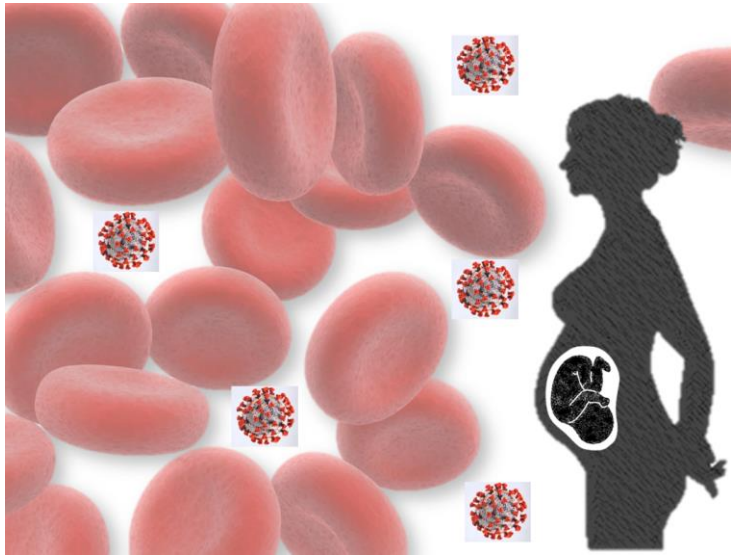
COVID Illness in the Pregnant Mom: How Does it Affect the Fetus?



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Division of Pediatric Infectious Diseases
04/21/2022

Educational Objectives

(1) To provide general information on the biology and epidemiology of SARS CoV-2 infection in pregnancy and repercussions to the infant.

(2) To describe the status of the pandemic in pregnant women and infants and knowledge to date.

(3) To review main research questions pertaining to COVID-19 in pregnancy and perinatal/ neonatal COVID-exposure.

(4) To present work in progress and preliminary study results of the COMP Study at UCLA

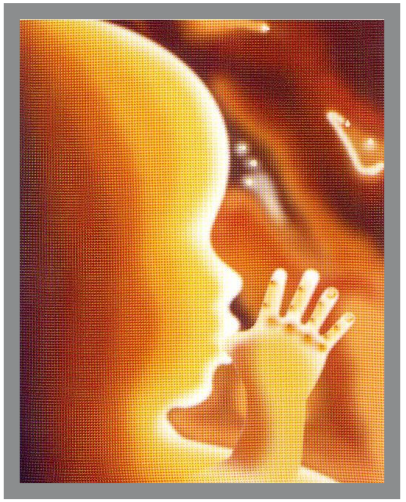
Disclosure

- Neither I nor any member of my immediate family has a financial relationship or interest (currently or within the past 24 months) with any proprietary entity producing health care goods or services consumed by, or used on, patients related to the content of this CME activity.

- I do not intend to discuss an unapproved/investigative use of a commercial product/device.

Congenital infections

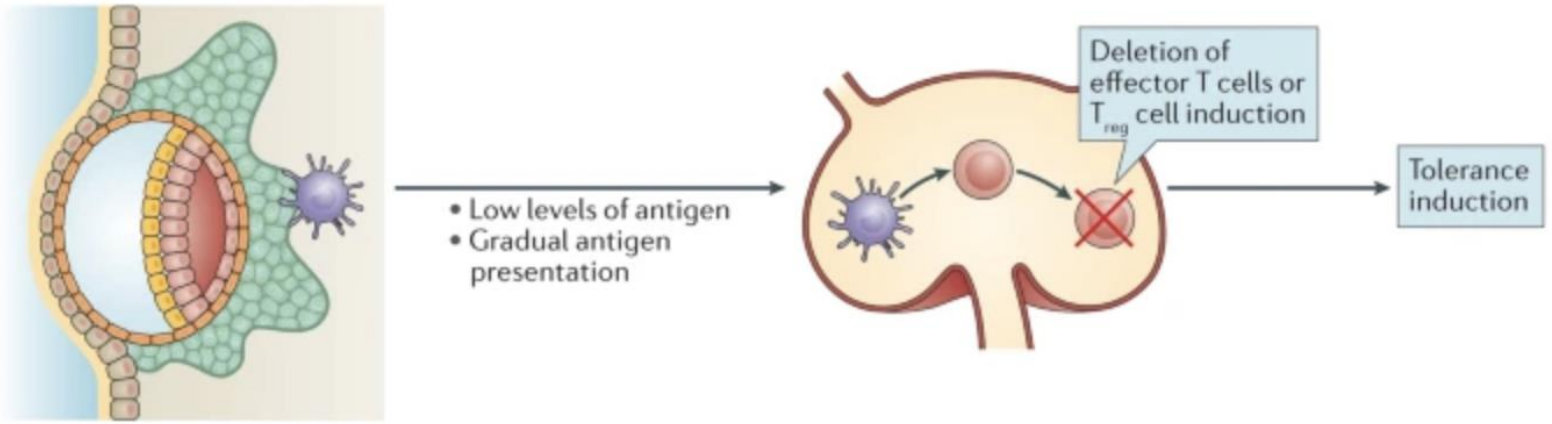
- Infections and illnesses in pregnancy are common.
- Pregnancy renders women more susceptible to:
  - CMV primary infection
  - HIV primary infection
  - Syphilis
- Or associated with worse outcomes in:
  - Influenza
  - Measles
  - Coccidiodomycosis



Introduction

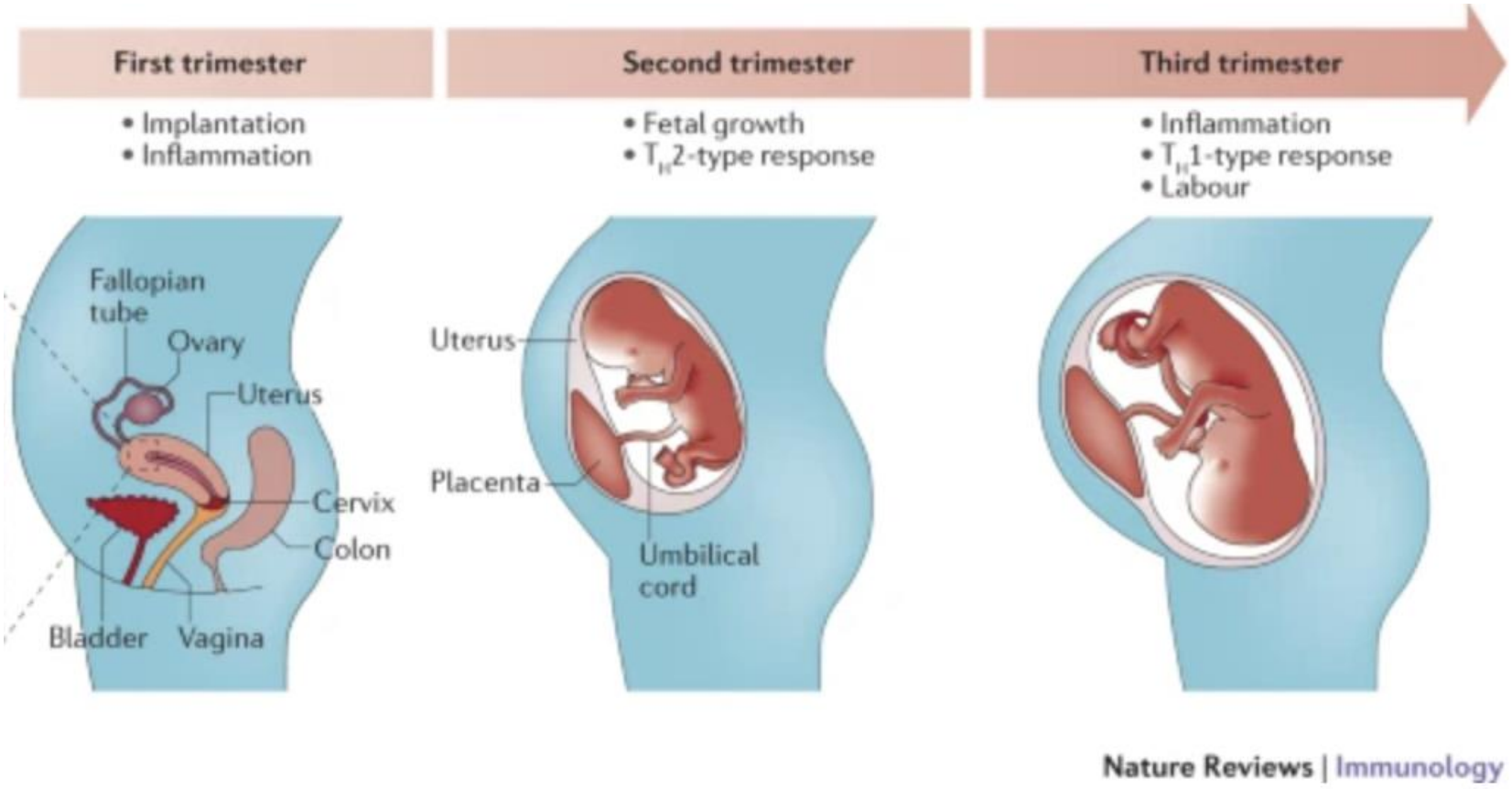
Pregnant women face increased risk of infection due to:

1. Immunologic paradox of pregnancy
2. Physiologic changes in pregnancy
3. Gender dynamics that impact transmission



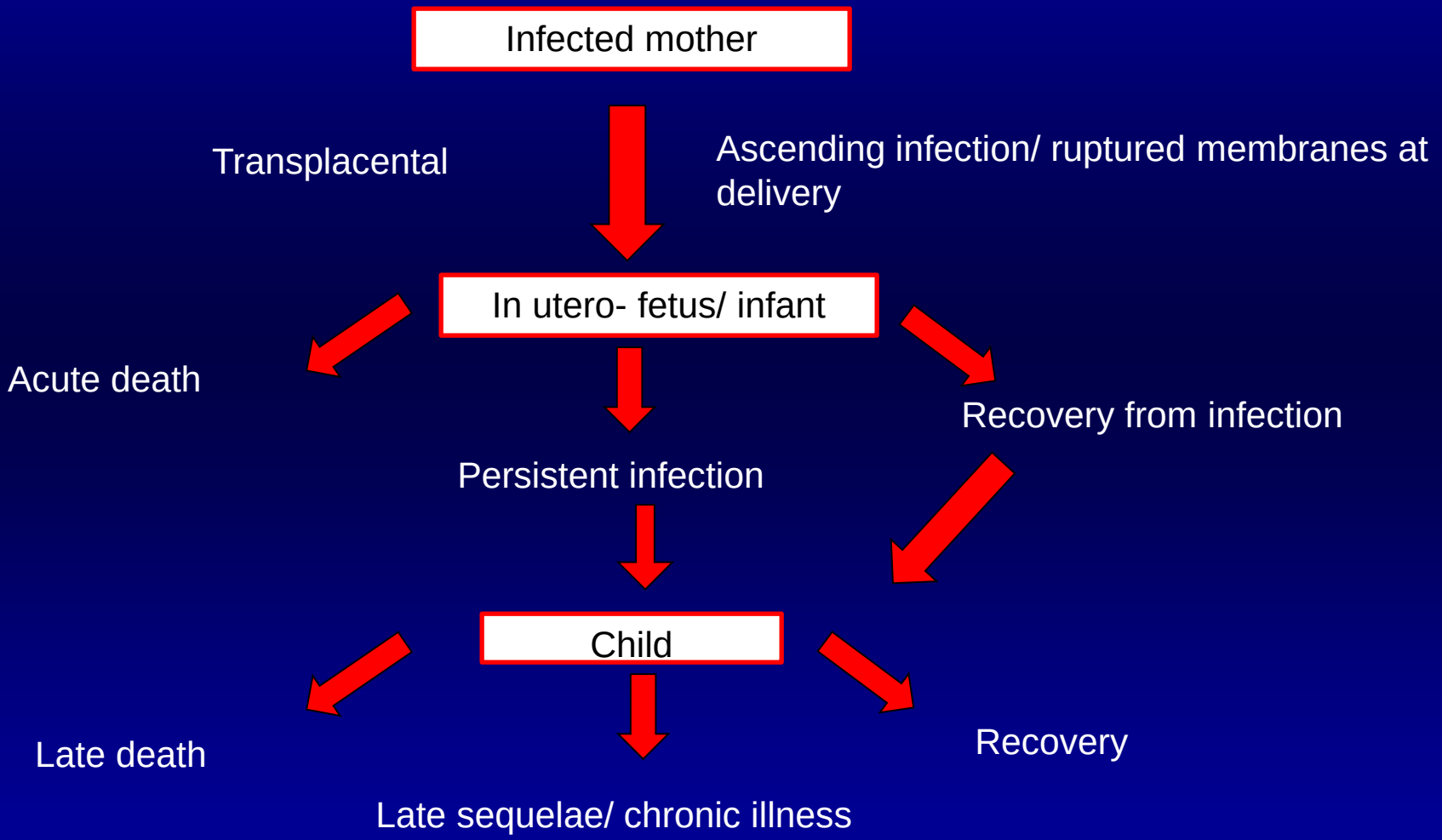
Mor et al. PMID: 28627518

Introduction



Mor et al. PMID: 28627518

Pathogenesis of congenital infections



Development of the fetal brain and gestational age of infection

1rst trimester:

- Rubella
- Zika
- CMV
- VZV

2nd trimester:

- Zika
- CMV
- Toxo

3rd trimester/ peripartum:

- HIV
- HSV
- VZV
- CMV
- Toxoplasma
- *T. pallidum*

Screening for congenital infections recommended for:

- Infants who are small for gestational age (IUGR).
- Infants with high risk maternal history.
- All infants with congenital defects.

Types of coronaviruses

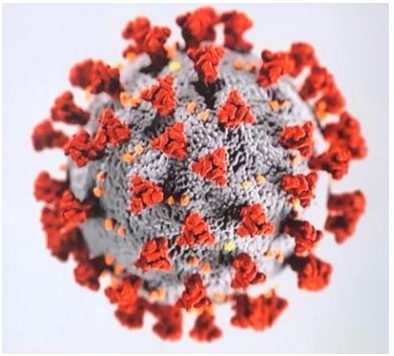


Table 1. History of Human Coronaviruses

Coronavirus	Year(s) Identified	First Identification
Alpha coronavirus: group 1		
HCoV-229E	1960s	Boy with cold, United Kingdom: B814 isolate; medical students with colds, Chicago, Illinois: 229E (note: B814 isolate described here not further propagated)
HCoV- NL63	2004	7-month-old and 8-month-old infants with bronchiolitis in the Netherlands
Beta coronavirus group 2, lineage A		
HCoV-OC43	1967–1972	Acute respiratory infections in adults at the National Institutes of Health
HCoV-HKU1	2004	71-year-old man with pneumonia in Hong Kong
Beta coronavirus group 2, lineage B		
SARS-CoV	2003–2004	Humans with severe pneumonia in China; natural host, Chinese horseshoe bats; presumed intermediate host, palm civet
SARS-CoV-2	2019–2020	Adults with acute respiratory distress syndrome/pneumonia from Wuhan, China; potential bat origin and related to SARS-CoV
Beta coronavirus group 2, lineage C		
Middle East respiratory syndrome-CoV	2012	Adults with acute respiratory distress syndrome in Saudi Arabia; dromedary camel as reservoir/intermediary

Abbreviations: HCoV, human coronavirus; SARS, severe acute respiratory syndrome.

Journal of the Pediatric Infectious Diseases Society

Ogimi et al, 2020

Korea, South
28-Day: 9,161,068 | 8,879
Totals: 15,169,189 | 19,092

Vietnam
28-Day: 4,810,197 | 1,576
Totals: 10,135,789 | 42,768

United Kingdom
28-Day: 2,073,903 | 6,817
Totals: 21,716,180 | 170,367

Brazil
28-Day: 836,122 | 6,848
Totals: 30,125,540 | 661,377

Germany
28-Day: 5,664,274 | 6,094
Totals: 22,629,378 | 131,679

France
28-Day: 3,245,668 | 3,150
Totals: 26,887,490 | 144,193

Italy
28-Day: 1,891,568 | 3,909
Totals: 15,173,707 | 160,546

US
28-Day: 834,271 | 21,905
Totals: 80,385,966 | 985,100

Total Cases
497,435,121

Total Deaths
6,174,225

Total Vaccine Doses Administered
11,089,978,537

28-Day Cases
42,989,539

28-Day Deaths
145,228

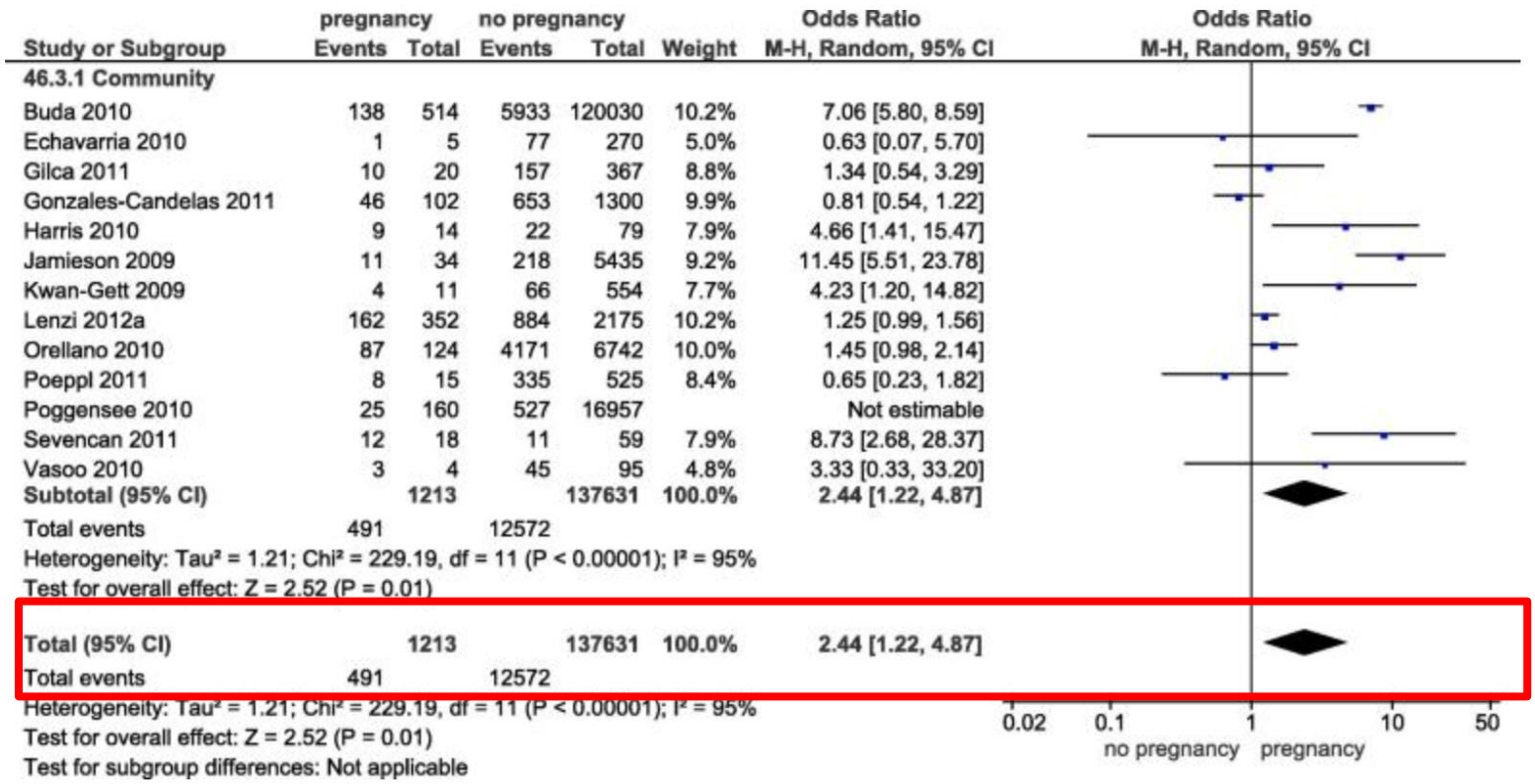
28-Day Vaccine Doses Administered
447,303,780

