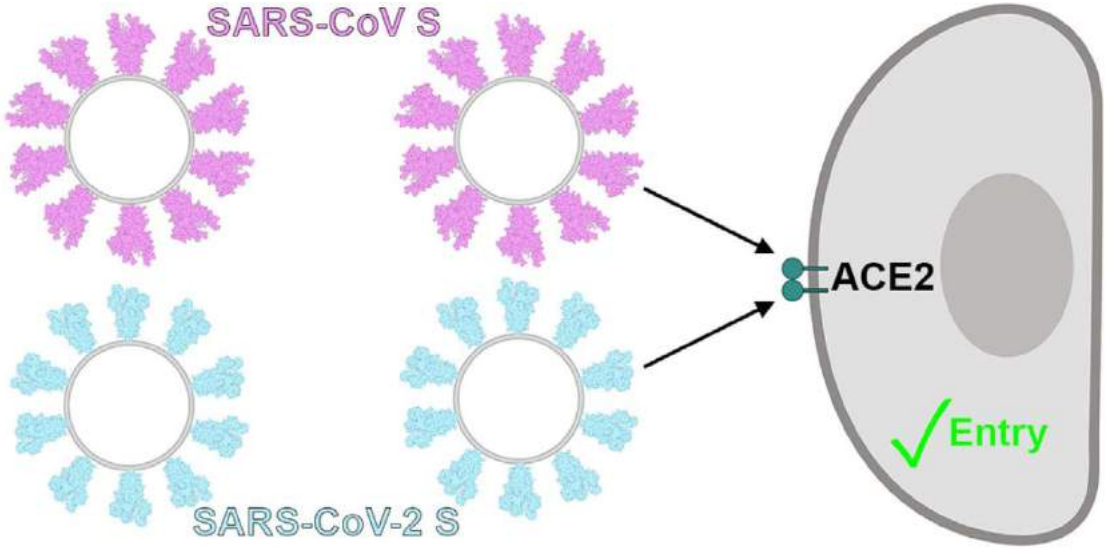


Lauer et al. *Am Intern Med*. 2020; Ferguson et al. Imperial College COVID-19 Response Team. 2020; Liu et al. Lancet. 2020.

SARS-CoV-2 virus

SARS-CoV-2 is a single-stranded RNA, enveloped virus, belonging to the β-coronavirus family. This virus is able to enter the human cells by binding of its spike (S) protein to ACE2 enzyme.





ACE2 (Angiotensin converting enzyme 2) is expressed in the membrane of different cell types as a part of the renin-angiotensin (RAS) system, involved in the regulation of blood pressure.

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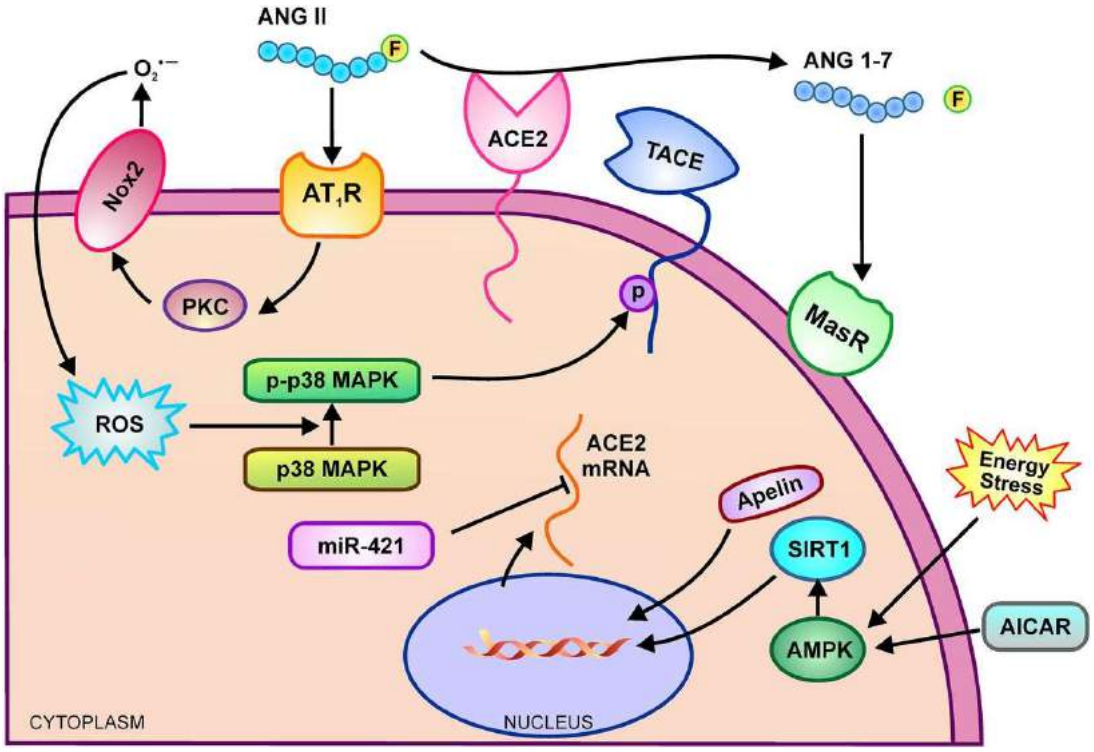
Walls et al. *Cell*. 2020.

ACE2 and Renin-Angiotensin Sytem



- The main role of ACE2 is the degradation of Ang II resulting in the formation of angiotensin 1–7 (Ang 1–7) which opposes the actions of Ang II.
- Ang-(1-7) is them able to bind to its Mas receptor in the cell membranes.
- ACE2 has a beneficial role in many diseases such as hypertension, diabetes, and cardiovascular disease where its expression is decreased.
- Current therapeutic strategies for ACE2 involve augmenting its expression using ACE2 adenoviruses, recombinant ACE2 or compounds to produce organ protection.

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Tikelis and Thomas. *Int J Pept*. 2012; Patel et al. *Circ Res*. 2016.

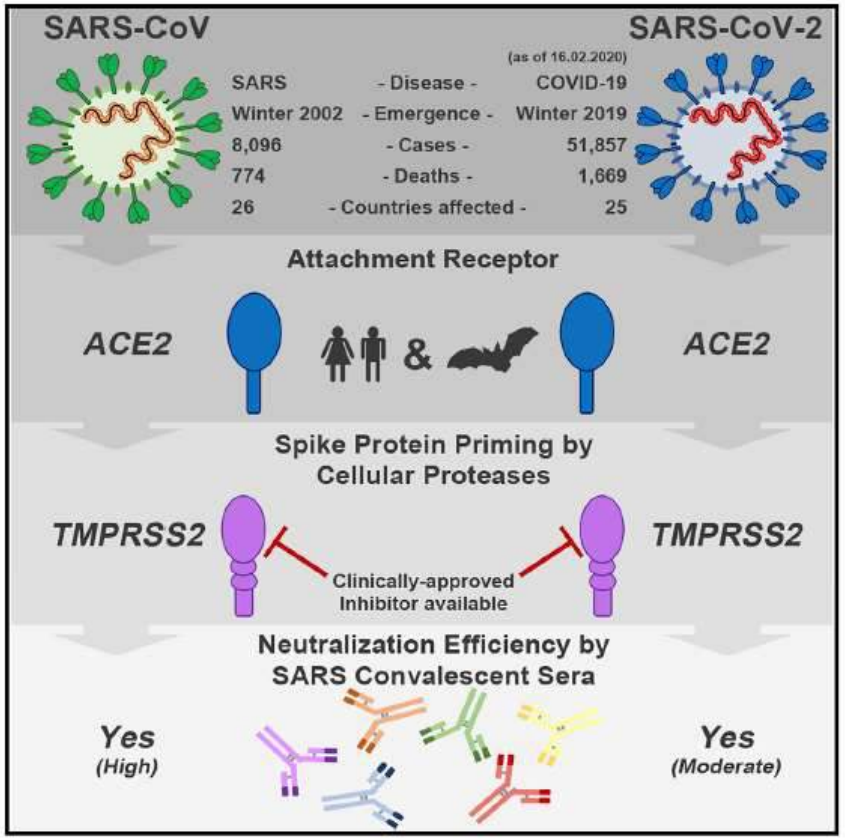
SARS-CoV-2 virus infection

Article

Cell

SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor

- SARS-CoV-2 infection depends on the host cell factors ACE2 and TMPRSS2.
- The cellular Serine Protease TMPRSS2 is essential in priming SARS-CoV-2 S-protein for entry.
- Camostat mesylate, a clinically proven inhibitor of TMPRSS2, blocks SARS-CoV infection in lungs cells.
- Antibodies against SARS-CoV spike (S-protein) may offer some protection against SARS-CoV-2.