Viral infections in Pregnancy

- During the 1918-1919 influenza pandemic
  - Higher mortality rates 5.7/1,000 vs 4.9/1,000
  - 50% higher chances of developing pneumonia
  - Higher rates of miscarriages and premature birth

- During the 2009 H1N1 influenza pandemic, pregnant women were disproportionately impacted and required high rates of ECMO
  - They represented 1% of the population; however, accounted for 5% of the deaths

Influenza in Pregnancy



Study or Subgroup	pregnancy Events	Total	no pregnancy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
46.3.1 Community						
Buda 2010	138	514	5933	120030	10.2%	7.06 [5.80, 8.59]
Echavarria 2010	1	5	77	270	5.0%	0.63 [0.07, 5.70]
Gilca 2011	10	20	157	367	8.8%	1.34 [0.54, 3.29]
Gonzales-Candelas 2011	46	102	653	1300	9.9%	0.81 [0.54, 1.22]
Harris 2010	9	14	22	79	7.9%	4.66 [1.41, 15.47]
Jamieson 2009	11	34	218	5435	9.2%	11.45 [5.51, 23.78]
Kwan-Gett 2009	4	11	66	554	7.7%	4.23 [1.20, 14.82]
Lenzi 2012a	162	352	884	2175	10.2%	1.25 [0.99, 1.56]
Orellano 2010	87	124	4171	6742	10.0%	1.45 [0.98, 2.14]
Poeppl 2011	8	15	335	525	8.4%	0.65 [0.23, 1.82]
Poggensee 2010	25	160	527	16957		Not estimable
Sevencan 2011	12	18	11	59	7.9%	8.73 [2.68, 28.37]
Vasoo 2010	3	4	45	95	4.8%	3.33 [0.33, 33.20]
Subtotal (95% CI)		**1213**		**137631**	**100.0%**	**2.44 [1.22, 4.87]**
Total events	491		12572			
Heterogeneity: Tau² = 1.21; Chi² = 229.19, df = 11 (P < 0.00001); I² = 95%						
Test for overall effect: Z = 2.52 (P = 0.01)						
Total (95% CI)		**1213**		**137631**	**100.0%**	**2.44 [1.22, 4.87]**
Total events	491		12572			
Heterogeneity: Tau² = 1.21; Chi² = 229.19, df = 11 (P < 0.00001); I² = 95%						
Test for overall effect: Z = 2.52 (P = 0.01)						
Test for subgroup differences: Not applicable						

Respiratory Pathogens in Pregnancy

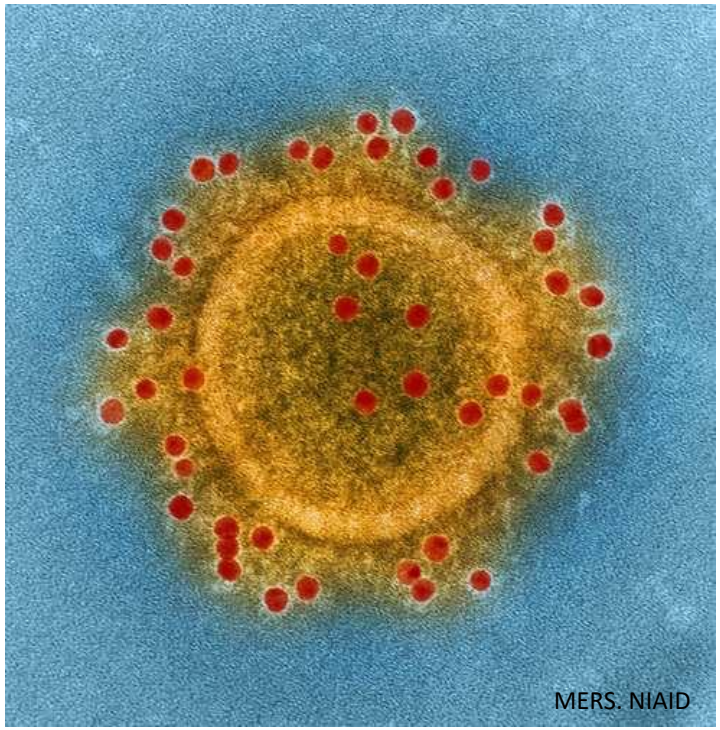
Highly-pathogenic beta-coronaviruses: SARS-CoV-1 and MERS

SARS-CoV-1: 25% maternal mortality rate

MERS: 30% infant mortality rate

>50% rate of miscarriage in both

>80% rate of preterm birth in both



MERS. NIAID

Pregnancy and SARS-CoV-2

- SARS-CoV-2 infection causes more severe disease in pregnant women compared to age-matched non pregnant women
  - Higher risk for hospitalizations and mechanical ventilation
  - Higher risk of mortality
  - Higher risk of preterm birth
- Maternal immune response to infection can have protective effects on neonatal health by transfer of COVID19 specific antibodies (IgG) trans-placentally
  - Infants are born with immunity
- Viral infections during perinatal and postnatal periods has a wide range in effects of fetal and neonatal development
  - Effects on developing fetal and neonatal brain and the development of the immune system

O MUNDO EM ALERT

Juliana Vidal e o filho Joaquim, que enfrentaram bravamente o coronavírus

NA LUTA PELA VITÓRIA DA VIDA

Médicos fazem alerta para aumento de internações de gestantes em UTIs nesta fase da pandemia

Ana Lucia Azevedo
ala@oglobo.com.br

Até a Covid-19 quase lhe roubar a vida, Juliana Vidal, de 28 anos, se considerava uma jovem saudável. Grávida de seu segundo filho, sem comorbidades e ativa, Juliana nunca entraria numa lista de grupo de risco. Mas seu caso, de tão grave, comove e impressiona os médicos do Instituto Estadual de Infectologia São Sebastião (IEISS). Também mostra como o coronavírus continua sendo um inimigo imprevisível.

A força dela e a dedicação dos médicos trouxeram ao mundo Joaquim. Ele chegou na virada de 24 para 25 de dezembro, num Natal inesquecível para a equipe que às pressas ajudou a grávida que lutava pela própria vida a dar à luz um menino.

Consultora de vendas, ela só ia de casa para o trabalho, em São Gonçalo. Começou a apresentar sintomas em 21 de novembro. Passou dez dias peregrinando por atendimento em hospitais de sua cidade, mas não conseguia sequer diagnóstico. Ouviu que não era Covid-19, era ansiedade e que "queria pegar o vírus". Pouco depois desmaiou e uma das últimas coisas que se lembra é que chegou transferida ao IEISS já com 95% dos pulmões comprometidos:

— Daí em diante, tudo o que via eram máscaras.

Ela teve alta da UTI e entrou em trabalho de parto. Mal nasceu, Joaquim, prematuro, de 29 semanas, precisou de uma máscara de oxigênio. A mãe foi para casa em fevereiro, após 52 dias de internação e 18 dias de tubo. O filho teve alta apenas em 3 de março, mas precisa de acompanhamento médico.

Gestantes personificam a celebração da vida. Mas na pandemia, a gravidez também é fator de risco de doença e morte. Médicos alertam que as gestantes correm um perigo maior e deveriam ter prioridade no acesso a tratamento, incluindo internação em UTI, e a testes de diagnóstico. Se na primeira onda, as gestantes não chegaram a causar especial preocupação, agora o quadro é outro. Médicos têm observado um número maior delas nas UTIs, à medida que aumentou também o de jovens — os casos entre eles, segundo a Fiocruz, cresceram mais de 500%, de janeiro a março.

Médica examina grávida em quarto isolado: faltam leitos

Estudos mostram fator de alto risco

A infectologista do IEISS Ana Luiza Oliveira conta que os idosos quase já não estão mais internando, possivelmente já pelos efeitos da vacina, mas que agora os jovens, muitos sem comorbidades, predominam nas UTIs e as gestantes estão entre eles. A situação das grávidas preocupa mais porque o risco delas é maior. Um estudo da Universidade de Washington publicado em fevereiro estima que a Covid-19 é 70% mais frequente em gestantes do que em mulheres da mesma faixa etária. Já uma pesquisa do Centro de Controle e Prevenção de Doenças dos EUA com 400 mil mulheres com coronavírus, 23.434 das quais grávidas, chegou à conclusão de que a gestação é fator de alto risco de agravamento da Covid-19. A chance de uma gestante ser internada em UTI foi 62% maior que a de mulheres da mesma faixa etária. A de intubação foi 88% maior.

A gestação reduz a atividade do sistema imunológico para que o bebê não seja rejeitado. O útero dilatado comprime o diafragma e isso reduz a capacidade pulmonar. A grávida costuma sofrer ainda inflamação e tem uma maior tendência à formação de trombos, ambos fatores de agravamento da Covid-19. E se soma a isso tudo o fato de que muitas gestantes apresentam com frequência as comorbidades mais associadas à Covid-19: obesidade, hipertensão e diabetes.

«Temia perder meu filho, minha vida. Tudo o que via eram máscaras»
Juliana Vida
Mãe que sobreviveu à Covid

«Agora os jovens predominam nas UTIs e as gestantes estão entre eles»
Ana Luiza Oliveira
Infectologista

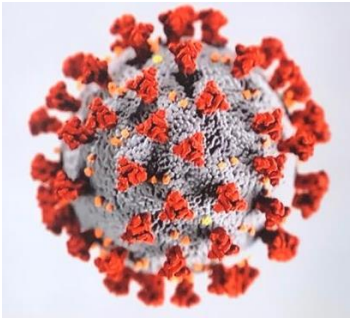
Na linha de frente, com a mão na barriga

Não há comprovação de que o coronavírus pode ser transmitido durante a gestação, mas a inflamação e a infecção da mãe podem afetar o feto, com consequências ainda incertas. Na linha de frente do tratamento de gestantes desde o início da pandemia, a infectologista Raíssa Perlingeiro diz que parte do agravamento se deve à demora no diagnóstico e em conseguir vaga para tratamento adequado.

Perlingeiro, de 32 anos,

Risk to the Mother

Epidemiology



- 2-4% of the infected population have died

- Very contagious- transmitted via respiratory droplets, though it can be airborne in some circumstances.
  - 1 person can infect on average 2.0-2.5 individuals at a time. With the Delta strain estimates are 8 to 9 people infected by 1 individual.
  - Reproduction number of the virus can be decrease if appropriate measures are taken:
    - Masking, cancellation of social gatherings, stay-at-home policies, and universal symptom screenings.

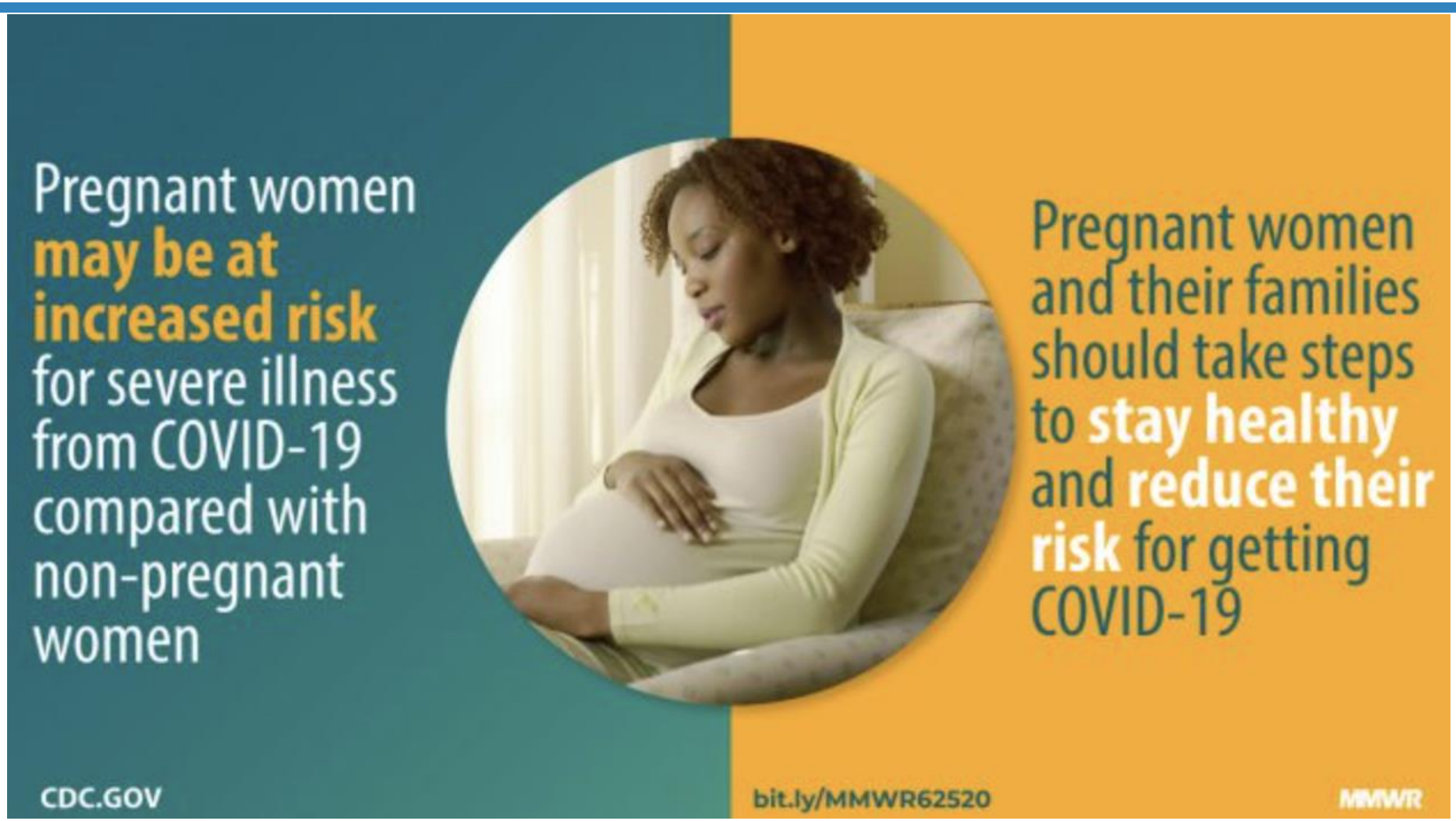
- Pregnant women and neonates are **2 populations at risk** for serious complications related to COVID19
  - Pregnancy allows for physiologic changes
  - Neonates have immature immune systems

Clinical Presentation, Diagnosis, Outcomes in Pregnant Women

- COVID19 may exacerbate comorbidities common to pregnancy which can lead to preterm birth

- Pregnant women infected with COVID19 need to be closely monitored

- COVID19 infection is not an indication for delivery.


Pregnant women may be at increased risk for severe illness from COVID-19 compared with non-pregnant women
Pregnant women and their families should take steps to stay healthy and reduce their risk for getting COVID-19
CDC.GOV
bit.ly/MMWR62520
MMWR

Epidemiology and High-Risk Groups

Data collected from standardized case reporting forms and via the voluntary National Notifiable Disease Surveillance System

From January 22 – October 3, pregnancy data was available for 35.5% of all cases in women aged 15 – 44 (reproductive age)

Data available for 409,462 women in the US with PCR-confirmed SARS-CoV-2 infection

23,434 were pregnant and 30% Latina

Morbidity and Mortality Weekly Report

Characteristics and Maternal and Birth Outcomes of Hospitalized Pregnant Women with Laboratory-Confirmed COVID-19 — COVID-NET, 13 States, March 1–August 22, 2020

Morbidity and Mortality Weekly Report

Birth and Infant Outcomes Following Laboratory-Confirmed SARS-CoV-2 Infection in Pregnancy — SET-NET, 16 Jurisdictions, March 29–October 14, 2020

Morbidity and Mortality Weekly Report

Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status — United States, January 22–October 3, 2020

Multivariate analysis by pregnancy status:

- ICU admission: adjusted RR 3.0 (2.6 – 3.4)
- Invasive ventilation: adjusted RR 2.9 (2.2 – 3.8)
- ECMO: adjusted RR 2.4 (1.4 – 5.0)
- Death: adjusted RR 1.7 (1.2 – 2.4)

Zambrano et al.

JAMA Pediatrics | Original Investigation

Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection

The INTERCOVID Multinational Cohort Study

JAMA Pediatrics Published online April 22, 2021

Villar et al.

- 706 pregnant women with COVID-19 diagnosis and 1424 without this diagnosis.
- Women with COVID-19 at higher risk for:
  - Preeclampsia- eclampsia RR 1.76 95% CI 1.27 – 2.43
  - Severe infections RR 3.38 95%CI 1.63 – 7.01
  - ICU admission RR 5.04 95% CI 3.13 - 8.10
  - Pre-term birth RR 1.59 95%CI 1.30 – 1.94
  - Perinatal mortality/morbidity RR 2.14 95%CI 1.66 – 2.75

CONCLUSIONS AND RELEVANCE In this multinational cohort study, COVID-19 in pregnancy was associated with consistent and substantial increases in severe maternal morbidity and mortality and neonatal complications when pregnant women with and without COVID-19 diagnosis were compared. The findings should alert pregnant individuals and clinicians to implement strictly all the recommended COVID-19 preventive measures.

Clinical Presentation of Coronavirus Disease 2019 (COVID-19) in Pregnant and Recently Pregnant People

Yalda Afshar, MD, PhD, Stephanie L. Gaw, MD, PhD, Valerie J. Flaherman, MD, Brittany D. Chambers, PhD, MPH, Deborah Krakow, MD, Vincenzo Berghella, MD, Alireza A. Shamshirsaz, MD, Adeline A. Boatin, MD, MPH, Grace Aldrovandi, MD, Andrea Greiner, MD, Laura Riley, MD, W. John Boscardin, PhD, Denise J. Jamieson, MD, and Vanessa L. Jacoby, MD, MAS, on behalf of the Pregnancy CoRonavIrus Outcomes RegIsTrY (PRIORITY) Study

Symptom	n (%)	95% CI (%)
1st symptom (check only 1)		
Cough	118 (20)	17–23
Sore throat	95 (16)	13–19
Body aches	72 (12)	10–15
Fever	69 (12)	9–14
Headache	45 (8)	6–10

scientific reports

Scientific Reports | (2021) 11:13898 | https://doi.org/10.1038/s41598-021-92357-y

nature portfolio

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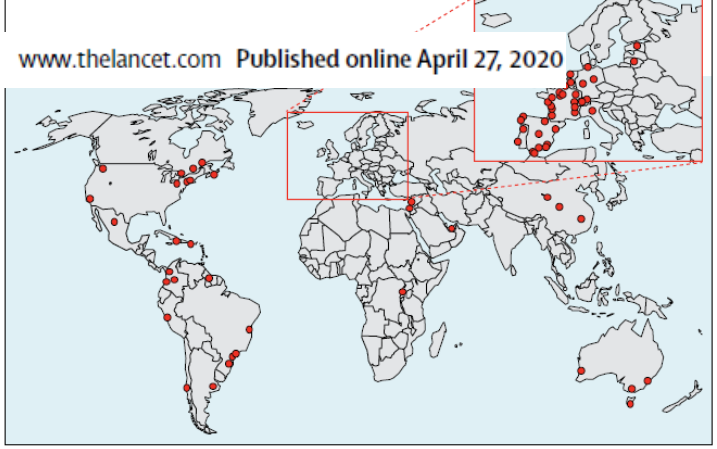
Maternal outcomes and risk factors for COVID-19 severity among pregnant women

Manon Vouga[1,82], Guillaume Favre[1,82], Oscar Martinez-Perez[2,82], Leo Pomar[1,82], Laura Forcen Acebal[3], Alejandra Abascal-Saiz[4], Maria Rosa Vila Hernandez[5], Najeh Hcini[6], Véronique Lambert[6], Gabriel Carles[6], Joanna Sichitiu[1,7], Laurent Salomon[7], Julien Stirnemann[7], Yves Ville[7], Begoña Martinez de Tejada[8], Anna Goncé[9], Ameth Hawkins-Villarreal[9], Karen Castillo[9], Eduard Gratacos Solsona[9], Lucas Trigo[10], Brian Cleary[11], Michael Geary[12], Helena Bartels[12], Feras Al-Kharouf[12], Fergal Malone[12], Mary Higgins[13], Niamh Keating[14], Susan Knowles[15], Christophe Poncelet[16], Carolina Carvalho Ribeiro-do-Valle[17], Fernanda Surita[17], Amanda Dantas-Silva[17], Carolina Borrelli[17], Adriana Gomes Luz[17], Javiera Fuenzalida[18], Jorge Carvajal[18], Manuel Guerra Canales[19], Olivia Hernandez[20], Olga Grechukhina[21], Albert I. Ko[22], Uma Reddy[22], Rita Figueiredo[23], Marina Moucho[23], Pedro Viana Pinto[23], Carmen De Luca[24], Marco De Santis[24], Diogo Ayres de Campos[25], Inês Martins[25], Charles Garabedian[26], Damien Subtil[26], Betania Bohrer[27], Maria Lucia Da Rocha Oppermann[28], Maria Celeste Osorio Wender[28], Lavinia Schuler-Faccini[29], Maria Teresa Vieira Sanseverino[29], Camila Giugliani[30], Luciana Friedrich[27], Mariana Horn Scherer[29], Nicolas Mottet[31], Guillaume Ducarme[32], Helene Pelerin[33], Chloe Moreau[33], Bénédicte Breton[34], Thibaud Quibel[35], Patrick Rozenberg[35], Eric Giannoni[1], Cristina Granado[36], Cécile Monod[36], Doris Mueller[36], Irene Hoesli[36], Dirk Bassler[37], Sandra Heldstab[38], Nicole Ochsenbein Kölble[39], Loïc Sentilhes[40], Melissa Charvet[40], Jan Deprest[41], Jute Richter[41], Lennart Van der Veeken[42], Béatrice Eggel-Hort[43], Gaetan Plantefeve[44], Mohamed Derouich[45], Albaro José Nieto Calvache[46], Maria Camila Lopez-Giron[46], Juan Manuel Burgos-Luna[46], Maria Fernanda Escobar-Vidarte[46], Kurt Hecher[47], Ann-Christin Tallarek[47], Eran Hadar[48], Karina Krajden Haratz[49], Uri Amikam[50], Gustavo Malinger[50], Ron Maymon[51], Yariv Yogev[49], Leonhard Schäffer[52], Arnaud Toussaint[53], Marie-Claude Rossier[54], Renato Augusto Moreira De Sa[55], Claudia Grawe[56], Karoline Aebi-Popp[57], Anda-Petronela Radan[58], Luigi Raio[58], Daniel Surbek[58], Paul Böckenhoff[59], Brigitte Strizek[59], Martin Kaufmann[60], Andrea Bloch[61], Michel Boulvain[62], Silke Johann[63], Sandra Andrea Heldstab[64], Monya Todesco Bernasconi[64], Gaston Grant[65], Anis Feki[65], Anne-Claude Muller Brochut[66], Marylene Giral[67], Lucie Sedille[67], Andrea Papadia[68], Romina Capoccia Brugger[69], Brigitte Weber[70], Tina Fischer[71], Christian Kahlert[72], Karin Nielsen Saines[73], Mary Cambou[74], Panagiotis Kanellos[75], Xiang Chen[76], Mingzhu Yin[77], Annina Haessig[78], Sandrine Ackermann[1], David Baud[1,81,82]✉ & Alice Panchaud[79,80,82]

Pregnant women may be at higher risk of severe complications associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which may lead to obstetrical complications. We performed a case control study comparing pregnant women with severe coronavirus disease 19 (cases) to pregnant women with a milder form (controls) enrolled in the COVI-Preg international registry cohort between March 24 and July 26, 2020. Risk factors for severity, obstetrical and



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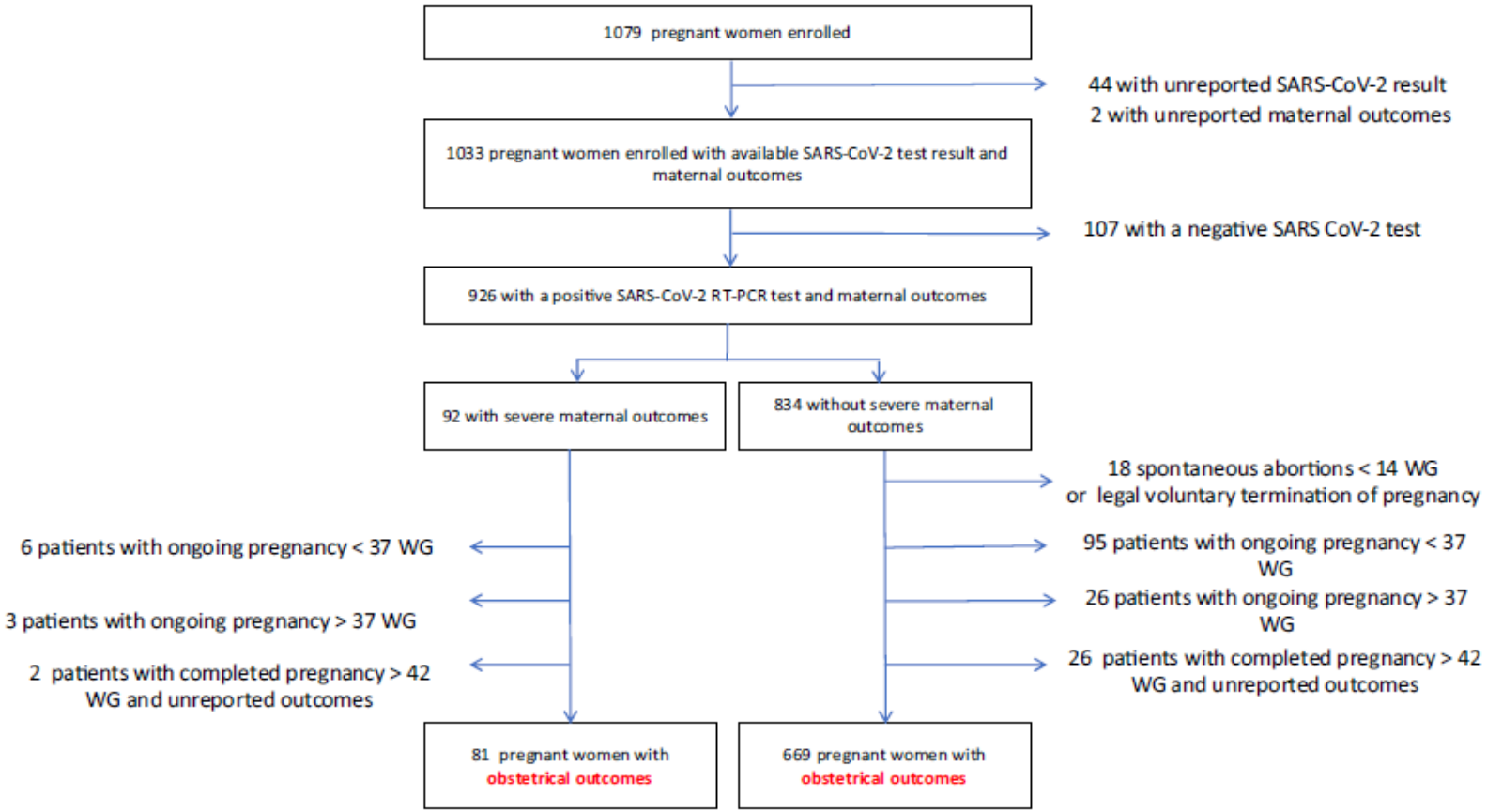
COVI-PREG

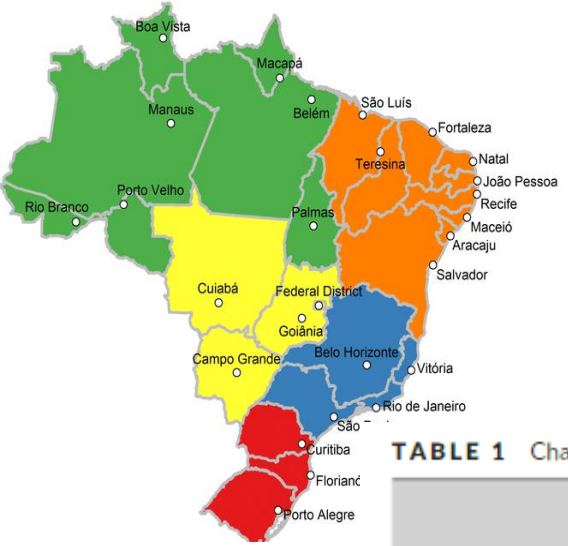
International COVID-19 and Pregnancy Registry

An international registry for emergent pathogens and pregnancy

www.nature.com/scientificreports/



Obstetrical/Neonatal outcomes	Severe maternal outcomes n=81		No / Mild adverse maternal outcomes n=671	
	n (%)	95% CI	n (%)	95% CI
Pregnancy outcomes > 14 WG				
Livebirth	**75 (92.6)**	84.6-97.2	**658 (98.1)**	96.7-99.0
Fetal loss > 14 WG	6 (7.4)	2.8-15.4	13 (19.4)	10.4-32.9
Termination of pregnancy	1 (1.4)	0.0-6.7	2 (0.3)	0.0-1.1
Obstetrical outcomes among live births	75		658	
GA at delivery (Weeks gestation)				
Median GA (IQR)	**37 (34-38)**		**39 (38-40)**	
Unknown GA at delivery	6 (8.0)	3.0-16.6	17 (25.8)	15.1-41.0
Obstetrical management				
All vaginal deliveries	22 (29.3)	19.4-41.0	447 (67.9)	64.2-71.5
Vaginal delivery after spontaneous onset of labour	10 (13.3)	6.6-23.2	280 (42.6)	38.7-46.4
Vaginal delivery after induction of labour	12 (16.0)	8.6-26.3	167 (25.4)	22.1-28.9
Caesarean sections – no (%)	**53 (70.7)**	59.0-80.6	**203 (30.9)**	27.3-34.5
Elective caesarean sections – no (%)	21 (28.0)	18.2-39.6	85 (12.9)	10.5-15.7
Emergency pre-labor caesarean sections – no (%)	12 (16.0)	8.6-26.3	16 (2.4)	1.4-39.2
In labour caesarean sections after induction	12 (16.0)	8.6-26.3	52 (7.9)	6.0-10.2
In labour caesarean sections after spontaneous	8 (10.7)	4.7-19.9	50 (7.6)	5.7-9.9
Unknown	0 (0.0)	0-4.8	8 (1.2)	0.5-2.4
Preterm birth among pregnancy with exposure < 37 WG	51		217	
All preterm birth < 37 WG – no (%)	**32 (62.7)**	48.1-75.9	**78 (35.9)**	29.6-42.7
Iatrogenic birth among preterm birth – no (%)	**26 (81.3)**	63.6-92.8	**49 (62.8)**	51.1-73.5
Unknown – no (%)	0 (0.0)	0.0-10.9	1 (1.3)	0.0-6.9
Unknown GA at delivery	0 (0.0)	0.0-7.0	3 (1.4)	0.3-4.0
Preterm birth among pregnancy with exposure < 34WG	27		118	
All preterm birth < 34 WG – no (%)	**14 (51.9)**	31.9-71.3	**24 (20.3)**	13.5-28.7
Iatrogenic birth among preterm birth– no (%)	12 (85.7)	57.2-98.2	14 (58.3)	36.6-77.9
Unknown – no (%)	0 (0.0)	0.0-23.2	0 (0.0)	0.0-14.2
Unknown GA at delivery	0 (0.0)	0.0-12.8	2 (1.7)	0.2-6.0



COVID-19 in Brazil: "So what?"

Editorial

www.thelancet.com Vol 395 May 9, 202

The number of maternal deaths in 2 months due to COVID-19 in Brazil was 10% of the annual maternal death rate in the country

Obstetrics

The tragedy of COVID-19 in Brazil: 124 maternal deaths and counting

29 July 2020

Maira L. S. Takemoto[1] | Mariane de O. Menezes[1,*] | Carla B. Andreucci[2] | Marcos Nakamura-Pereira[3] | Melania M.R. Amorim[4] | Leila Katz[4] | Roxana Knobel[5]

International Journal of Gynecology & Obstetrics FIGO

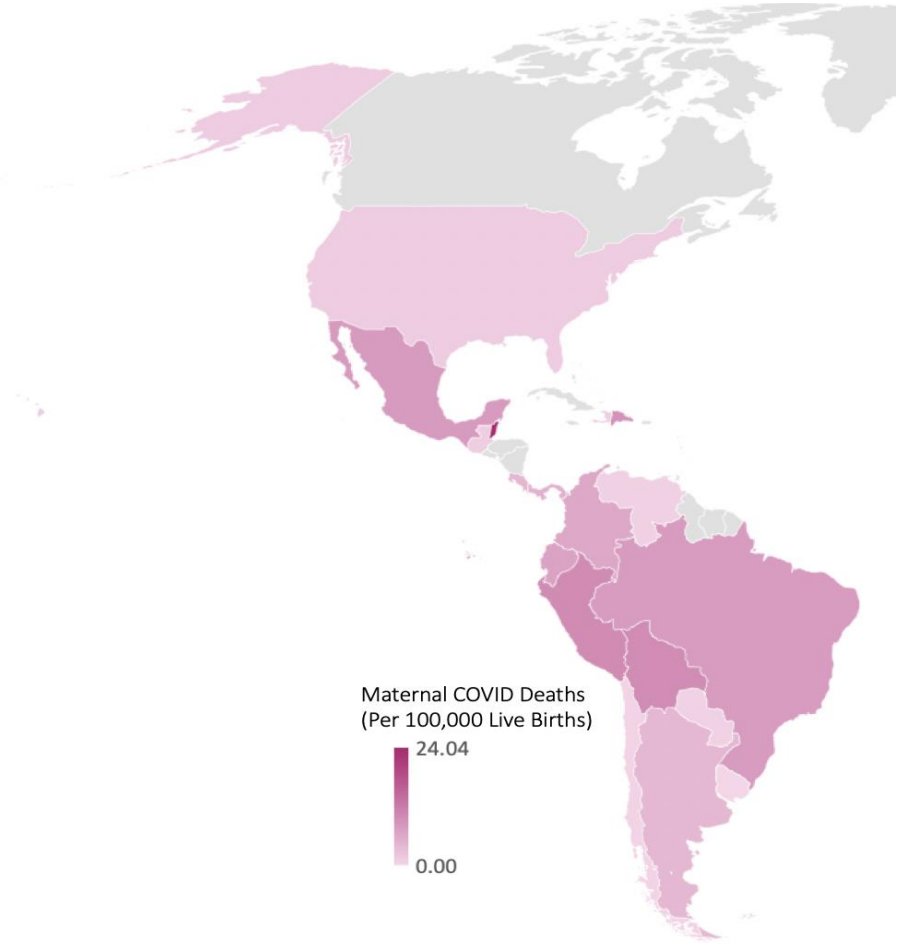
TABLE 1 Characteristics of Brazilian COVID-19 obstetric cases according to the outcome (recovery or death) (n = 978).

	Recovery		Death		p-value[b]
	n	%	n	%	
Total	854	87.3	124	12.7	–
Age—mean (SD)	29.5 (6.9)		31.5 (7.5)		–
Timing in relation to birth (at notification date)					
Pregnancy	680	90.2	74	9.8	<0.001
Postpartum	174	77.7	50	22.3	
Race					
White	212	90.2	23	9.8	0.116
Non-white	440	86.1	71	13.9	
Missing/Unknown	202	87.1	30	12.9	
Region					
North	116	84.7	21	15.3	0.032
Northeast	245	83.9	47	16.1	
Midwest	32	97.0	1	3.0	
Southeast	426	88.6	55	11.4	
South	35	100.0	0	0.0	
Prevalence of selected comorbidities					
Cardiovascular disease					
Yes	41	6.7	13	16.3	0.002
No	573	93.3	67	83.7	
Missing/Unknown (%)[a]	28.1		35.5		

TABLE 1 Characteristics of Brazilian COVID-19 obstetric cases according to the outcome (recovery or death) (n = 978).