Hoffmann et al. *Cell*. 2020.

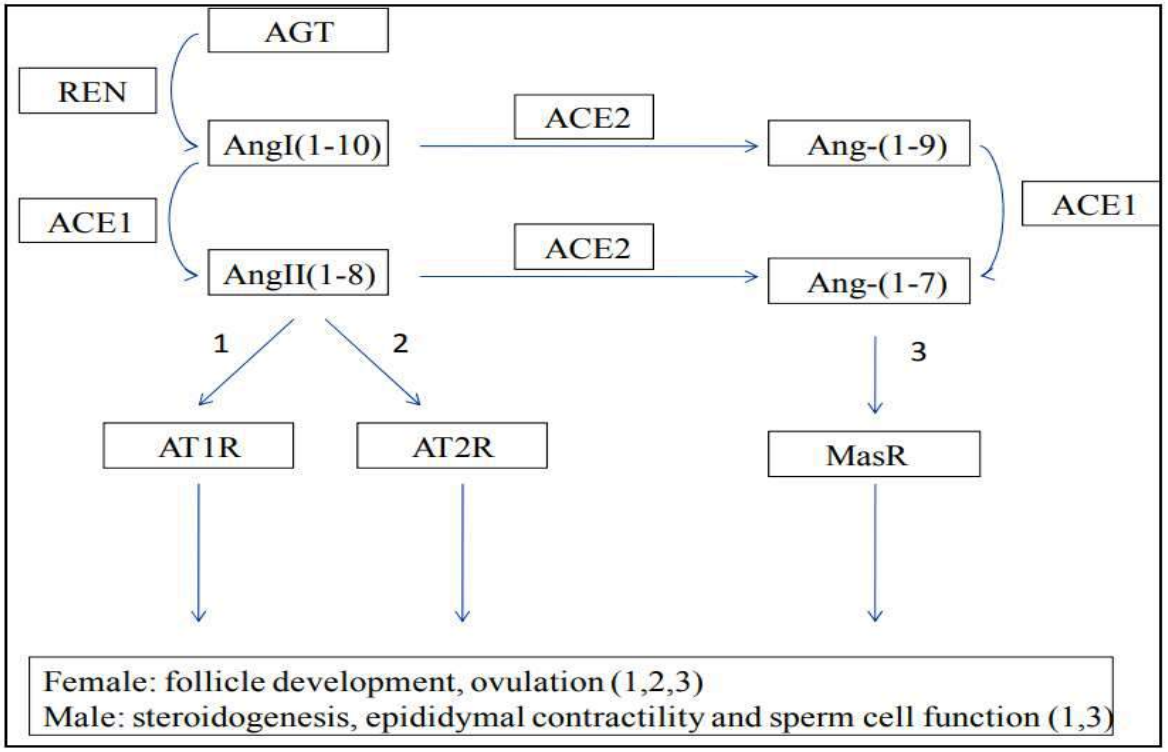
Detection of ACE2 and RAS system

RAS system has been found to be key for physiological functions in different organs and tissues...

Tissue	Physiological Role of RAS
Blood vessel	Vasomotor regulation, oxidative metabolism
Heart	Vasomotor tone, fibrotic regulation, oxidative metabolism
Kidney	Blood pressure regulation
CNS	Sympathetic regulation of blood pressure
Adipose tissue	Adipogenesis
Eye	Aqueous humor dynamics
Liver	Glucose metabolism

Nehme et al. *J Cardiovasc Dev Dis.* 2019.

...being also important for reproductive physiology



Pan et al. *Int J Mol Sci.* 2013.

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Detection of ACE2 and RAS system in reproductive organs

OVARY: May be involved in follicular development, steroidogenesis, oocyte maturation, ovulation and atresia

- ACE2 is present in human ovaries.
- Gonadotropin induces changes in ovarian expression of ACE2.
- ACE2 participates in ovarian physiology through Ang-(1-7).

TESTIS: It may participate in spermatogenesis

- ACE2 is only expressed by Leydig cells.
- Men with severe spermatogenesis defects present lower levels of ACE2, Ang-(1-7) and MasR than fertile men.

UTERUS: Posible roles in implantation and parturition are unknown

- ACE2 is expressed in endometrial epithelium of reproductive-age women, increasing in the secretory phase.
- ACE2 mRNA is highly expressed in decidua and placenta, amnion and chorion.

Reiss et al. *Fertil Steril.* 2011; Pereira et al. *Reprod Sci.* 2009; Costa et al. *Endocrinol.* 2003.
Reiss et al. J Mol Histol. 2010.
Vaz-Silva et al. Reprod Sci. 2009; Marques et al. Placenta. 2011.

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Detection of SARS-CoV-2 in reproductive organs

Four SARS patients defined by WHO criteria: 3 men (25, 38 and 57 years) and 1 woman (62 years).

	A1061[b]		A1062[b]		A1065[b]		A1076[b]	
Organs and tissues	**IHC**	**ISH**	**IHC**	**ISH**	**IHC**	**ISH**	**IHC**	**ISH**
Lung	+++	+++	+++	+++	+++	+++	+++	+++
Stomach	++	++	+	+	+	+	+	+
Small intestine	++	++	+	+	+	+	+	+
Kidney	++	++	++	++	++	++	++	++
Adrenal	++	++	++	++	++	++	++	++
Skin	++	++	++	++	++	++	++	++
Parathyroid	++	++	++	++	++	++	++	++
Pituitary	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+
Cerebrum	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	−	−
Oesophagus	−	−	−	−	−	−	−	−
Bone marrow	−	−	−	−	−	−	−	−
Thyroid	−	−	−	−	−	−	−	−
Spleen	−	−	−	−	−	−	−	−
Lymph node	−	−	−	−	−	−	−	−
Cerebellum	−	−	−	−	−	−	−	−
Heart	−	−	−	−	−	−	−	−
Striated muscle	−	−	−	−	−	−	−	−
Testis	−	−	−	−	−	−	−	−
Ovary	−	−	−	−	−	−	−	−
Uterus	−	−	−	−	−	−	−	−

Gu et al: "The testes of the seven male patients displayed focal atrophy. However, SARS viral sequences and viral particles were not identified".

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Ding et al. J Pathol. 2004; Gu et al. J Exp Med. 2005.