	Recovery		Death		*p*-value[b]
	n	%	n	%	
Prevalence of selected comorbidities					
Cardiovascular disease					
Yes	41	6.7	13	16.3	0.002
No	573	93.3	67	83.7	
Missing/Unknown (%)[a]	28.1		35.5		
Diabetes (gestational or previous)					
Yes	67	20.8	22	33.8	0.023
No	255	79.2	43	66.2	
Missing/Unknown (%)[a]	62.3		47.6		
Obesity					
Yes	31	10.3	13	21.3	0.016
No	270	89.7	48	78.7	
Missing/Unknown (%)[a]	64.8		50.8		
Asthma					
Yes	18	5.9	5	9.3	0.360
No	285	94.1	49	90.7	
Missing/Unknown (%)[a]	64.5		56.5		
Frequency of supportive care					
ICU admission					
Yes	134	17.5	73	72.3	<0.001
No	630	82.5	28	27.7	
Missing/Unknown (%)[a]	10.5		18.5		
Respiratory support					
Invasive	32	4.4	66	64.0	<0.001
Non-invasive	197	27.1	22	21.4	
None	497	68.5	15	14.6	
Missing/Unknown[a]	15.0		16.9		

Epidemiology and High-Risk Groups



Virus deaths. Health inequality

Brazil reels from expectant mother tragedies

More infectious Covid variant and lack of adequate access to already stretched care take toll

MICHAEL POOLER AND CAROLINA PULICE
SÃO PAULO

Following two difficult pregnancies, it seemed it might be third time lucky for Vanessa de Oliveira Silverio. But in her 34th week of gestation, she began to feel unwell and developed a cough. A coronavirus test returned positive, and breathing became difficult.

"She said that she was afraid to die, of having a caesarean [birth] and the baby not surviving," said Douglas Silverio, her husband. Yet it was Vanessa, 33, who died during an emergency operation to deliver her baby in March.

Her death is one of hundreds of such tragedies to strike families in Brazil, leading to a mortality rate among new or soon-to-be mothers that has alarmed doctors and public health experts.

In total, more than 1,600 pregnant or post-partum women have succumbed since the start of the pandemic, said the Brazilian Obstetric Observatory.

"Before the pandemic began, we already had a maternal death ratio of 55.3 for every 100,000 babies born alive, which is considered extremely high," said Rossana Pulcinelli Vieira Francisco, a professor at the University of São Paulo's department of obstetrics and gynaecology, who leads the research.

"It is not possible to say for sure that Brazil is where pregnant and post-partum women die the most by Covid, as there are not many population studies on death by Covid in these women," added Francisco. "But we can certainly say the numbers here are very high."

Overall, maternal deaths in Brazil averaged 10 each week during 2020, according to the observatory. This year, that has quadrupled to above 40, as mortality in the population doubled.

Many explanations proposed echo those for the country's wider virus disaster, which has already claimed more than half a million lives. The death toll is the second-highest in absolute terms after the US, and seventh on a per capita basis, according to FT analysis. In the case of mothers to be, experts blame a strained healthcare system, inadequate and unequal provision of services, a lack of confidence in treating such patients and a more contagious virus variant.

Jab reassurance: a pregnant woman watches a nurse before receiving the BioNTech/Pfizer vaccine in São Paulo
Carla Carniel/Reuters

Dr Lilian Cristina Moreira, a paediatrician for Rio de Janeiro, said research showed about half those pregnant in certain states who died from Covid did not have access to an intensive care unit or intubation: "In every 100 pregnant women diagnosed, 12 die. In the population, the fatality rate is 2.8 per cent."

Pregnancy suppresses a woman's immune system, while pressure on abdominal organs and the diaphragm can restrict breathing. Along with greater inflammation, the body is under stress.

Although congenital infection with Covid-19 is thought to be rare, asymptomatic mothers can pass the virus on to newborns. More than 600 children in Brazil under a year old have died from the illness during the pandemic, according to government data.

Experts said they did not believe the Gamma, or P.1, strain of Sars-Cov-2, which originated in the Amazon, was in itself more harmful to pregnant women. But its transmissibility, about twice that of earlier variants, has led to a surge of infections that has overwhelmed hospitals. The closure of many health services during the outbreak also affected prenatal classes and family planning services, Moreira added.

"Pregnant women were more vulnerable due to access to the health system and socio-economic status," she said. "Black and poor women died more."

Even where full facilities and equipment were available, medical staff were often unprepared to deal with severely ill pregnant women, said Marcelo Otsuka, a doctor and co-ordinator at the Brazilian Society of Infectology.

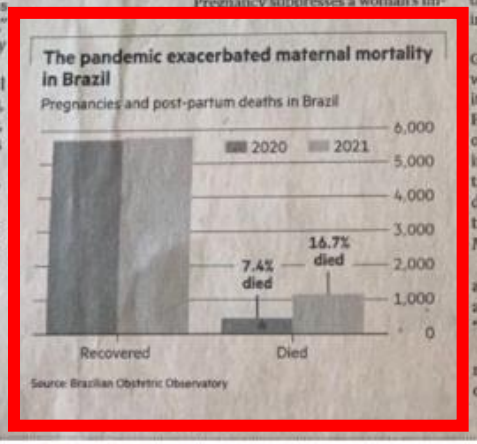
> 'Pregnant women were more vulnerable . . . Black and poor women died more'

Treatment involves finely balanced clinical decisions. Douglas Silverio said: "One of the doctors told me they didn't know why the caesarean didn't happen earlier. If they had, would it have been more effective?"

Fabiana Alves Sousa, from Ceará state in the poorer north-east, had an emergency caesarean at almost 30 weeks after contracting coronavirus. Her son is "full of health", but she said: "There were several mothers with Covid. And many did not survive childbirth."

Many health professionals cite a failure of public health policy as a factor. Critics accuse the government of a lax, even negligent, attitude to the pandemic that has contributed to its spread.

Fears are rising about the Delta variant, too. About 14 per cent of Brazil's population of 212m is fully immunised and health minister Marcelo Queiroga announced last week the resumption of jabs for some expectant and new mothers. "More than 2.5m women are expected to benefit," he tweeted.



FINANCIAL TIMES

INTERNATIONAL

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

COVID-19 and pregnancy

Based on what we know at this time, pregnant people are at an increased risk for severe illness from COVID-19 compared to non-pregnant people. Additionally, pregnant people with COVID-19 might be at increased risk for other adverse outcomes, such as preterm birth.

Treatment

Remdesivir: recommended for pregnant women if they meet criteria otherwise, although excluded from trials

Dexamethasone: recommended for pregnant women who meet criteria (require supplemental oxygen or ventilatory support)

Convalescent Plasma: pregnant women were eligible in 2 clinical trials, good safety data

Monoclonal Antibodies: placental transfer may be expected

Vaccine

Pregnant women were excluded from the major vaccine trials

(Pfizer, Moderna, AstraZeneca, Johnson & Johnson, Novavax)

U.S.News & World Report

CDC Recommends Pregnant Women Get Coronavirus Vaccine

Chelsea Cirruzzo · 1 hr ago

The Centers for Disease Control and Prevention recommends that pregnant women get vaccinated against COVID-19, the agency's director said Friday during a White House coronavirus briefing.

Previously, the CDC followed the guidance laid out by leading maternal health organizations that said pregnant women should be offered vaccines if they want one and providers should not withhold vaccines from them but should discuss available data. The CDC has said that evidence shows pregnant women are at higher risk of severe COVID-19 infection.

COVID-19 vaccines and neglected pregnancy

*Pradip Dashraath, Karin Nielsen-Saines, Shabir A Madhi, *David Baud*

www.thelancet.com **Published online August 27, 2020**

The development of an effective COVID-19 vaccine is a global health priority. Pregnant women, who are at increased risk of adverse outcomes from COVID-19, would be additionally harmed if they were unable to access evidence-based chemoprophylaxis from vaccine trials. WHO's global commitment to fair access to COVID-19 vaccines should, therefore, include pregnant women. Accordingly, we advocate that pregnant women should be included in the phase 3 trial protocols of adenovirus-vectored vaccines and also protein-based vaccines (eg, NVX-

Can SARS-Cov-2 be transmitted from the mother to the newborn?

What are the short and long term neonatal outcomes?

IS THERE TRANSMISSION OF SARS COV-2 DURING PREGNANCY?

- It is still unclear if the virus can be transmitted during pregnancy from mother to child.
- There are several reports of newborns who were found to be positive shortly after birth, but unclear if they were infected right after being born or before.
- Infants who contract the virus tend to do well and do not develop pneumonia.
- They do tend to shed the virus for a number of weeks.
- The virus has been identified in the placenta of women who had miscarriages because of complications of COVID-19.

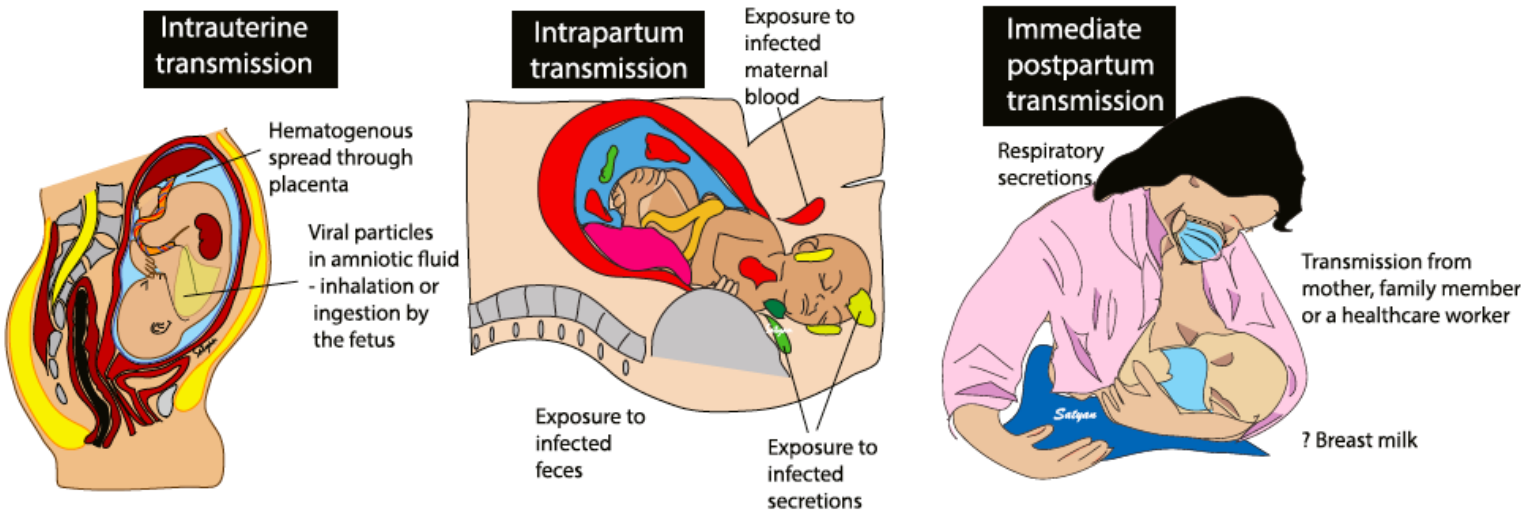
THE LANCET

Detection of SARS-CoV-2 in human breastmilk

Rüdiger Groß • Carina Conzelmann • Janis A Müller • Steffen Stenger • Karin Steinhart • Frank Kirchhoff • et al.

Published: May 21, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)31181-8

Maternal Transmission to the Newborn



Transmission rate

- Intrauterine transmission while low, is possible
- 1-3% of births to U.S mothers with active infection

(AAP National registry for perinatal COVID19 infection)

Horizontal transmission>>>> Vertical Transmission

Sankaran et al. Neoreviews 202

Transplacental Transmission of SARS CoV-2 appears to be rare

JAMA Network Open

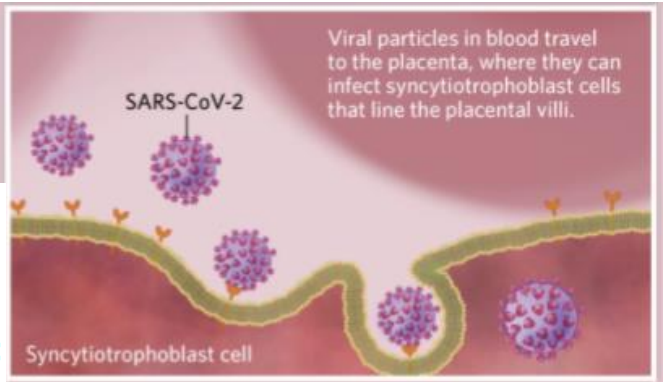
December 22, 2020

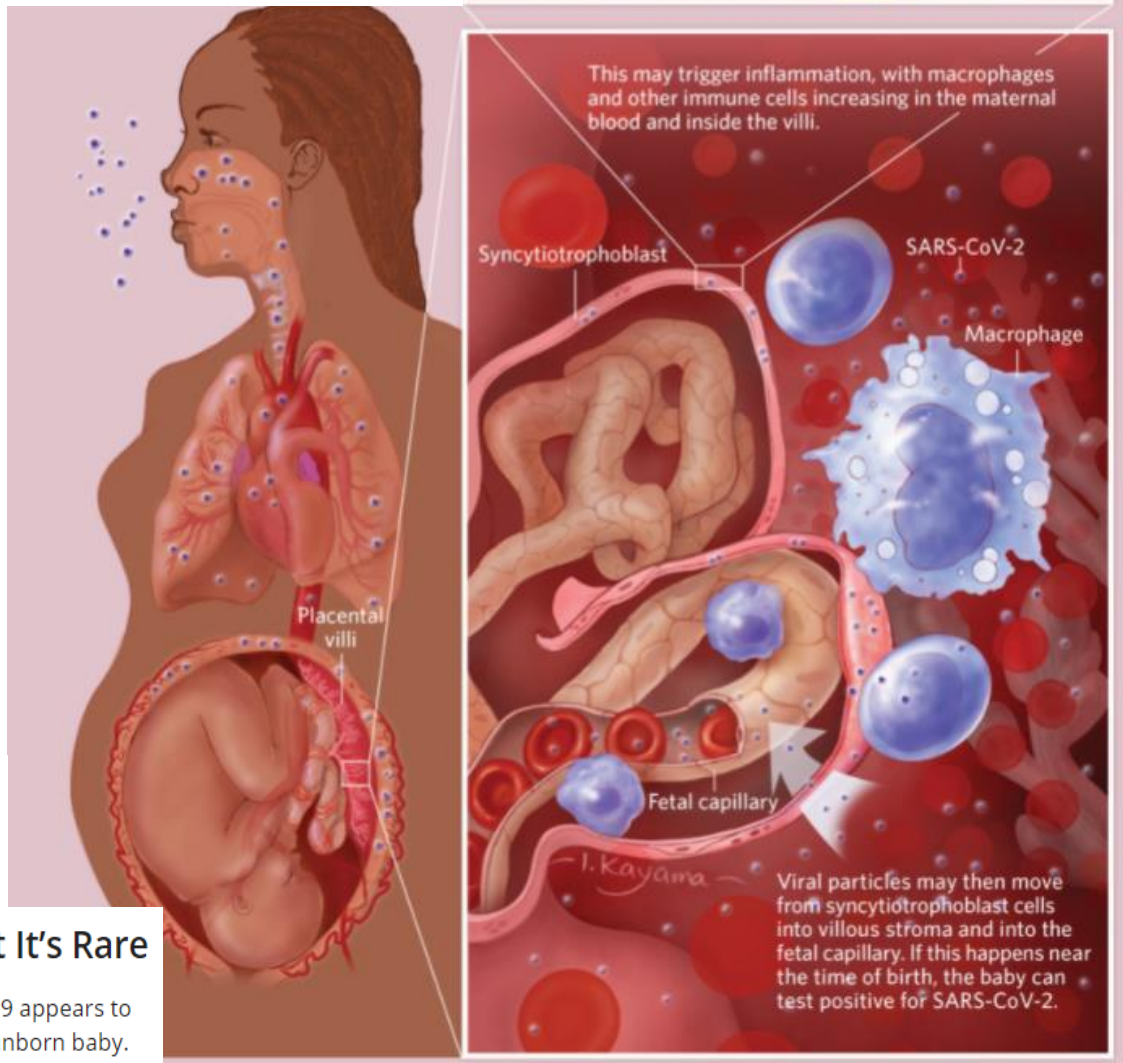
Assessment of Maternal and Neonatal SARS-CoV-2 Viral Load, Transplacental Antibody Transfer, and Placental Pathology in Pregnancies During the COVID-19 Pandemic

Edlow et al.

In 66 placentas tested in women with confirmed COVID-19, SARS CoV-2 was not present in any.

Studies have suggested in utero transmission rates vary from 0 to 4.3%





TheScientist
EXPLORING LIFE, INSPIRING INNOVATION

Ashley Yeager
Jan 1, 2021

Human Fetuses Can Contract SARS-CoV-2, but It's Rare

Compared with Zika and cytomegalovirus, the virus that causes COVID-19 appears to have a harder time penetrating the placenta and moving to a woman's unborn baby.

TheScientist
EXPLORING LIFE. INSPIRING INNOVATION

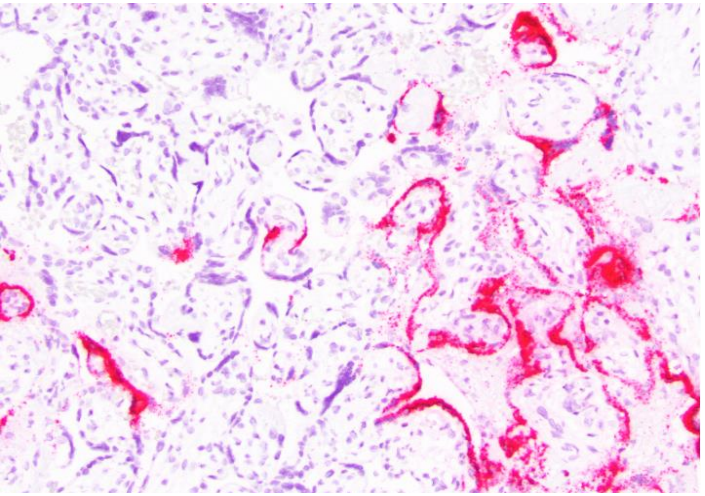
Doctors Investigate Several Stillbirths Among Moms with COVID-19

Anthony King
Apr 23, 2021

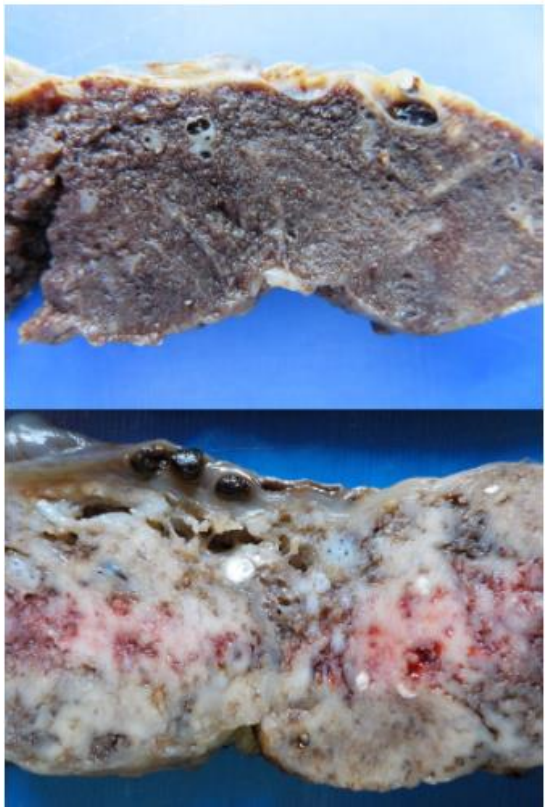
After a handful of cases in Ireland, clinicians there are warning that the virus might infect the placenta in very rare instances and cause fetal distress, but a rise in stillbirths has not been seen in epidemiological studies.