Lessons from previous Coronavirus epidemics

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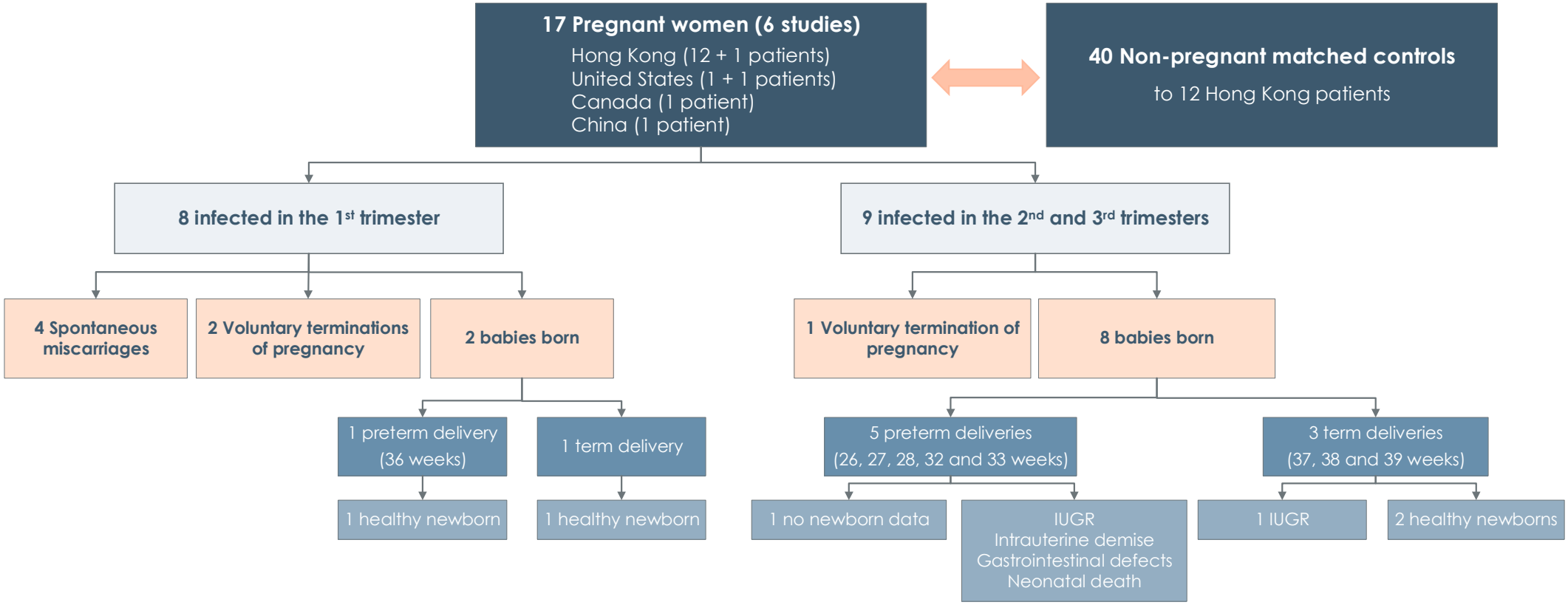
SARS and Pregnancy



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Wong et al. *Am J Obstet Gynecol*. 2004; Shek et al. *Pediatrics*. 2003; Ng et al. *Biol Neonate*. 2004; Robertson et al. *Emerg Infect Dis*. 2004; Stockman et al. *Emerg Infect Dis*. 2004; Yudin MH et al. *Obstet Gynecol*. 2005; Jiang et al. *Clin Diagn Lab Immunol*. 2004; Lam et al. *BJOG*. 2004;111:771-774.

SARS and Pregnancy

MATERNAL COMPLICATIONS:

- High mortality (all from the Hong Kong study, 25%).
- Equivalent clinical symptoms and lab work in pregnant vs. non-pregnant women.
- Pregnant patients required more ICU admissions compared to non-pregnant women.
- Increased spontaneous miscarriage in first Hong Kong study.

FETAL and NEONATAL COMPLICATIONS:

- 35% PTB associated with neonatal morbidity (80% in first Hong Knong study).
- Increased IUGR, intrauterine demise, and neonatal death.

TRANSMISSION:

- Vertical transmission of SARS-CoV, either transplacental or perinatal is unlikely.
- Absence of virus and viral particles in the POC.
- Negative RT-PCR and viral culture of newborn's nasopharyngeal and throat swabs, gastric aspirate, urine, meconium and later stool, amniotic fluid, cord blood, placenta, and breast milk.

Wong et al. Am J Obstet Gynecol. 2004; Shek et al. Pediatrics. 2003; Ng et al. Biol Neonate. 2004; Robertson et al. Emerg Infect Dis. 2004; Stockman et al. Emerg Infect Dis. 2004; Yudin MH et al. Obstet Gynecol. 2005; Jiang et al. Clin Diagn Lab Immunol. 2004; Lam et al. BJOG. 2004;111:771-774.

SARS and Pregnancy

OPEN QUESTIONS:

Causes of miscarriage:

- Severe maternal respiratory failure and hypoxemia may disrupt uterine placental flow.
- Use of Ribavirin:
  - 1st and 2nd trimester infected patients not treated with ribavirin had uncomplicated pregnancies.
  - Ribavirin is embryo lethal and teratogenic effects found in animal studies.

Cause of fetal complications:

- Severe maternal respiratory illness.
- Decreased oxygen supply to the fetus.
- Severe maternal debilitating illness.

Recommendations for patient management:

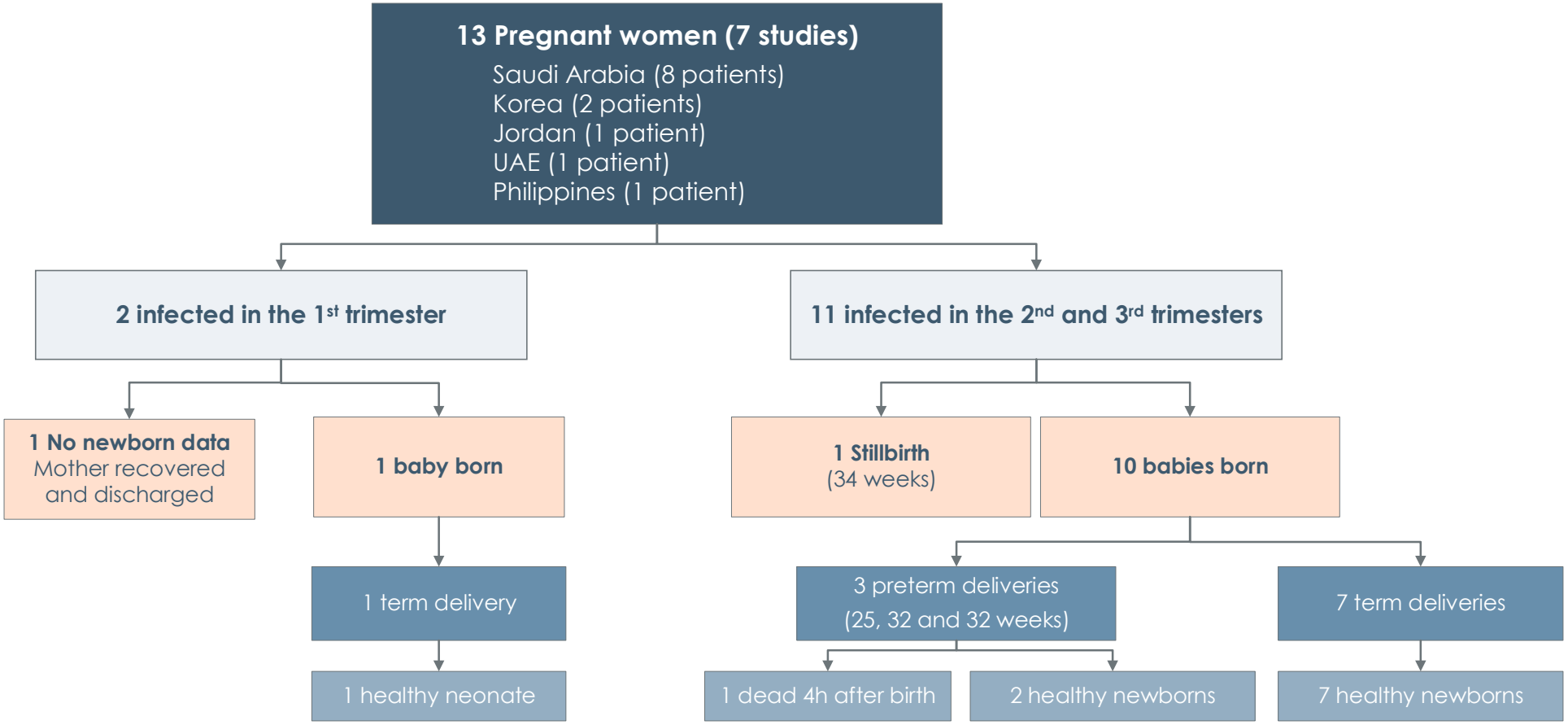
- Theoretical advantage of delaying delivery to avoid exposure to virus at birth.
- Transplacental passage of SARS-CoV antibodies to fetal circulation may protect the fetus/neonate.

CONCLUSIONS:

The adverse pregnancy outcomes might be due to the effects of SARS infection on the mother as well as to the medical treatment received for SARS.

Wong et al. Am J Obstet Gynecol. 2004; Shek et al. Pediatrics. 2003; Ng et al. Biol Neonate. 2004; Robertson et al. Emerg Infect Dis. 2004; Stockman et al. Emerg Infect Dis. 2004; Yudin MH et al. Obstet Gynecol. 2005; Jiang et al. Clin Diagn Lab Immunol. 2004; Lam et al. BJOG. 2004;111:771-774.

MERS and Pregnancy



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Park et al. Korean J Anesthesiol. 2016. Alfaraj SH et al. J Microbiol Immunol Infect. 2019; Alserehi et al. BMC Infect Dis. 2016; Assiri et al. Clin Infect Dis. 2016; Malik et al. Emerg Infect Dis. 2016; Payne et al. J Infect Dis. 2014; Racelis et al. Western Pac Surveill Response J. 2015; Jeong et al. J Korean Med Sci. 2017.

MERS and Pregnancy

MATERNAL COMPLICATIONS:

- Mortality 23% (3 cases).
- Equivalent clinical symptoms and lab work in pregnant vs. non-pregnant women.
- 7 patients were admitted to ICU and 5 required mechanical ventilation.
- 5 emergency C-sections.
- 1 preeclampsia.
- 8 women recovered and had healthy neonates.

FETAL and NEONATAL COMPLICATIONS:

- 1 stillbirth and 1 neonatal death.
- 2 placental abruption.
- No evidence of relationship between MERS-CoV and placental disorder.

TRANSMISSION:

- Negative RT-PCR and antibody tests in newborn's nasopharyngeal swabs and peripheral blood and placenta.
- Fetal specimen and/or placenta were not available for evaluation in the most cases.

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Park et al. Korean J Anesthesiol. 2016. Alfaraj SH et al. J Microbiol Immunol Infect. 2019; Alserehi et al. BMC Infect Dis. 2016; Assiri et al. Clin Infect Dis. 2016; Malik et al. Emerg Infect Dis. 2016; Payne et al. J Infect Dis. 2014; Racelis et al. Western Pac Surveill Response J. 2015; Jeong et al. J Korean Med Sci. 2017.

MERS and Pregnancy

OPEN QUESTIONS:

It is unclear whether MERS directly or indirectly produce stillbirth or preterm birth.

Role of maternal treatment in miscarriage and PTB:

- patients were treated with Ribavirin after babies were born.

CONCLUSIONS:

Various factors may have contributed to better outcome of MERS pregnant patients:

- Younger age.
- MERS infection late in pregnancy (also 2 patients infected at 1st trimester).

One pregnant patient using ART with no obstetric complications delivered a healthy neonate.

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Park et al. Korean J Anesthesiol. 2016. Alfaraj SH et al. J Microbiol Immunol Infect. 2019; Alserehi et al. BMC Infect Dis. 2016; Assiri et al. Clin Infect Dis. 2016; Malik et al. Emerg Infect Dis. 2016; Payne et al. J Infect Dis. 2014; Racelis et al. Western Pac Surveill Response J. 2015; Jeong et al. J Korean Med Sci. 2017.

Animal models of Coronavirus infection – SARS and MERS

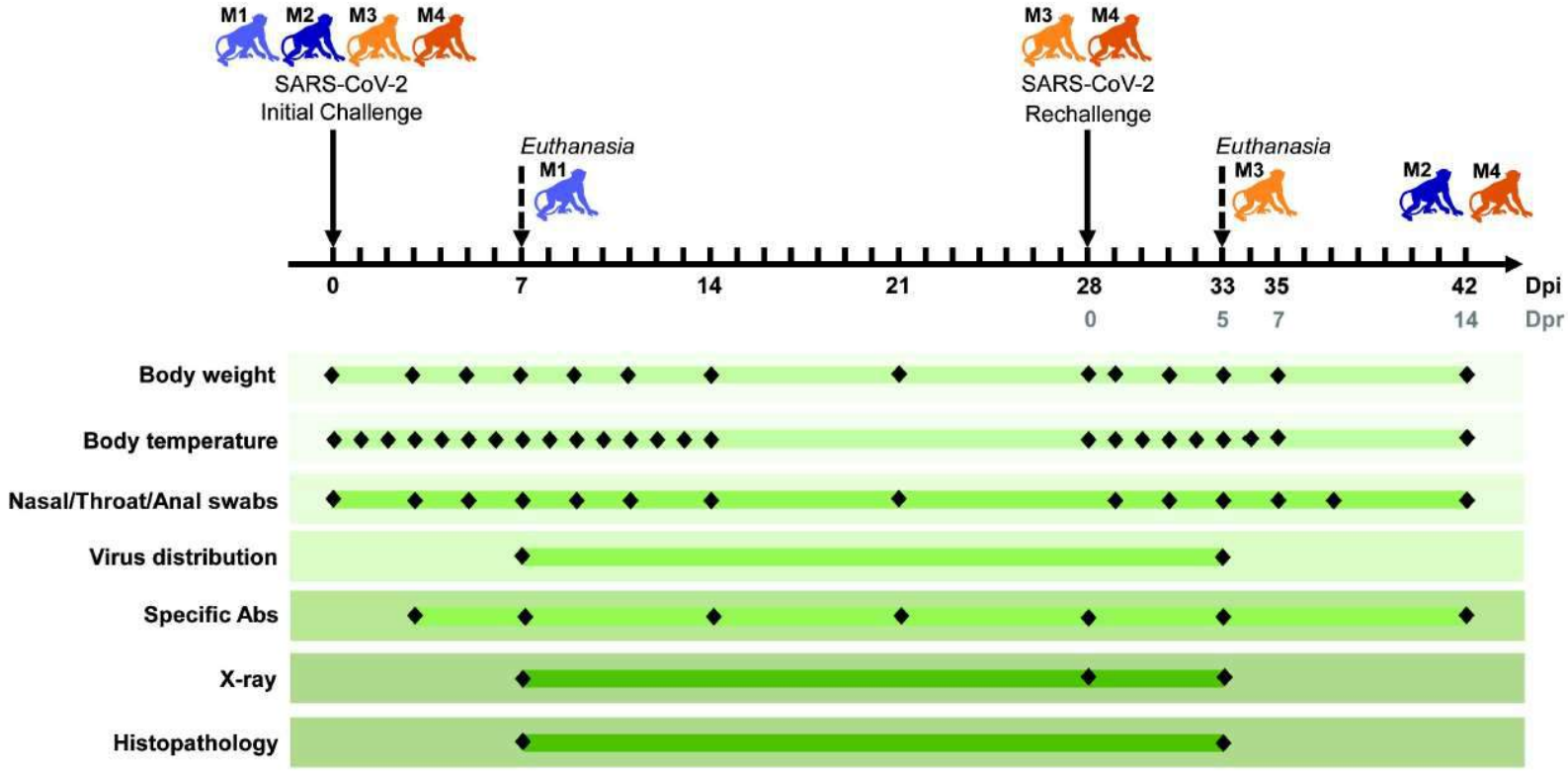
- Different animal models have been developed for SARS and MERS focused on the effects of the virus in the lung, hearth, liver and brain.
- No information is available regarding reproductive function, teratogenicity and or vertical transmission.