Estimates are quite hard at the moment, in terms of working out the true risk, but we think we are seeing one in one hundred to one in two hundred cases [of stillbirth] in women with [COVID-19].

—Keelin O'Donoghue, Cork University Maternal Hospital



Placental cells infected with SARS CoV-2



Cases of necrotic placentas reported from 6 cases in Ireland where women experienced miscarriages.

Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study

Nan Yu, Wei Li *, Qingling Kang, Zhi Xiong, Shaoshuai Wang, Xingguang Lin, Yanyan Liu, Juan Xiao, Haiyi Liu, Dongrui Deng, Suhua Chen, Wanjiang Zeng, Ling Feng, Jianli Wu*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Pregnancy outcome	Discharged	Discharged	Discharged	Discharged	Discharged	Discharged	Discharged
Neonatal outcome	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Birthweight, g	3250	3350	3200	3000	3500	3300	3250
Apgar score (1 min)	8–9	8–9	8–9	8–9	8–9	8–9	8–9
Apgar score (5 min)	9–10	9–10	9–10	9–10	9–10	9–10	9–10
Admission to neonatology department	Yes	No	Yes	No	No	No	Yes
Nucleic acid test of SARS-CoV-2	Positive (36 h)	Not tested	Negative	Not tested	Not tested	Not tested	Negative
Days of follow-up	40	28	28	28	28	28	28
Neonatal complications	No	No	No	No	No	No	No

None of the women were admitted to intensive care. Normal=no respiratory symptoms or fever or neonatal complications, such as neonatal respiratory distress syndrome, feeding abnormalities, or abnormal growth or development. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Table 2: **Maternal and neonatal outcomes of seven patients with COVID-19**

Shifting perception of infant outcomes

JAMA | Original Investigation

Association of Maternal SARS-CoV-2 Infection in Pregnancy With Neonatal Outcomes

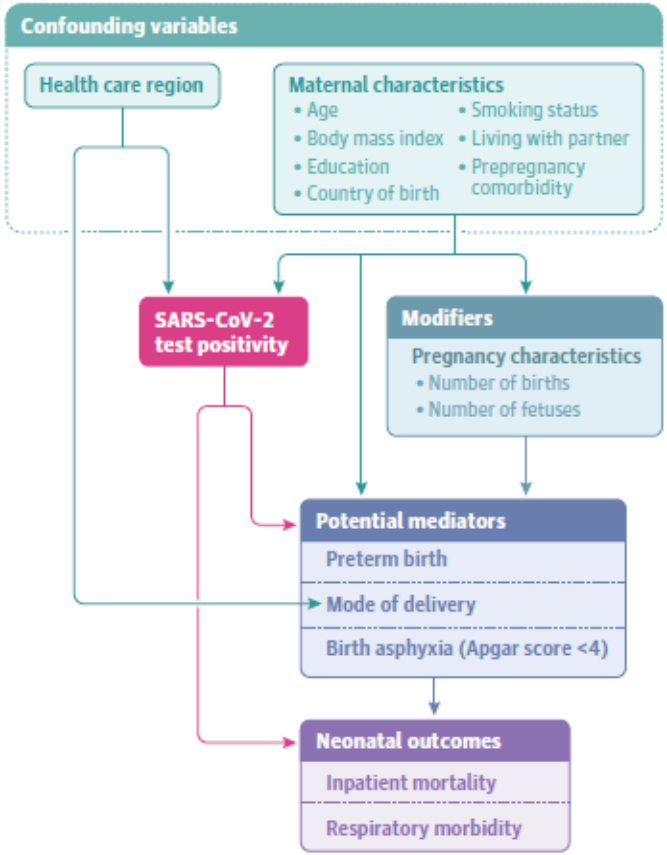
JAMA Published online April 29, 2021

Mikael Norman, MD; Lars Navér, MD; Jonas Söderling, PhD; Mia Ahlberg, PhD; Helena Hervius Askling, MD; Bernice Aronsson, MD; Emma Byström, MSc; Jerker Jonsson, MD; Verena Sengpiel, MD; Jonas F. Ludvigsson, MD; Stellan Håkansson, MD; Olof Stephansson, MD

Understanding Risk for Newborns Born to SARS-CoV-2–Positive Mothers

EDITORIAL

Dani Dumitriu, MD, PhD; Cynthia Gyamfi-Bannerman, MD, MS



- 88,159 infants in Sweden from 3/20 – 3/21
- 2323 (1.6%) to SARS CoV-2 + mothers
- Prematurity rate:
  + mothers: 8.8%, neg mothers: 5.5%

- Maternal positivity associated with:
  - Infant admission: OR 1.5 (1.26-1.70)
  - Infant resp distress: OR 2.4 (1.50-3.84)
  - Any resp disorder: OR 1.4 (1.07-1.90)
  - Hyperbillirubinemia: OR 1.47 (1.13-1.90)

Infant mortality not different between groups.

- 21 infants (1%)+ for SARS CoV-2 in the neonatal period.

UCLA Health

Neonates with SARS-CoV-2 Infection

- Early onset neonatal COVID19 (between 2-7 days)
  - Mainly **asymptomatic** but can have mild, moderate or severe symptoms
  - Labs- leukocytosis, lymphopenia, thrombocytopenia and elevated inflammatory markers
  - Tx: supportive
- Late onset neonatal COVID19 (>7 days)
  - Mainly **symptomatic**- fever, coryza, respiratory symptoms, apnea, poor feeding, vomiting and lethargy.
  - Many have negative PCR test results in the hospital after birth
  - CXR- ground glass changes
  - Labs: leukocytosis, thrombocytopenia, elevated lactate, elevated CRP, and lymphopenia. DIC may also occur.

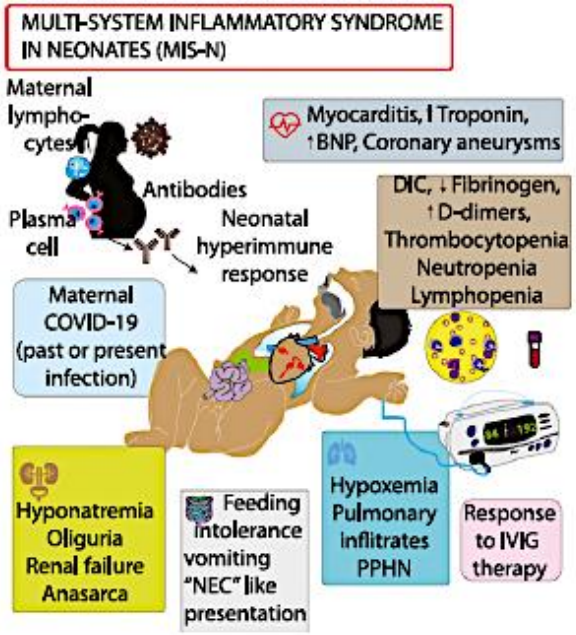
Multisystem Inflammatory Syndrome in Children (MIS-C)

- Characterized by fever, elevated inflammatory markers, and high levels of pro- and anti-inflammatory cytokines.

- Children present with symptoms related to:
  - CV system- Shock, LV dysfunction, elevated cardiac enzymes, coronary artery abnormalities
  - GI system- nausea, vomiting, diarrhea
  - Mucocutaneous symptoms resembling Kawasaki disease

- Can Neonates have MIS-C?
  - Rare but possible

Neonatal MIS-C



Neonatal Multisystem Inflammatory Syndrome (MIS-N) Associated with Prenatal Maternal SARS-CoV-2: A Case Series

Ravindra Pawar,[1,*] Vijay Gavade,[2] Nivedita Patil,[1] Vijay Mali,[1,3] Amol Girwalkar,[4,5] Vyankatesh Tarkasband,[5] Sanjog Loya,[2] Amit Chavan,[2] Narendra Nanivadekar,[6] Rahul Shinde,[7] Uday Patil,[2] and Satyan Lakshminrusimha[8]

Multisystem Inflammatory Syndrome in Children Associated With Severe Acute Respiratory Syndrome Coronavirus-2 in an 8-Week-Old Infant

Esther Orlanski-Meyer [1], Dotan Yogev [1 2], Adi Auerbach [3], Orli Megged [2 4], Daniel Glikman [5],

Maternal SARS-CoV-2 Infection Associated to Systemic Inflammatory Response and Pericardial Effusion in the Newborn: A Case Report

Andressa R O Lima [1], Cynthia C Cardoso [2], Priscilla R B Bentim [1], Carolina M Voloch [2],

MULTISYSTEM INFLAMMATORY SYNDROME IN A CHILD ASSOCIATED WITH CORONAVIRUS DISEASE 19 IN THE BRAZILIAN AMAZON: FATAL OUTCOME IN AN INFANT

Emmerson Carlos Franco de Farias, [a,*] Maria Cleonice Aguiar Justino, [b] and Mary Lucy Ferraz Maia Fiuza de Mello [a]

COVID-19-Related Potential Multisystem Inflammatory Syndrome in Childhood in a Neonate Presenting as Persistent Pulmonary Hypertension of the Newborn

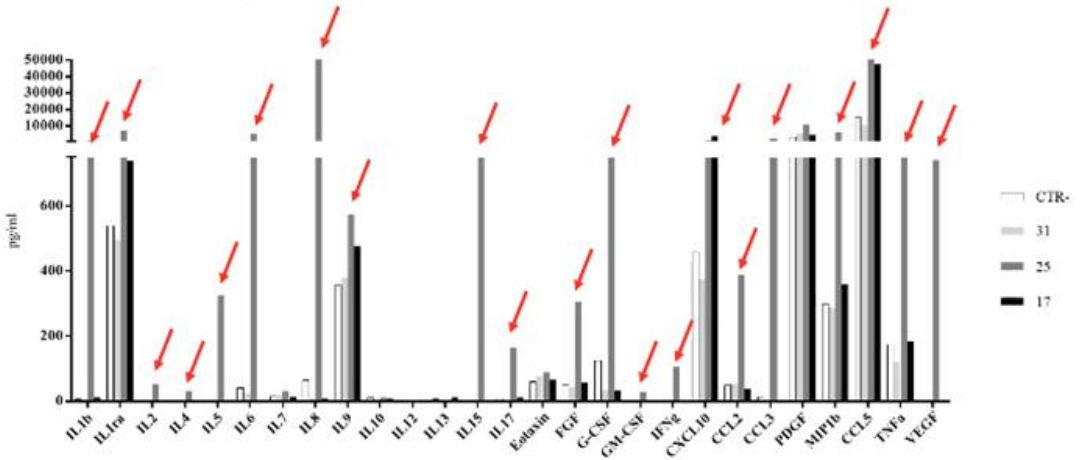
Transplacental transmission of SARS-CoV-2 infection

nature COMMUNICATIONS

July 2020

Alexandre J. Vivanti[1,8], Christelle Vauloup-Fellous[2,8], Sophie Prevot[3], Veronique Zupan[4], Cecile Suffee[5], Jeremy Do Cao[6], Alexandra Benachi[1] & Daniele De Luca[4,7]✉

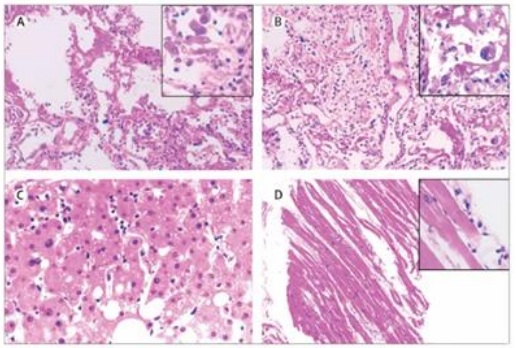
INFLAMMATORY PROFILE: CYTOKINES/CHEMOKINES in MATERNAL PLASMA



Cytokine release in plasma is increased in SARS-CoV-2 positive patients

Rare cases of virus identified in cord blood by PCR

- Cytokine release syndrome (CRS)
  - High level of immune activation + inflammatory cytokines
  - Hyaline membrane & lymphocytes in lungs on autopsy of COVID-19 patient



Neonatal Management

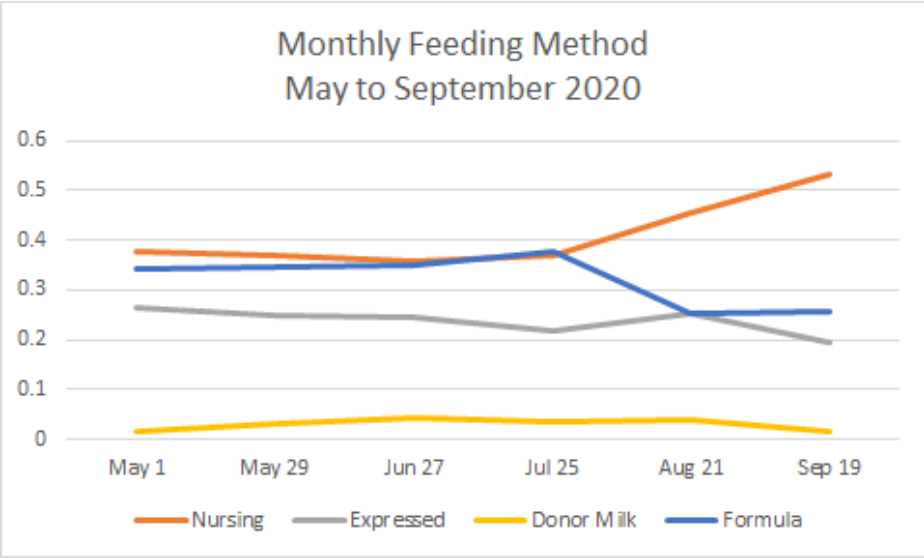
Only case reports of SARS-CoV-2 detected in breastmilk

Primary concern with breastfeeding is transmission via respiratory droplets

CDC recommends frequent handwashing and feeding, with discussion with clinical team regarding risks/benefits

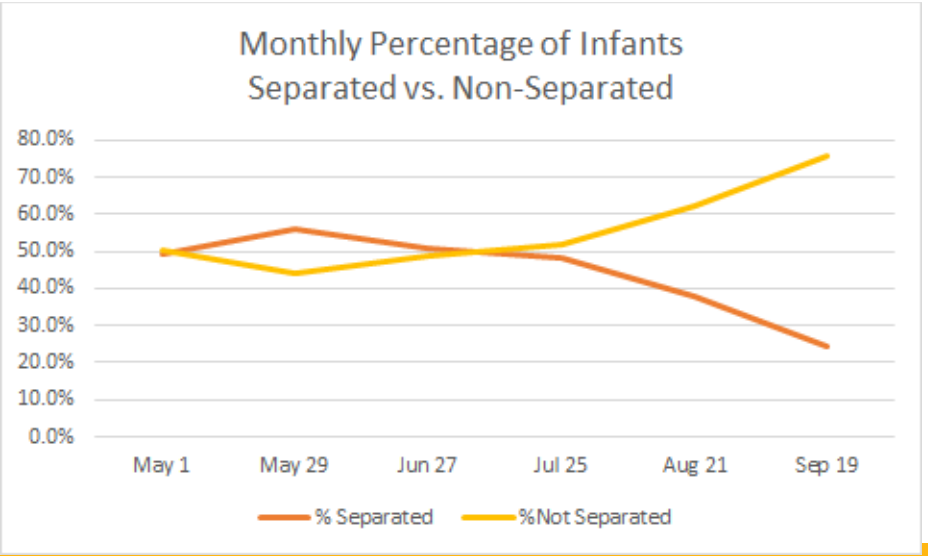
Is Breastfeeding Safe?

- Similar guidelines have also transitioned to encourage breast feeding
  - No evidence to suggest that it poses an increase risk that an infant tests positive when nursed.
- Replicable virus has not been conclusively demonstrated to be present in breast milk



Maternal-infant separation if Covid19+?