Species	Virus	
	SARS-CoV	MERS-CoV
Humans	• Clinical signs include fever and respiratory illness. • Lung pathology is consistent with pneumonia and acute lung injury.	• Clinical signs include fever and respiratory illness. Some patients develop renal failure. • Lung pathology samples are not available for investigation.
NHP	• **Rhesus macaques, cynomolgus macaques, African green monkeys and common marmosets** are susceptible to infection. Clinical signs, viral replication and pathology depend on the species.	• **Rhesus macaques** develop a transient infection with moderate viral replication and pathology in the lung. • **Common marmosets** have a more severe response to the virus with higher viral titers and severe pathology in the lungs. Lethality is also observed in this model.
Mice	• **Young inbred mice** (BALB/c, C57BL6, 129S) support viral replication but fail to show clinical signs of disease. • **Older inbred mice** (BALB/c), **knockout mice** (STAT 1−/−, Rag 1 −/−, CD1 −/−, Beige) **and transgenic mice** (K18-hACE2, A70-hACE2) develop generalized illness, robust viral growth and pronounced lung pathology consistent with pneumonia and acute lung injury. The K18-hACE2 transgenic mice develop central nervous system disease, which is not a feature in humans.	• **Inbred mice** are not naturally susceptible to infection. • **Transduced mice** (Ad5-hDPP4) develop clinical signs and support replication of virus with interstitial pneumonia and viral antigen found in the lungs. • **Transgenic mice** (hCD26/DPP4) develop robust respiratory and generalized illness with high viral titers and extensive inflammation in the lungs. Lethality was also observed in this model.
Hamsters	• Clinical illness (measured by a decrease in activity on the exercise wheel) is accompanied by viral replication and pronounced histopathological changes such as inflammation, pneumonitis and consolidation in the lungs.	• Hamsters do not support replication.
Ferrets	• Clinical illness (fever and sneezing), is accompanied by viral replication and histologic changes in the lungs.	• Ferrets do not support replication.
Rabbits	• The rabbit model has not been investigated.	• The rabbit model is currently under investigation.

Gretebeck and Subbarao. Curr Opin Virol. 2015; Gong and Bao. Animal Model Exp Med. 2018.

Animal models of Coronavirus infection – COVID-19

No evidence about the effect of SARS-CoV-2 infection in the non-human primate model (R. macaque).



Bao et al. BioRxiv. 2020

COVID-19 and Pregnancy

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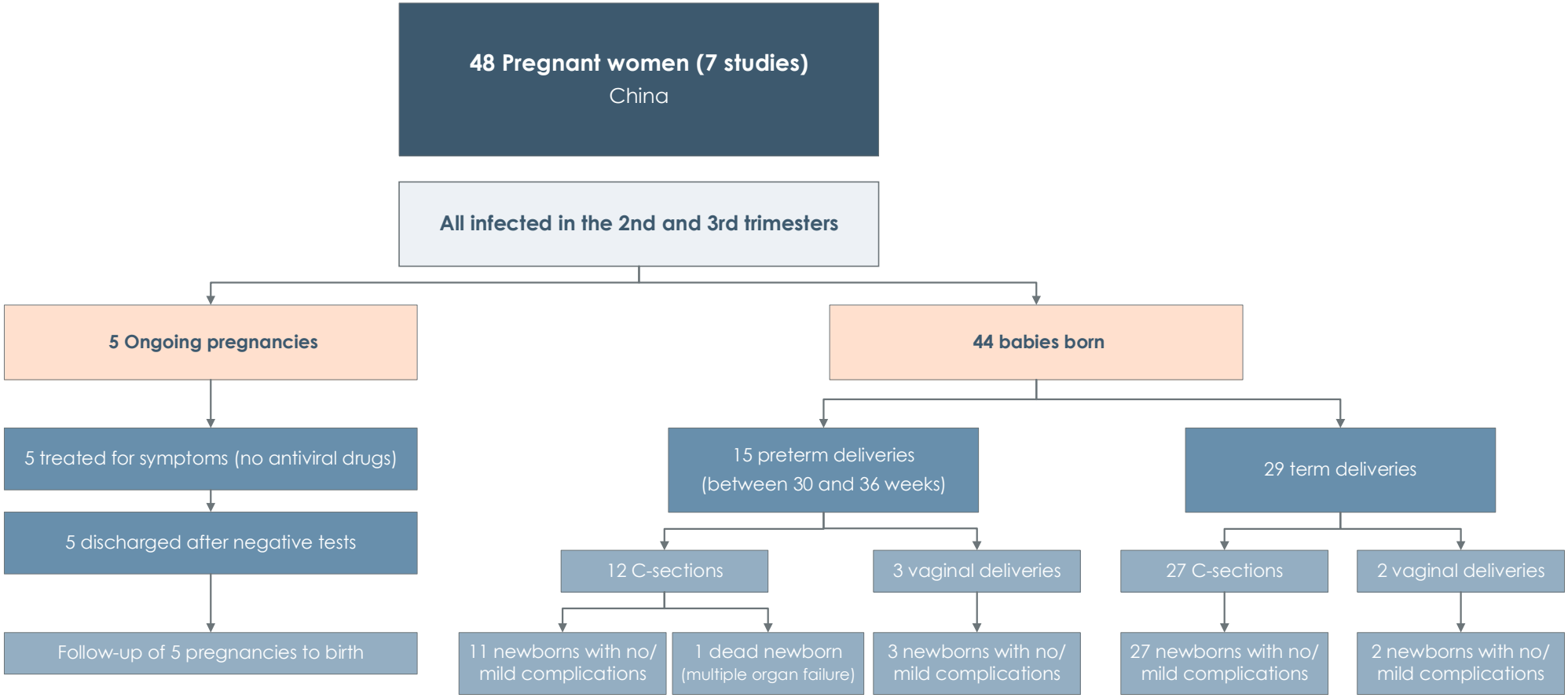
COVID-19 and Pregnancy



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Chen et al. The Lancet. 2020; Wang X et al. Clin Infect Dis. 2020; Wang S et al. Clin Infect Dis. 2020; Wen et al. J Microbiol Immunol Infect. 2020; Zhu et al. Transl Pediatr. 2020; Liu et al. www.preprints.org (not peer-reviewed); Liu et al. AJR Am J Roentgenol. 2020.

COVID-19 and Pregnancy

MATERNAL COMPLICATIONS (43 patients):

- Pre-eclampsia (2 cases).
- Premature rupture of membranes (5 cases).
- Chorioamnionitis (1 case).

FETAL and NEONATAL COMPLICATIONS:

- 1 newborn deceased with multiple organ failure and disseminated intravascular coagulation.
- Fetal distress (8 cases).
- Oligohydramnios and polyhydramnios (2 cases).

All the patients in these studies were treated with antiviral drugs AFTER delivery.

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Chen et al. The Lancet. 2020; Wang X et al. Clin Infect Dis. 2020; Wang S et al. Clin Infect Dis. 2020; Wen et al. J Microbiol Immunol Infect. 2020; Zhu et al. Transl Pediatr. 2020; Liu et al. www.preprints.org (not peer-reviewed); Liu et al. AJR Am J Roentgenol. 2020.

COVID-19 and Pregnancy

VERTICAL TRANSMISSION?

- No reported evidence of vertical transmission.
- ALL the samples tested were NEGATIVE in the following specimens:
  - ✓ Nasopharyngeal, oropharyngeal and throat swabs.
  - ✓ Gastric aspirate.
  - ✓ Urine.
  - ✓ Feces.
  - ✓ Plasma and/or peripheral blood.
  - ✓ Amniotic fluid.
  - ✓ Umbilical cord blood.
  - ✓ Placenta.
  - ✓ Breast milk.

- Throat swab from deceased neonate tested negative for SARS-CoV-2 virus.

- Media news from 2 cases of neonates positive for SARS-CoV-2 with no evidence of infection before, during or after delivery.(???)

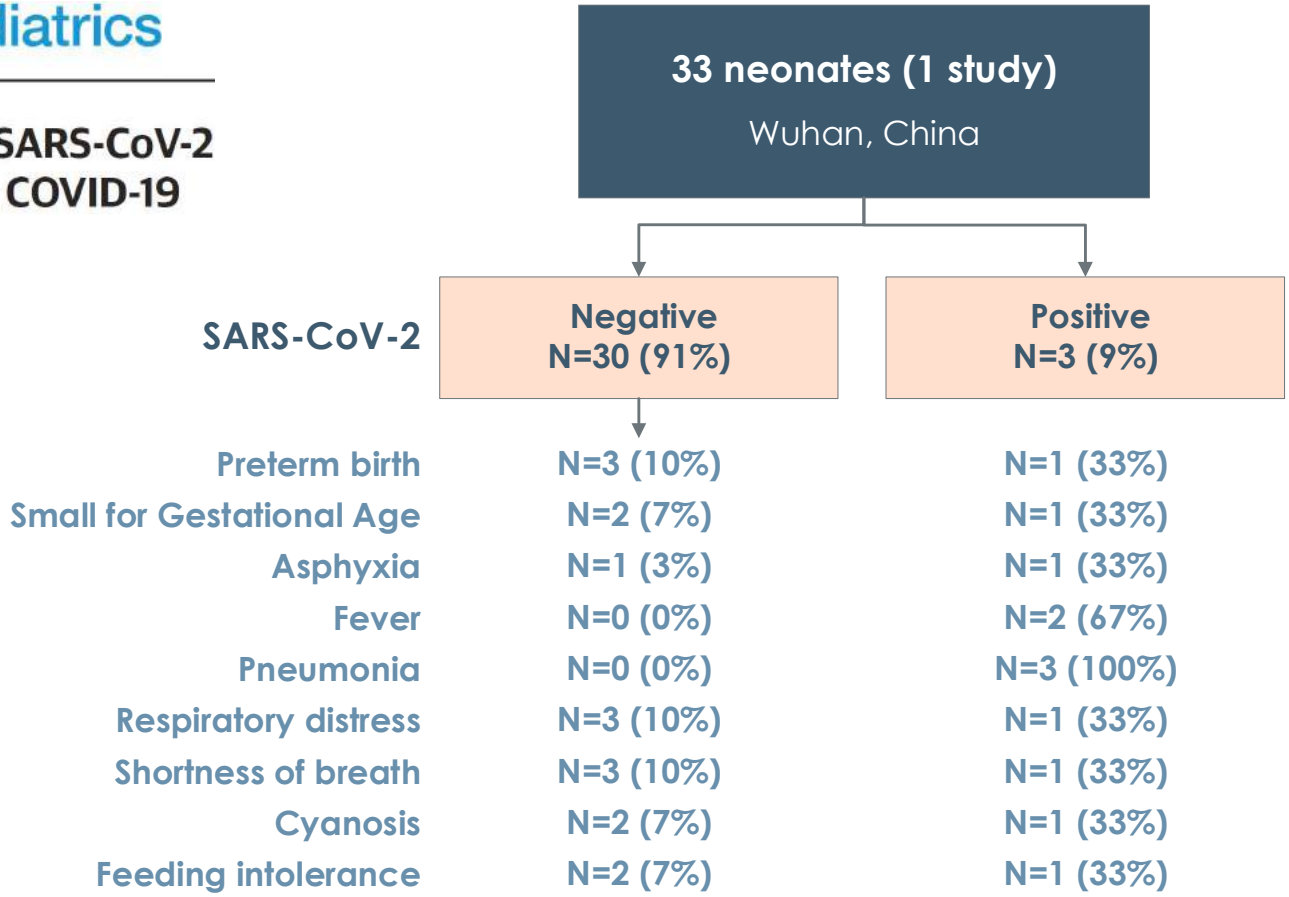
Chen et al. The Lancet. 2020; Wang X et al. Clin Infect Dis. 2020; Wang S et al. Clin Infect Dis. 2020; Wen et al. J Microbiol Immunol Infect. 2020; Zhu et al. Transl Pediatr. 2020; Liu et al. preprints.org (not peer-reviewed); Liu et al. AJR Am J Roentgenol. 2020.
https://www.theguardian.com/world/2020/mar/14/newborn-baby-tests-positive-for-coronavirus-in-london
https://www.bbc.com/news/world-asia-china-51395655

COVID-19 and Vertical transmission during pregnancy

RESEARCH LETTER

JAMA Pediatrics

Neonatal Early-Onset Infection With SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China



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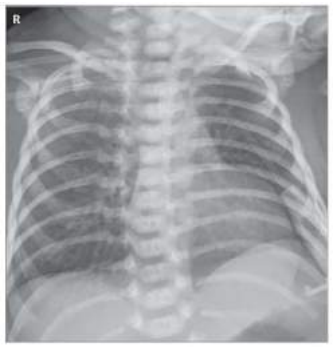
Zeng et al. JAMA Pediatr. 2020.

COVID-19 and Vertical transmission during pregnancy

NEONATE 1



Patient 1

Father: RT-PCR+

Mother: fever, RT-PCR+ CT outcome: pneumonia

Quarantine immediately after delivery

NICU admission with radiographic image: pneumonia

First RT-PCR+ (nasopharyngeal and anal)

PCT: 0.09 µg/L↑

Second RT-PCR+ (nasopharyngeal and anal)

PCT-

Third RT-PCR- (nasopharyngeal and anal)

Stable vital signs

30 31 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

January

February

Delivery Gestational age 40 wk

SARS-CoV-2 + Day 2

SARS-CoV-2 + Day 4

SARS-CoV-2 - Day 6

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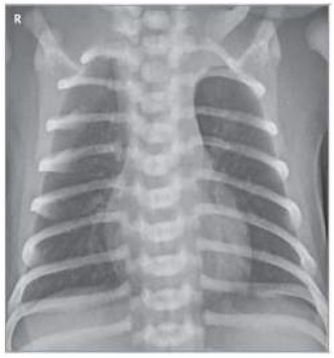
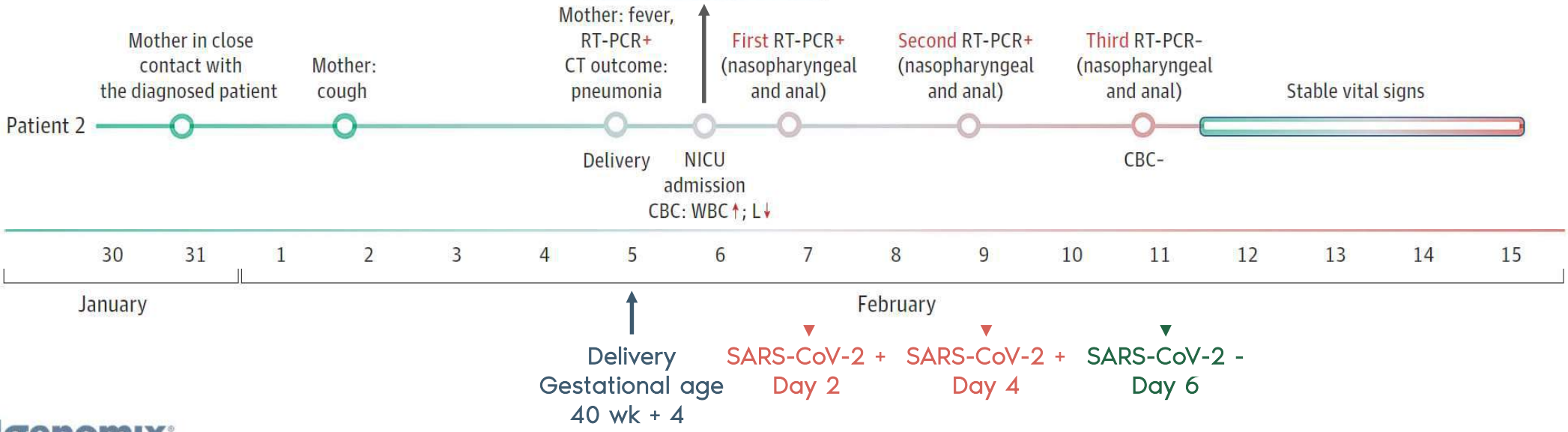
Zeng et al. JAMA Pediatr. 2020.