- Evidence has accumulated and guidance has shifted from safety preference of temporary maternal-infant separation to one that encourages infants to room in with mothers.
- Mother healthy enough to provide self care
- Appropriate prevention precautions

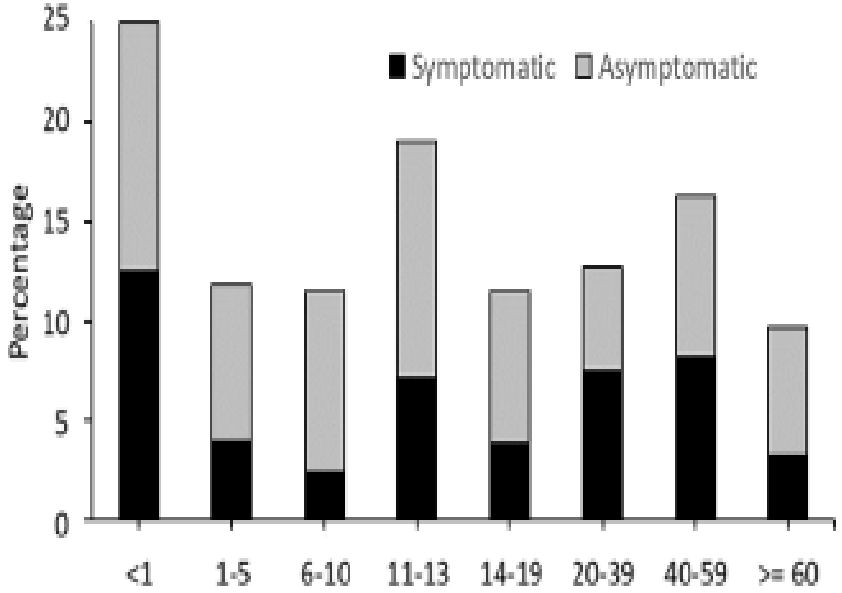


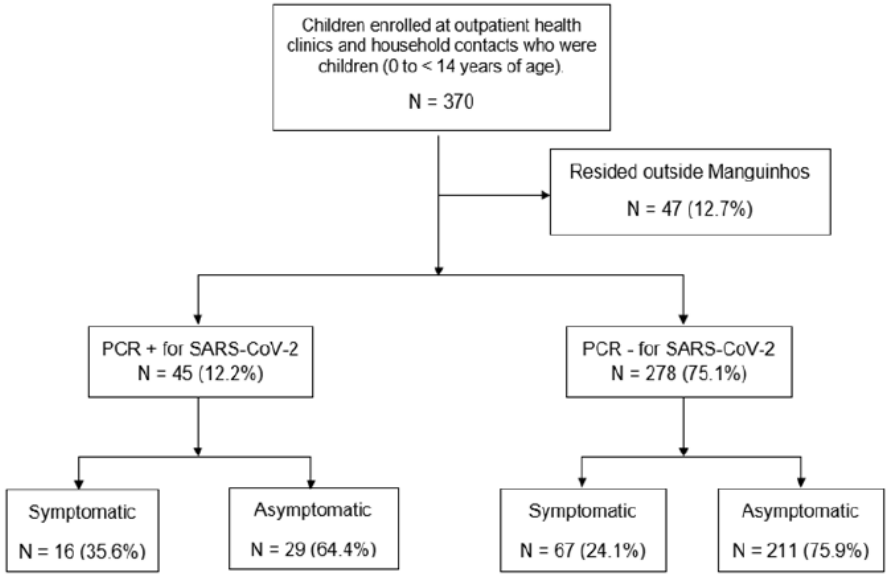
SARS-CoV-2 Infection Dynamics in Children and Household Contacts in a Slum in Rio de Janeiro

Pâmella Lugon, Trevon Fuller, Luana Damasceno, Guilherme Calvet, Paola Cristina Resende, Aline Rocha Matos, Tulio Machado Fumian, Fábio Correia Maltaa, Aline Dessimoni Salgado, Fernanda Christina Morone Fernandes, Liege Maria Abreu de Carvalho, Lusiele Guaraldo, Leonardo Bastos, Oswaldo Gonçalves Cruz, James Whitworth, Chris Smith, Karin Nielsen-Saines, Marilda Siqueira, Marília Sa Carvalho and Patricia Brasil

Pediatrics originally published online April 16, 2021;

PEDIATRICS





Why are so many babies dying of Covid-19 in Brazil?

BBC NEWS

By Nathalia Passarinho and Luis Barrucho
BBC Brazil

15 April

Andre Penner/Associated Press

The New York Times

May 16, 2021

Why Is Covid Killing So Many Young Children in Brazil? Doctors Are Baffled

Experts believe Brazil's overloaded hospital system and uneven access to health care are among the reasons babies and small children are succumbing to the virus at a high rate.

Dr. Marinho, who is leading a study tallying the death toll among children based on both suspected and confirmed cases, estimates that more than 2,200 children under 5 have died since the start of the pandemic, including more than 1,600 babies less than a year old.

"We are seeing a huge impact on children," said Dr. Marinho. "It's a number that's absurdly high. We haven't seen this anywhere else in the world."

David Geffen School of Medicine


What about pediatric long term outcomes?

The present work builds upon a large collaborative effort initiated during the ZIKV epidemic in Brazil in 2015-2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Zika Virus Infection in Pregnant Women in Rio de Janeiro — Preliminary Report

Patrícia Brasil, M.D., Jose P. Pereira, Jr., M.D., Claudia Raja Gabaglia, M.D., Luana Damasceno, M.S., Mayumi Wakimoto, Ph.D., Rita M. Ribeiro Nogueira, M.D., Patrícia Carvalho de Sequeira, Ph.D., André Machado Siqueira, M.D., Liege M. Abreu de Carvalho, M.D., Denise Cotrim da Cunha, M.D., Guilherme A. Calvet, M.D., Elizabeth S. Neves, M.D., Maria E. Moreira, M.D., Ana E. Rodrigues Baião, M.D., Paulo R. Nassar de Carvalho, M.D., Carla Janzen, M.D., Stephanie G. Valderramos, M.D., James D. Cherry, M.D., Ana M. Bispo de Filippis, Ph.D., and Karin Nielsen-Saines, M.D.

88 women with rash during pregnancy, 72 (82%) ZIKV PCR+ in blood, urine or both

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 15, 2016 VOL. 375 NO. 24

Zika Virus Infection in Pregnant Women in Rio de Janeiro

P. Brasil, J.P. Pereira, Jr., M.E. Moreira, R.M. Ribeiro Nogueira, L. Damasceno, M. Wakimoto, R.S. Rabello, S.G. Valderramos, U.-A. Halai, T.S. Salles, A.A. Zin, D. Horovitz, P. Daltro, M. Boechat, C. Raja Gabaglia, P. Carvalho de Sequeira, J.H. Pilotto, R. Medialdea-Carrera, D. Cotrim da Cunha, L.M. Abreu de Carvalho, M. Pone, A. Machado Siqueira, G.A. Calvet, A.E. Rodrigues Baião, E.S. Neves, P.R. Nassar de Carvalho, R.H. Hasue, P.B. Marschik, C. Einspieler, C. Janzen, J.D. Cherry, A.M. Bispo de Filippis, and K. Nielsen-Saines

* 125 pregnancies with known outcomes; 117 live births in 116 pregnancies (one set of twins)

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

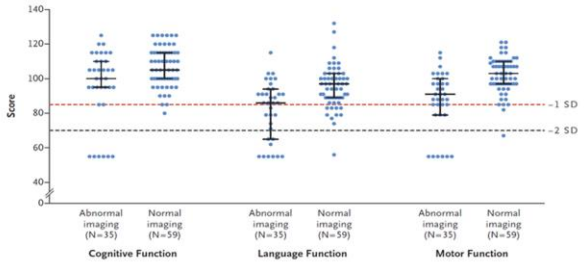
Neurodevelopment in Infants Exposed to Zika Virus In Utero

Moreira et al, NEJM 379: 24 Dec 13, 2018

Bebeth Moreira and team

In the Rio prospective cohort, among 131 ZIKV *in utero* exposed children with neuroimaging, neurodevelopmental and/ or sensory organ assessments, 19 (14.5%) were found to have severe neurodevelopmental delay (-2SD) and/or sensory organ dysfunction.

Figure 1. Individual Scores on the Bayley-III Scales at 12 to 18 Months of Age, According to Neuroimaging Results.



Neuroimaging and neurodevelopment:

A significant association was noted between normal brain imaging and higher Bayley-III scores, but neuroimaging failed to predict developmental delay in 16% of children and normal development in 2% of cases.

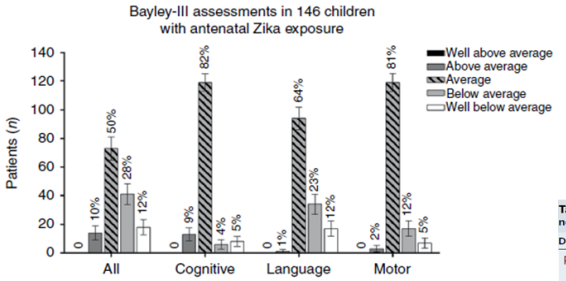
nature medicine

LETTERS

https://doi.org/10.1038/s41591-019-0496-1

Delayed childhood neurodevelopment and neurosensory alterations in the second year of life in a prospective cohort of ZIKV-exposed children

In utero Zika exposure and neurodevelopmental outcomes



A normal distribution of neurodevelopmental outcomes is not present in children with antenatal Zika exposure- there is a shift to abnormal outcomes

Definitions	SD	Scores
High functioning	> 2 SD	≥ 131
Above average	1 SD to 2 SD	116 to 130
Average	- 1 SD to 1 SD	85 to 115
Moderately impaired	-1 SD to -2 SD	84 to 70
Severely impaired	< -2 SD	≤ 69

Table 1 | Characteristics of ZIKV-exposed neonates and neurodevelopmental and neurosensory assessments

Demographics at birth	*n* (out of 216)	Percentage
Preterm infants	28	13.0
<37 to ≥35 weeks	18	8.3
<35 weeks	10	4.6
Small for gestational age	10	4.6
Microcephaly	8	3.7
Primary	4	1.9
Secondary[a]	2	0.9
Resolved[b]	2	0.9

Below-average neurodevelopment and/or abnormal eye or hearing noted in 31.5% of children

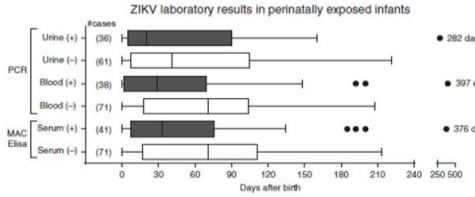
- Language function most affected, 35% of 146 children below average.
- Improved neurodevelopment in female children, term babies, children with normal eye exams and maternal infection later in pregnancy.
- ASD identified in 2% of children

Zika virus vertical transmission in children with confirmed antenatal exposure

nature COMMUNICATIONS

July 2020

Patrícia Brasil[1,7✉], Zilton Vasconcelos[1,7], Tara Kerin[2], Claudia Raja Gabaglia[3], Ieda P. Ribeiro[1], Myrna C. Bonaldo[1], Luana Damasceno[1], Marcos V. Pone[1], Sheila Pone[1], Andrea Zin[1], Irena Tsui[2], Kristina Adachi[2], Jose Paulo Pereira Jr.[1], Stephanie L. Gaw[4], Liege Carvalho[1], Denise C. Cunha[1], Leticia Guida[1], Mirza Rocha[1], James D. Cherry[2], Lulan Wang[2], Saba Aliyari[2], Genhong Cheng[2], Suan-Sin Foo[5], Weiqiang Chen[5], Jae Jung[5], Elizabeth Brickley[6], Maria Elisabeth L. Moreira[1] & Karin Nielsen-Saines[2✉]



84 of 130 children (65%) + in at least 1 assay

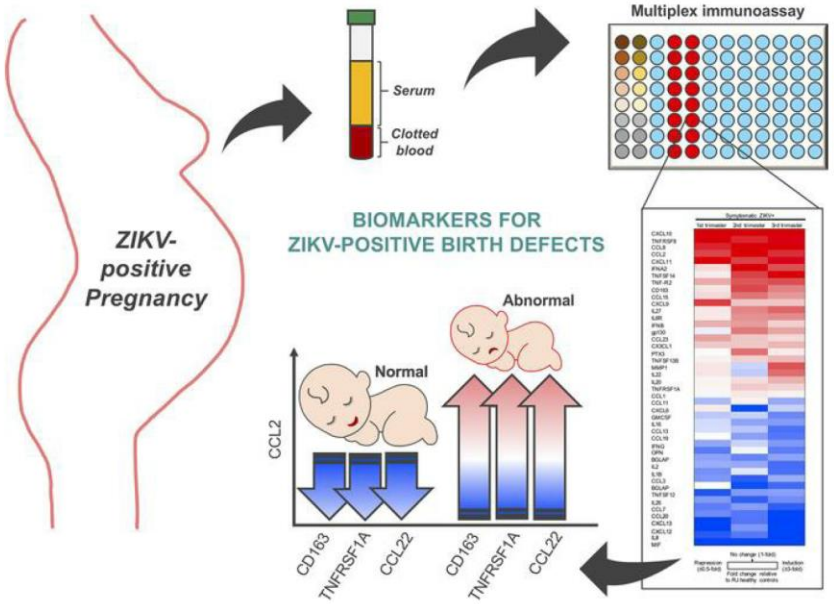
Table 2 ZIKV vertical transmission by age and assay type.

	No. of children	Positive	%
Tested within the first 3 months of age	94 (72%)	66	70%
PCR serum	76 (81%)	30	39%
IgM	75 (80%)	29	39%
PCR urine	54 (57%)	26	48%
First tested after 3 months of age[a]	36 (28%)	18	50%
PCR serum	33 (92%)	7	21%
IgM	36 (100%)	7	19%
PCR urine	19 (53%)	8	42%
Tested after 3 months of age	78 (60%)	26	33%
PCR serum	62 (79%)	9	15%
IgM	65 (83%)	13	20%
PCR urine	23 (29%)	10	43%
All time points	130 (100%)	84	65%
PCR serum	109 (84%)	38	35%
IgM	112 (86%)	41	37%
PCR urine	73 (56%)	36	49%

Biomarkers and immunoprofiles associated with fetal abnormalities of ZIKV-positive pregnancies

Jolin Suan-Sin Foo

Suan-Sin Foo,[1] Weiqiang Chen,[1] Yen Chan,[2] Wai-Suet Lee,[1,3] Shin-Ae Lee,[1] Genhong Cheng,[4] Karin Nielsen-Saines,[5] Patrícia Brasil,[6] and Jae U. Jung[1]



We can identify surrogate markers of abnormal pregnancy outcomes in Zika :

- Extensive multiplexing analysis of 69 cytokines in 74 pregnant patients revealed that CXCL10, CCL2, and CCL8 chemokines specifically associated with symptomatic ZIKV+ infection during pregnancy.
- Distinct immune profiles were detected at different trimesters in ZIKV-infected pregnant women.
- CCL2 levels and its inverse correlation with CD163, TNFRSF1A, and CCL22 levels was associated with ZIKV-induced abnormal birth outcomes.

JCI Insight. 2018;3(21):e124152. https://doi.org/10.1172/jci.insight.124152.

Maternal Immune Activation (MIA) During Pregnancy and Implications to the Fetus

- Epidemiological data and animal data implicating maternal immune activation in pregnancy and CNS disorders: ASD, Schizophrenia and Cerebral Palsy
- MIA can affect fetal brain development
  - Changes in brain structure and function
  - Neuronal dysfunction and behavioral phenotypes
- Mechanisms:
  - Maternal and fetal immune dysregulation: Cytokines/chemokines
  - "2 Hit Hypothesis"
  - Early vs Late infection in pregnancy


Stem Cell Reports
ISSCR
Report
OPEN ACCESS
Maternal Inflammation Contributes to Brain Overgrowth and Autism-Associated Behaviors through Altered Redox Signaling in Stem and Progenitor Cells
REVIEWS
Maternal immune activation and abnormal brain development across CNS disorders

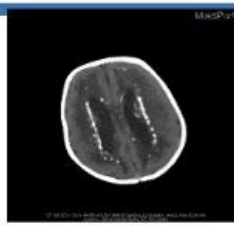

REVIEW
Maternal immune activation: Implications for neuropsychiatric disorders

UCLA MATTEL Childrens Hospital

UCLA Health

If fetus is in MIA environment infant may be more susceptible to infection- 2 hit hypothesis

Maternal Immune Activation (MIA) and Implications to the Fetus



- Zika Virus turned public attention to the detrimental effects of maternal infection
  - Risk of microcephaly
- Historic outbreaks of flu, MMR, Polio correlate with increases in neuropsychiatric illnesses.
  - 1964 Rubella pandemic, incidence of ASD and Schizophrenia rose from 1% to 13 and 20%
- Majority of pregnancies will lead to a healthy offspring, and the resulting CNS disorders often do not appear for many years after birth.
  - Dx of Autism can be made starting at 2 years of age
  - Schizophrenia- mid to late 20's

Potential risk for neurodevelopmental disorders in neonates

COVID-19 during pregnancy: Potential risk for neurodevelopmental disorders in neonates?

Paulo Ricardo Martins-Filho* and Diego Moura Tanajura

Pregnant women with COVID infection have high IL-6 levels which in turn can influence placental-fetal interactions and subsequently fetal brain development.

COVID-19 Infection During Pregnancy and Risk of Neurodevelopmental Disorders in Offspring: Time for Collaborative Research

Álvaro López-Díaz,[a,b,e] Rosa Ayesa-Arriola,[e,f] Benedicto Crespo-Facorro,[b,c,d,e,*] and Miguel Ruiz-Veguilla[b,c,d]

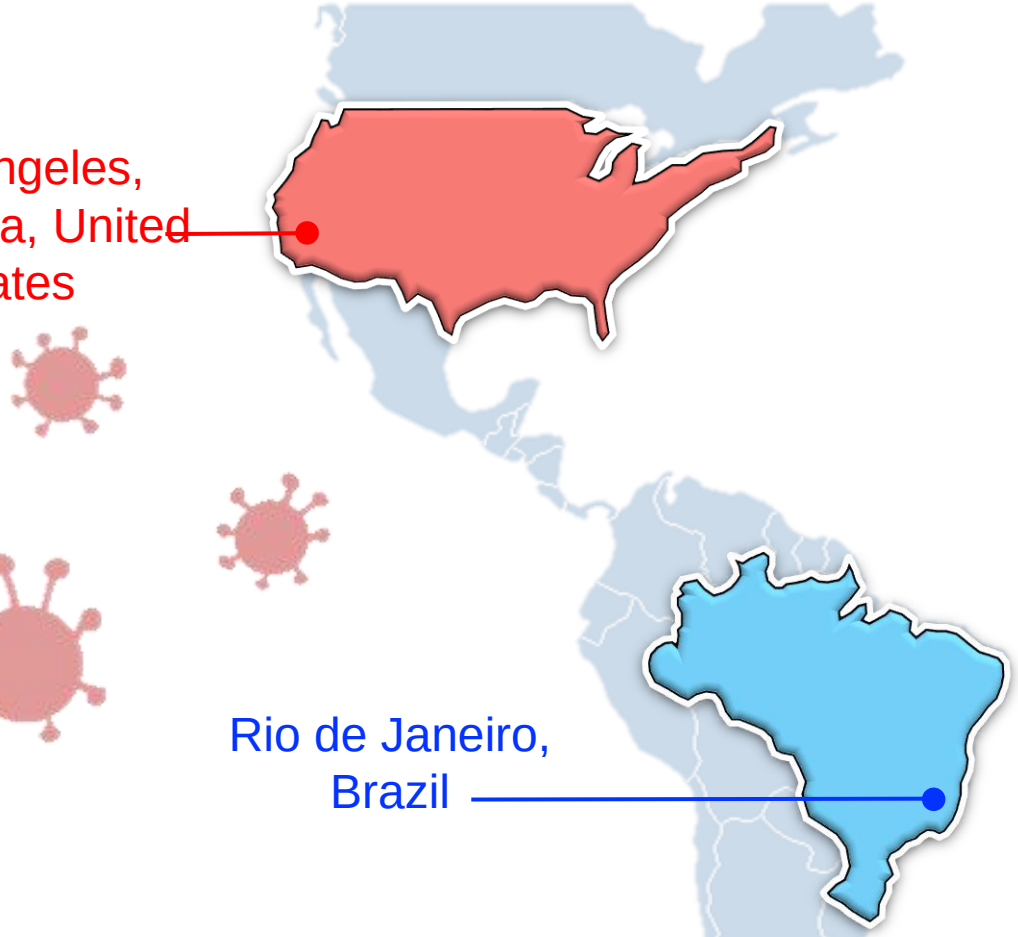
Advocating for collaborative research to explore the mechanisms underlying breakdown in fetal neurodevelopment during maternal infection.

Correspondence

Anticipating the long-term neurodevelopmental impact of the COVID-19 pandemic on newborns and infants: A call for research and preventive policy

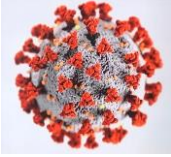
How prenatal maternal stress impacts fetal epigenetic and neurodevelopmental programming leading to offspring psych disorders later in life.

COVID Outcomes Mother-Infant Pair Study (COMP Study)



A study of immuno-pathogenesis in mother-infant pairs affected by SARS Cov2 infection in Los Angeles and Rio de Janeiro, started on 4/4/2020

COVID Outcomes Mother-Infant Pair Study (COMP Study)



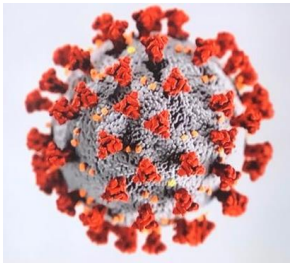
An observational study evaluating clinical outcomes, viral shedding and immune responses in mother-infant pairs affected by COVID-19

Objectives:

1. To characterize clinical, obstetrical and neurodevelopmental outcomes in mother-infant pairs with SARS CoV-2 infection from the time of maternal infection/ birth up to 36 months of follow-up.
2. To evaluate viral shedding in the first month after infection and humoral immune responses over 3 years in mother-infant pairs.
3. To evaluate chemokine-cytokine proteomics and T cell responses (single-cell RNAseq) in mother-infant pairs during the time of acute infection in pregnancy until 3 years postpartum.

Specimens collected at the time of acute infection, labor and delivery, 6 months and 12 months, 24 and 36 months post-partum in mother-infant pairs.

COMP Study



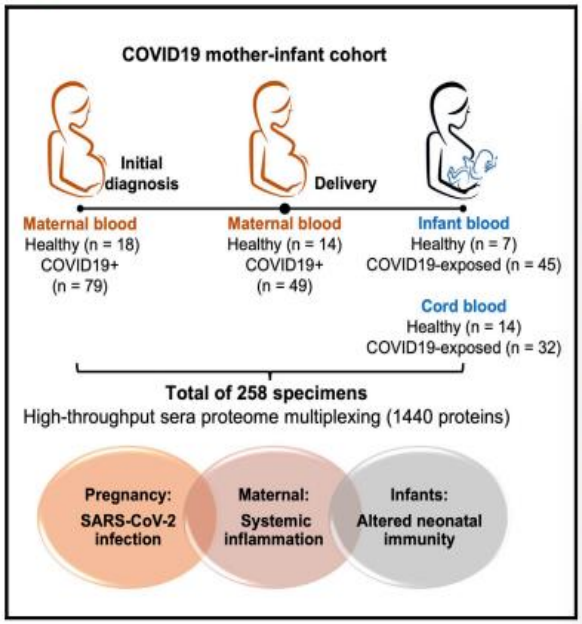
- Population (Original sample size): 100 mother-infant pairs affected by COVID-19 and 100 mother-pair controls.
- Enrolling study sites: UCLA & Fiocruz (Brazil); both sites have IRB approval, functioning Redcaps and are actively recruiting.
- Study enrollment to date: n = 605 pregnancies
  - UCLA: **205**pregnancies
  - Rio: **400** pregnancies

  - Variable disease expression, some mothers required ICU care, a small group ECMO. Maternal deaths and fetal demise reported.

Cell Reports
Medicine

The systemic inflammatory landscape of COVID-19 in pregnancy: Extensive serum proteomic profiling of mother-infant dyads with *in utero* SARS-CoV-2

Graphical abstract



Highlights

- Prenatal SARS-CoV-2 infection triggers NF-κB-dependent immune activation
- Pregnant women with severe COVID-19 show antiviral IFN-λ signaling
- SARS-CoV-2 infection re-shapes maternal immunity at delivery
- COVID-19-exposed infants exhibit altered neonatal immunity at birth

Authors

Suan-Sin Foo, Mary Catherine Cambou, Thalia Mok, ..., Rashmi Rao, Jae U. Jung, Karin Nielsen-Saines

Cell Reports Medicine
Article

CellPress
OPEN ACCESS

Table 1. Demographics and clinical characteristics of mother-infant dyads infected with SARS-CoV-2 during pregnancy[a]

A. Maternal demographics and medical history (N = 93)	All women, N = 93	Asymptomatic, N = 12 (12.9%)	Mild/moderate, N = 61 (65.6%)	Severe/critical, N = 20 (21.5%)	*P*
Median age, y, median (range)	33 (16–44)	33 (19–40)	34 (16–44)	33 (18–44)	0.74
Race/ethnicity, N (%)					<0.001
Latina	44 (47.3)	4 (33.3)	28 (45.9)	12 (60.0)	
White	23 (24.7)	3 (25.0)	17 (27.9)	3 (15.0)	
Black/African American	8 (8.6)	2 (16.7)	2 (3.3)	4 (20.0)	
Asian/other	18 (19.4)	3 (25.0)	14 (23.0)	1 (5.0)	
Insurance, N (%)					0.039
Public	37 (39.8)	5 (41.7)	21 (34.4)	11 (55.0)	
Private	56 (60.2)	7 (58.3)	40 (65.6)	9 (45.0)	
Occupation, N (%)					<0.001
Healthcare worker	16 (17.2)	1 (8.3)	13 (21.3)	2 (10.0)	
Other	77 (82.8)	11 (91.7)	48 (78.7)	18 (90.0)	
Parity, median (range)	2 (1–10)	3 (1–6)	2 (1–10)	3 (1–7)	0.32
Gestational age at diagnosis, N (%)					<0.001
1st trimester	18 (19.4)	1 (8.3)	15 (24.6)	2 (10.0)	
2nd trimester	31 (33.3)	2 (16.7)	17 (27.9)	12 (60.0)	
3rd trimester	44 (47.3)	9 (75.0)	29 (47.5)	6 (30.0)	

Table 1. *Continued*

A. Maternal demographics and medical history (N = 93)	All women, N = 93	Asymptomatic, N = 12 (12.9%)	Mild/moderate, N = 61 (65.6%)	Severe/critical, N = 20 (21.5%)	*P*
Complications during the course of pregnancy pre-delivery, N (%)					
Gestational diabetes	9 (12.8)	2 (16.7)	3 (6.8)	4 (28.6)	0.10
Hypertensive disorder	23 (32.9)	3 (25.0)	14 (31.8)	6 (42.9)	0.61
Late pregnancy and postpartum complications, N (%)					
Fetal growth restriction	11 (15.7)	2 (16.7)	8 (18.2)	1 (7.1)	0.07
Chorioamnionitis	6 (8.6)	1 (8.3)	3 (6.8)	2 (14.3)	0.05
Postpartum hemorrhage	11 (15.7)	0 (0.0)	5 (11.4)	6 (42.9)	<0.001
Preeclampsia/HELLP	11 (15.7)	3 (25.0)	6 (13.6)	2 (14.3)	0.72
Preterm rupture of membranes	4 (5.7)	0 (0.0)	2 (4.5)	2 (14.3)	0.02
Unknown	4 (5.7)	0 (0.0)	1 (2.3)	3 (21.4)	0.05
Mode of delivery/pregnancy endpoint, N (%)					0.10
NSVD	33 (47.1)	6 (50.0)	25 (56.8)	2 (14.3)	
C-section	25 (35.7)	5 (41.7)	14 (31.8)	6 (42.9)	
Vacuum-assisted vaginal delivery	1 (1.4)	0 (0.0)	1 (2.3)	0 (0.0)	
Unknown	4 (5.7)	0 (0.0)	1 (2.3)	3 (21.4)	
Miscarriage/termination/fetal loss	7 (10.0)	1 (8.3)	3 (6.8)	3 (21.4)	
Miscarriage (<20 weeks)	2 (2.9)	0 (0.0)	1 (2.3)	1 (7.1)	
Fetal loss (≥20 weeks)	2 (2.9)	0 (0.0)	1 (2.3)	1 (7.1)	
Pregnancy termination	2 (2.9)	1 (8.3)	1 (2.3)	0 (0.0)	
Maternal-fetal demise	1 (1.4)	0 (0.0)	0 (0.0)	1 (7.1)	
Pregnancies resulting in live births (N = 70)	63 (90.0)	11 (91.7)	41 (93.2)	11 (78.6)	0.28
No. multiple gestations[e]	5 (7.1)	1 (8.3)	2 (4.5)	2 (14.3)	0.46
No. infants born as of March 1, 2021	69 (98.6)	13 (18.57)	43 (61.43)	13 (18.57)	
C. Infant outcomes with associated O-link data[f] (N = 45), N (%)	All women	Asymptomatic, N = 11 (24.44%)	Mild/moderate, N = 28 (62.22%)	Severe/critical, N = 6 (13.34%)	*P*
Preterm delivery	14 (31.1)	0 (0.0)	8 (28.6)	6 (100)	<0.001
Small-for-gestational-age	5 (12.5)	1 (9.1)	4 (14.3)	0 (0.0)	0.58
Low birth weight (<2,500 g)	13 (41.7)	1 (9.1)	6 (21.4)	6 (100)	<0.001

JAMA. doi:10.1001/jama.2022.1190
Published online February 7, 2022.

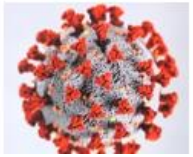
JAMA | Original Investigation

Association of SARS-CoV-2 Infection With Serious Maternal Morbidity and Mortality From Obstetric Complications

Torri D. Metz, MD, MS; Rebecca G. Clifton, PhD; Brenna L. Hughes, MD, MS; Grecio J. Sandoval, PhD; William A. Grobman, MD, MBA; George R. Saade, MD; Tracy A. Manuck, MD, MS; Monica Longo, MD, PhD; Amber Sowles, BSN, RN; Kelly Clark, BSN, RN; Hyagriv N. Simhan, MD; Dwight J. Rouse, MD; Hector Mendez-Figueroa, MD; Cynthia Gyamfi-Bannerman, MD, MS; Jennifer L. Bailit, MD, MPH; Maged M. Costantine, MD; Harish M. Sehdev, MD; Alan T. N. Tita, MD, PhD; George A. Macones, MD; for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network

Table 2. Maternal and Neonatal Outcomes for Individuals With and Without a Positive SARS-CoV-2 Test Result

	SARS-CoV-2 positive, No. (%)				
	Yes (n = 2352)	No (n = 11 752)	Difference (95% CI)	Relative risk (95% CI)	Adjusted relative risk (95% CI)
Maternal outcomes					
Primary composite outcome of death or serious morbidity from hypertensive disorders of pregnancy, postpartum hemorrhage, or non-SARS-CoV-2 infection	316 (13.4)	1076 (9.2)	4.2 (2.8 to 5.6)	1.45 (1.29 to 1.64)	1.41 (1.23 to 1.61)[a]
Death (any cause)	5 (0.2)	0			
Hypertensive disorders of pregnancy[b]	238 (10.1)	761 (6.5)	3.6 (2.4 to 4.8)	1.56 (1.35 to 1.79)	1.53 (1.31 to 1.79)[a]
Postpartum hemorrhage[c]	61 (2.6)	282 (2.4)	0.1 (−0.5 to 0.8)	1.06 (0.81 to 1.40)	1.13 (0.83 to 1.53)[a]
Infection other than SARS-CoV-2[d]	55 (2.3)	103 (0.9)	1.4 (0.8 to 2.1)	2.61 (1.88 to 3.63)	2.08 (1.41 to 3.05)[a]



Maternal demographics and clinical characteristics of COMP U.S. study participants excluding 27 controls (**N = 177**)

Median Maternal Age (Range)	32 (16 - 56)
Race/Ethnicity	(%)
Latina	47.7
White	23.6
Black	6.4
Asian	12.1
Mixed/Other	10.2
COVID-19 Severity	
Asymptomatic	11.9
Mild/ Moderate	71.7
Severe/ Critical	16.4
Trimester of Diagnosis	
1st	13.0
2nd	34.5
3rd	52.5
Cardiovascular Co-Morbidities	
Hypertensive Disorder	**24.2**
Pre-Eclampsia	14.0

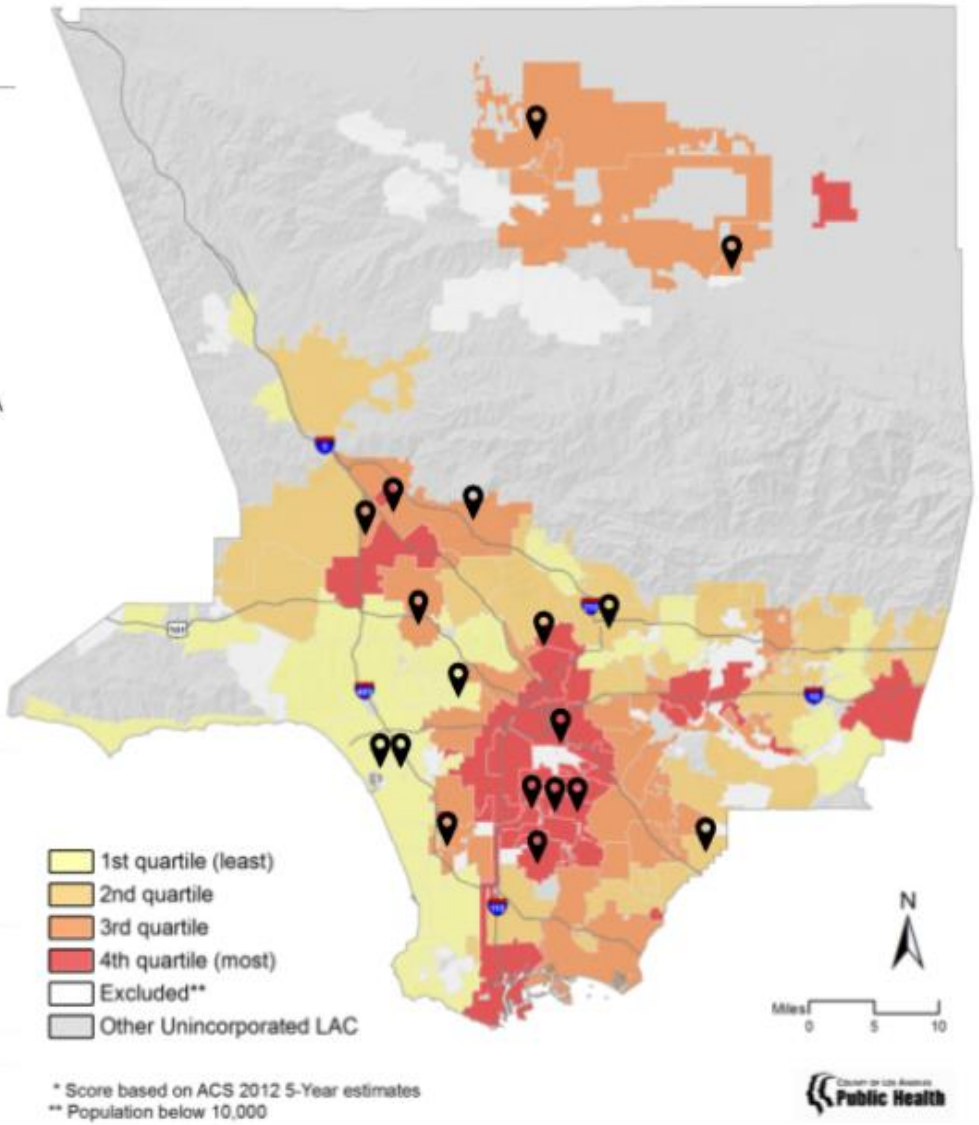
COVID Outcomes Mother-Infant Pair Study (COMP Study)

COVID-19 IN PREGNANCY AND SOCIAL DETERMINANTS OF HEALTH

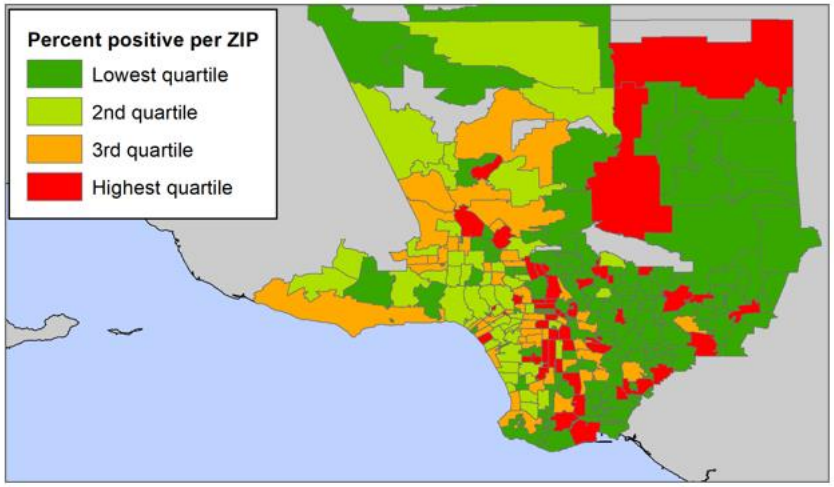
Sophia Finn Tiene[1], Jessica S. Cranston[1], Mary Catherine Cambou[1], Sophia Paiola[1], Thalia Wong[1], Jenny Mei[1], Vivianna Fajardo[1], Debika Bhattancharya[1], Grace Aldrovandi[1], Tara Kerin[1], Rashmi Rao[1], Trevon Fuller[1], Patricia Brasil[2], Karin Nielsen-Saines[1]
[1] University of California Los Angeles, CA, United States [2] Fiocruz, Rio de Janeiro, Brazil

Figure 1. Residence of patients with severe/critical Covid-19 superimposed on a map of Economic Hardship Index

Zip Code	City / Neighborhood	County
90036	Fairfax	
90066	Mar Vista	
90066	Mar Vista	
90638	La Mirada	
91101	Pasadena	
90250	Hawthorne	
91040	Shadow Hills	
91331	Hansen Hills	
91343	North Hills	Los Angeles, CA
91423	Van Nuys	
93536	Lancaster	
93543	Little Rock	
90002	Watts	
90023	Boyle Heights	
90041	Eagle Rock	
90220	Crystal City	
90280	South Gate	
90280	South Gate	
92562	Murrieta	Riverside, CA
92703	Santa Ana	
92780	Tustin	
92782	Tustin	Orange, CA
92870	Placentia	
92870	Placentia	
93004	Ventura	
93036	Oxnard	Ventura, CA
93066	Somis	
93274	Visalia	Tulare, CA
78735	Austin	Travis, TX



Geographic, Social and Epidemiologic Predictors of SARS-CoV-2 Infection in Youth in Southern California



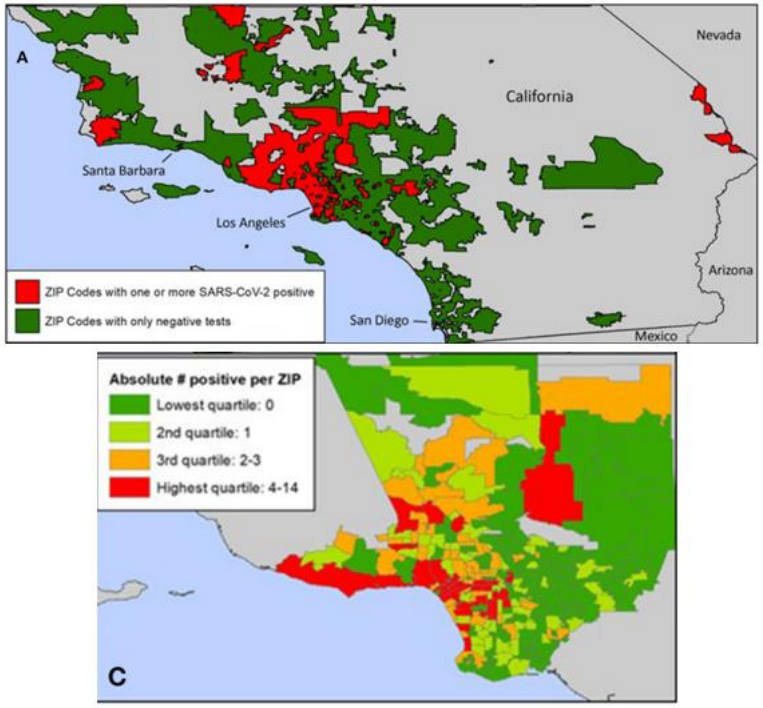
Youth under 25 years of age living in the ZIP codes reflective of the most disenfranchised populations in LA county were proportionally most affected by COVID-19 early in the pandemic.