COVID-19 and Vertical transmission during pregnancy

NEONATE 2

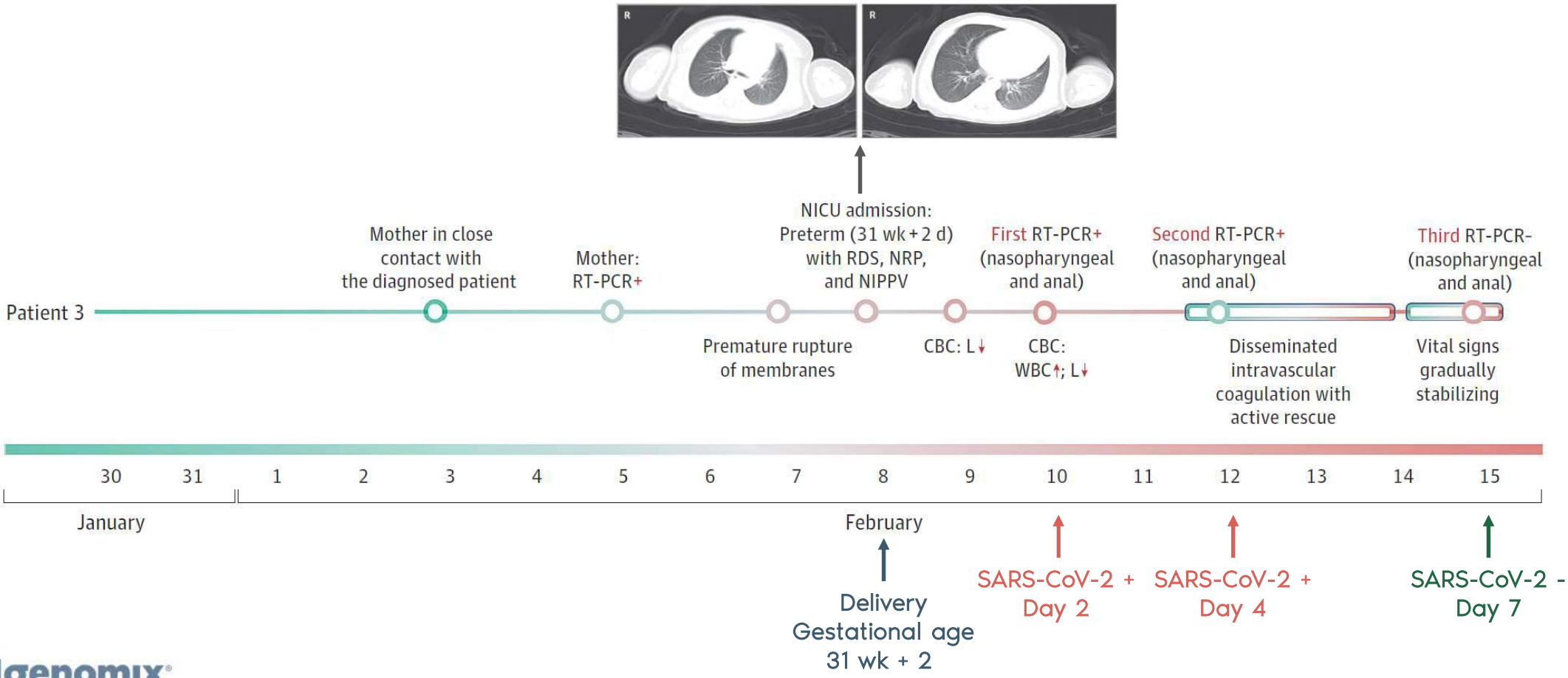




Zeng et al. JAMA Pediatr. 2020.

COVID-19 and Vertical transmission during pregnancy

NEONATE 3



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Zeng et al. JAMA Pediatr. 2020.

COVID-19 and Vertical transmisión during pregnancy

CONCLUSIONS

- The clinical symptoms from 33 neonates with or at risk of COVID-19 were mild and outcomes were favourable.

- Three neonates with symptomatic COVID-19. The most seriously affected was also preterm and septic, in addition to the SARS-CoV-2 infection.

- As strict infection control and prevention procedures were implemented during the delivery, the most likely source of SARS-CoV-2 in the neonates may be of maternal origin.

- Therefore, testing of pregnant women should be mandatory implementing strict infection control measures, quarantine of infected mothers and close monitoring of neonates at risk of COVID-19.

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Zeng et al. JAMA Pediatr. 2020.

Reasons for caution when analysing COVID-19 and SARS-CoV-2

1. Limited availability of reliable scientific data due to the novelty of the pandemic.

2. Potential duplication of reported COVID-19 cases.

3. Lack of evidence of the effect of coronaviruses on reproductive function in animal models of COVID-19, SARS and MERS.

JAMA Network

EDITORIAL

Editorial Concern—Possible Reporting of the Same Patients With COVID-19 in Different Reports

Howard Bauchner, MD; Robert M. Golub, MD; Jody Zylke, MD

Since January 1, 2020, *JAMA* and the JAMA Network journals have received hundreds of manuscripts and direct queries related to coronavirus disease 2019 (COVID-19), including research reports, case series and case reports, and opinion pieces. The editors have become aware that some of the patients described in some of these manuscripts, sometimes with overlapping authorship, have been reported in more than 1 submission. This inclusion of the same patients in more than 1 report has not been clearly indicated in the submitted manuscripts. This is of concern and may represent a lapse in ethical standards of scientific reporting.[1]

Viewpoint

Related article

Reporting of the same patients in different articles (without clear indication of the duplicate reporting) creates an inaccurate scientific record, may affect the accuracy of subsequent estimates of prevalence of the disease or outcomes, and may preclude valid meta-analyses, unless authors of the meta-analyses are able to obtain individual patient data to ensure that patients are not being counted more than once in any publication.

The potential for harm that could accrue from this type of misleading reporting is particularly concerning for studies of COVID-19. They are related to a rapidly evolving pandemic with only limited information available for decision-making, so that inaccurate data and analyses not only affect understanding the disease and its epidemiology, but have the potential to result in inappropriate changes in clinical care, ineffective public health responses, exacerbations of the economic consequences from this epidemic, and increasing anxiety about the pandemic.

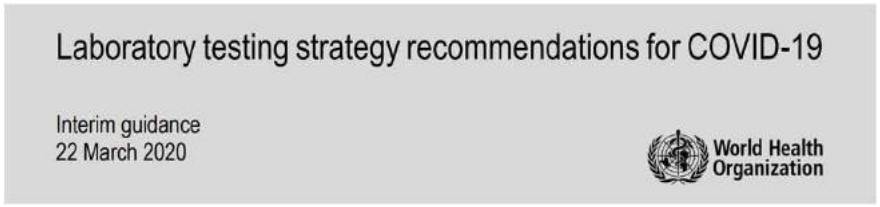
We recognize the important efforts of authors in rapidly communicating information about COVID-19 to the clinical and scientific community. However, we urge all authors of reports related to COVID-19 to clearly identify if any patients in any submitted manuscript have been reported in any previous submissions or publications.

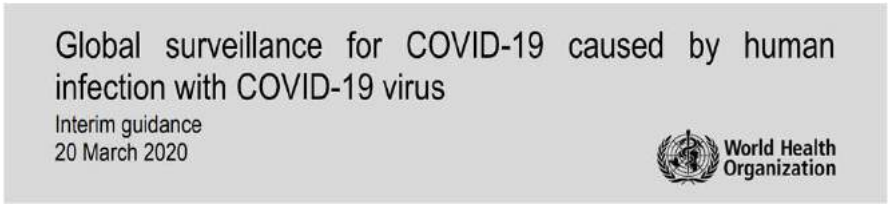
https://jamanetwork.com/journals/jama/fullarticle/2763371

Recommendations from Ob/Gyn professional bodies & Reproductive Medicine Societies

Igenomix® foundation FORWARD THINKING

WHO testing recommendations





- All countries should increase their level of preparedness, alert, and response to identify, manage, and care for new cases of COVID-19; laboratory testing is an integral part of this strategy.
- Any persons meeting the criteria for testing should be tested for COVID-19 infection using available molecular tests.

Countries that have not yet reported cases
Countries dealing with sporadic cases
Considerations for countries dealing with clusters of cases

WHO recommends that all suspect cases be tested for COVID-19.

Countries dealing with community transmission

Laboratories will need to be prepared for the significant increase in the number of specimens that need to be tested for COVID-19. Testing constraints should be anticipated, and prioritization will be required.

https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov)
https://apps.who.int/iris/bitstream/handle/10665/331509/WHO-COVID-19-lab_testing-2020.1-eng.pdf

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American College of Obstetrics and Gynecology (ACOG) & British Royal College of Obstetricians and Gynaecologists (RCOG)

Specific guidance for pregnant women based on limited experience with SARS-CoV and MERS-CoV

- Compared to the general population, pregnant women may be at higher risk of:
  - ✓ Severe illness.
  - ✓ Morbidity or mortality.
  - ✓ Adverse **perinatal** outcomes, including preterm birth.
- There is little historical information available for women considering pregnancy or embarking on ART.
- Given the modelling of the pandemic, including the time to peak and subsequent tail, considerable delays in conception to substantially mitigate risk may be required.

https://www.acog.org/Clinical-Guidance-and-Publications/Practice-Advisories/Practice-Advisory-Novel-Coronavirus2019
https://www.rcog.org.uk/coronavirus-pregnancy
Chen et al. Lancet 2020; Zhu et al. Transl Pediatr. 2020.

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Coronavirus Covid-19: ESHRE Statement on Pregnancy and Conception: March 14th, 2020

"There is no strong evidence of any negative effects of Covid-19 infection on pregnancies, especially those at early stages, as indicated by the latest updates from the CDC in the USA and others in Europe."

PATIENT'S MANAGEMENT

As a precautionary measure we advise that:

1) **Suspend initiation in all fertility patients**, **even if they do not meet the diagnostic criteria for Covid-19 infection**, should avoid becoming pregnant at this time.

2) For those **patients already having treatment**, we suggest considering deferred pregnancy with oocyte or embryo freezing for later embryo transfer.

3) Patients **who are pregnant or** those (men and women) **planning or undergoing fertility treatment** should avoid travel to known areas of infection and contact with potentially infected individuals.

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https://www.cdc.gov/coronavirus/2019-ncov/prepare/pregnancy-breastfeeding.html?CDC_AA_refVal=https://www.cdc.gov/coronavirus/2019-ncov/specific-groups/pregnancy-faq.html
https://www.rcog.org.uk/globalassets/documents/guidelines/coronavirus-covid-19-infection-in-pregnancy-v2-20-03-13.pdf

ASRM Patient Management and Clinical Recommendations during the Coronavirus (COVID-19) Pandemic: March 17th, 2020

"Given the information we do have, while it would be wise for individuals with confirmed or presumed COVID-19 infection to avoid pregnancy, there appears to be no cause for alarm for those already pregnant."

PATIENT'S MANAGEMENT

1) **Suspend initiation of new treatment cycles**, including ovulation induction, intrauterine inseminations (IUIs), in vitro fertilization (IVF) including retrievals and frozen embryo transfers, as well as non-urgent gamete cryopreservation.

2) Strongly consider **cancellation of all embryo transfers** whether fresh or frozen.

3) Continue to care for patients who are currently "in-cycle" or who require urgent stimulation and cryopreservation.

4) Suspend elective surgeries and non-urgent diagnostic procedures.

5) Minimize in-person interactions and increase utilization of telehealth.

6) **Patients with active COVID-19 should not undergo fertility treatment**, unless they require urgent fertility preservation.

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https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/covidtaskforce.pdf

Reactions to the ASRM Patient Management and Clinical Recommendations

FERTILITY PROVIDERS ALLIANCE

The Fertility Providers Alliance (FPA) that represents over **400 fertility specialists**, requested ASRM to revisit and reshape it's recommendations to the reproductive endocrinology community, based in 3 reasons:

1) The actual public health burden created by the continuation of fertility care
The vast majority of fertility centers across USA are free-standing medical facilities that operate without hospital affiliation.

2) The classification of infertility treatment as 'non-urgent' or elective
The reproductive health community has fought diligently to recognize infertility for what it is: a disease state that includes many diverse medical conditions.

3) The harmful consequences of an indeterminate delay in access to care
For these patients, "revisiting guidelines periodically as the pandemic evolves" creates an anguishing and indeterminate state of reproductive limbo.

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Source: FPA Communicate

ASRM Patient Management and Clinical Recommendations during the Coronavirus (COVID-19) Pandemic: March 17th, 2020

"*Given the inform* *VID-19 infection to*

PATIENT'S MA

1) **Suspend initi** ions (IUIs), in vitro fertilization (IVF) in ation.

2) Strongly consid

3) Continue to car ervation.

4) Suspend electiv

5) Minimize in-pers

6) **Patients with** lity preservation.

UPDATE March 30, 2020

asrm
American Society for Reproductive Medicine

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE (ASRM)
PATIENT MANAGEMENT AND CLINICAL RECOMMENDATIONS
DURING THE CORONAVIRUS (COVID-19) PANDEMIC

Update #1 (March 30, 2020 through April 13, 2020)

At this time, the ASRM Coronavirus/COVID-19 Task Force affirms all of the stated recommendations of March 17, 2020 as timely and appropriate, including:

1. Suspend initiation of new treatment cycles, including ovulation induction, intrauterine inseminations (IUIs), *in vitro* fertilization (IVF) including retrievals and frozen embryo transfers, as well as non-urgent gamete cryopreservation.
2. Strongly consider cancellation of all embryo transfers whether fresh or frozen.
3. Continue to care for patients who are currently "in-cycle" or who require urgent stimulation and cryopreservation.
4. Suspend elective surgeries and non-urgent diagnostic procedures.
5. Minimize in-person interactions and increase utilization of telehealth.

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https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/covidtaskforce.pdf
https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/covid-19/covidtaskforceupdate1.pdf

COVID-19 in Reproductive Medicine Research Task Forces

- ✓ Teratogenic effect of the SARS-CoV-2 infection in the 1st trimester
- ✓ Vertical transmission of the virus

Igenomix foundation FORWARD THINKING

Food for thought

- ✓ LIFE FIRST
- ✓ But life goes on: we might stop Assisted Reproduction but Natural Reproduction continues.
- ✓ Creation of free-COVID-19 clinics and hospitals.
- ✓ More than ever, scientific research is needed in teratogenic effect of the virus, possible vertical transmission..... and we are accountable for it.

Igenomix foundation FORWARD THINKING



Inmaculada Moreno, PhD
Felipe Vilella, PhD
Xavi Santamaria, MD, PhD
Jaime Herrero

+

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