ORIGINAL RESEARCH
published: 17 November 2021
doi: 10.3389/fped.2021.752247

Predictors of SARS-CoV-2 Infection in Youth at a Large, Urban Healthcare Center in California, March–September 2020

frontiers in Pediatrics

Caitlin N. Newhouse[1,2], Tawny Saleh[2], Trevon Fuller[3,4], Tara Kerin[2], Mary C. Cambou[5], Emma J. Swayze[6], Catherine Le[7], Wonjae Seo[7], Marisol Trejo[7], Omai B. Garner[7], Sukantha Chandrasekaran[7] and Karin Nielsen-Saines[2]*



COVID Outcomes Mother-Infant Pair Study
(COMP Study)

An observational study evaluating clinical outcomes, viral shedding and immune responses in mother-infant pairs affected by COVID-19

Sera immunoprofiling of COVID-19-positive pregnancies

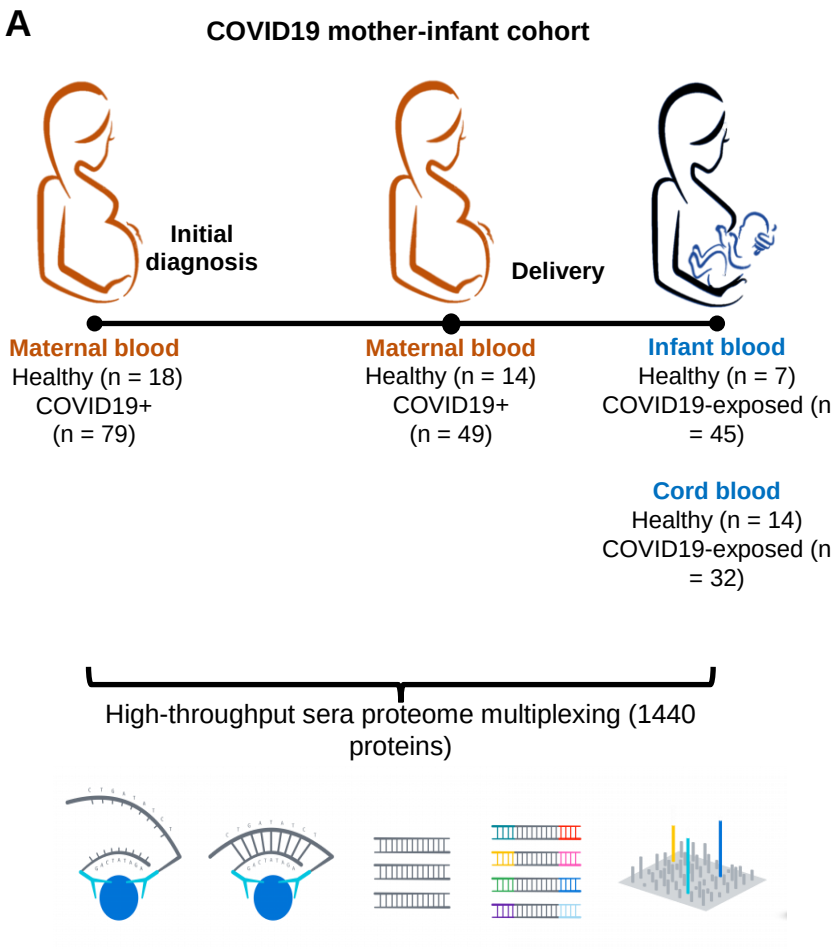
Jae Jung, PhD

Sera proteomics

Olink proteomics multiplex

(1536-plex)

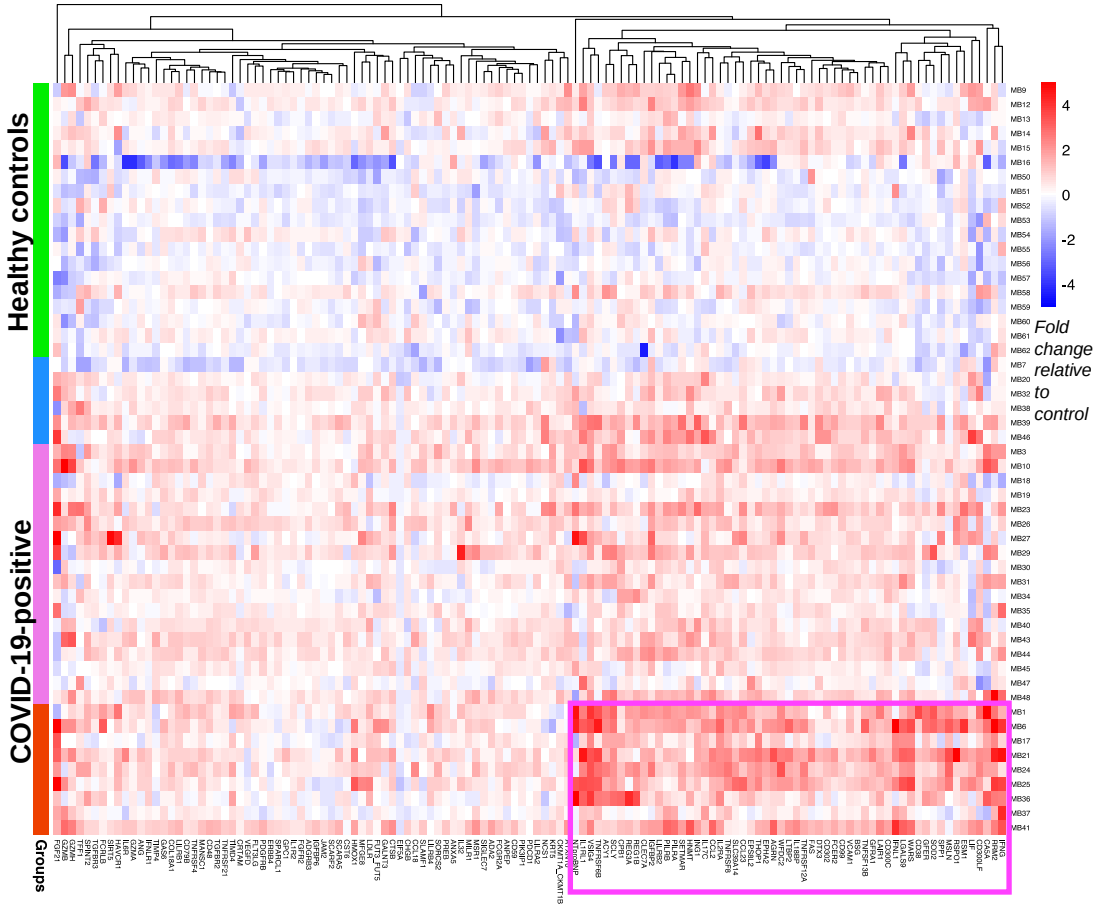
- **Maternal sera (*n* = 93)**
- **Infant's sera (*n* = 45)**
- **Cord sera (*n* = 32)**



Mother

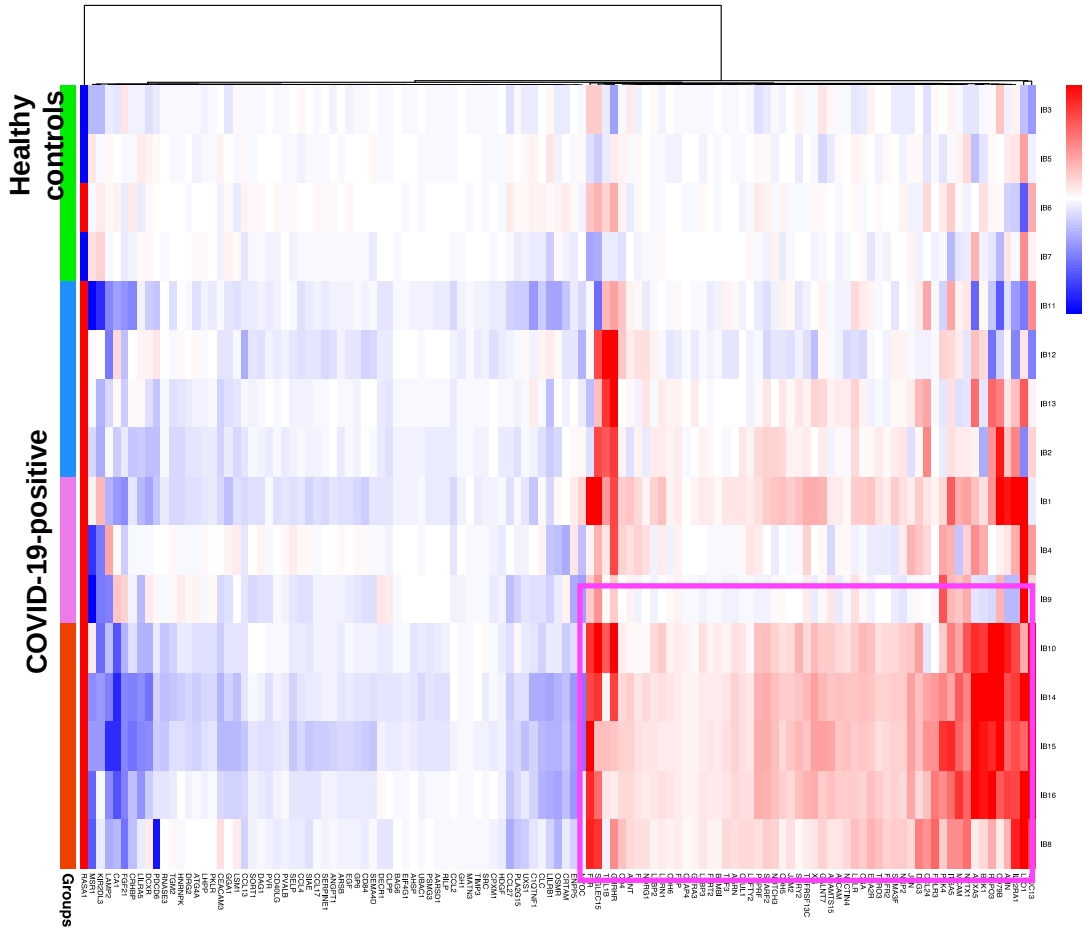
COVID-19 induced robust immune activation during pregnancy

- ~1400 sera cytokines screened
- 125 cytokines significantly altered in COVID-19 pregnancies
- Severe/Critical pregnancies displayed distinct immune signatures



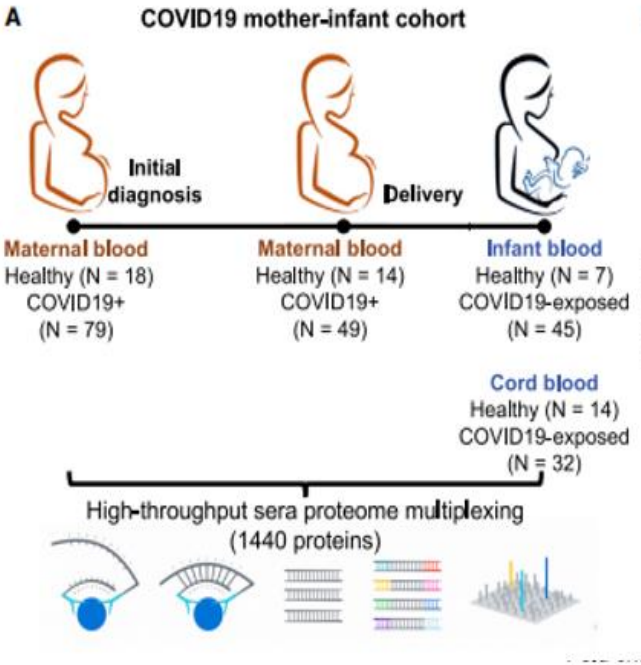
- Healthy controls
- Asymptomatic
- Mild
- Severe/critical

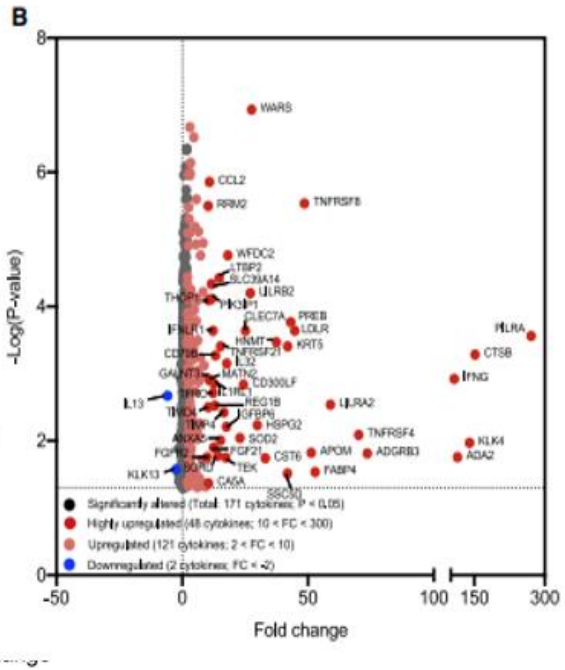
Infants of Severe/Critical COVID-19 mothers reveal strikingly unique immune profiles

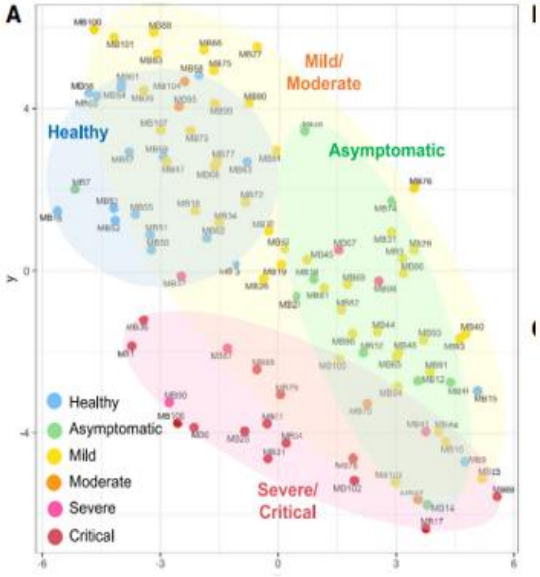


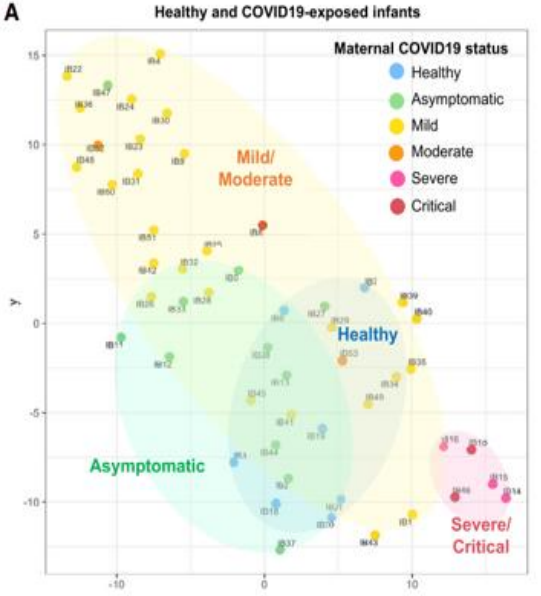
- ~1400 sera cytokines screened
- 120 cytokines significantly altered in COVID-19-exposed infants
- Infants of Severe/Critical COVID-19 mothers displayed distinct immune signatures

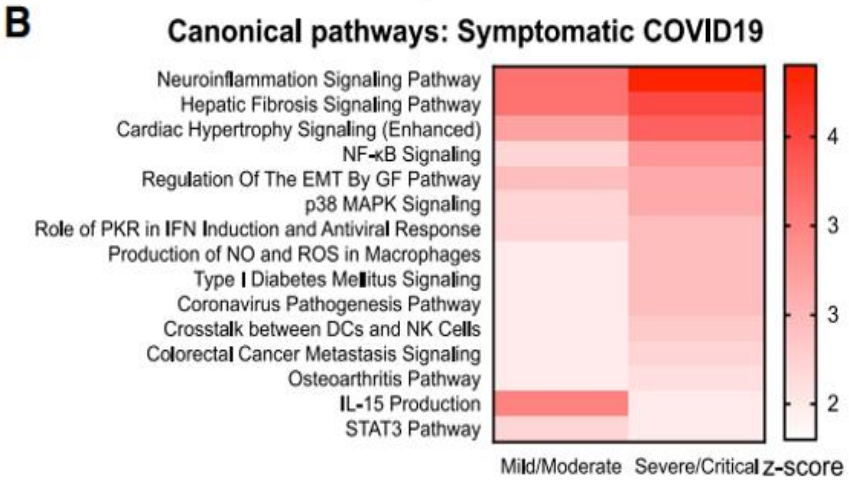
Healthy controls
Asymptomatic
Mild
Severe/critical


A
COVID19 mother-infant cohort
Initial diagnosis
Delivery
Maternal blood
Healthy (N = 18)
COVID19+
(N = 79)
Maternal blood
Healthy (N = 14)
COVID19+
(N = 49)
Infant blood
Healthy (N = 7)
COVID19-exposed
(N = 45)
Cord blood
Healthy (N = 14)
COVID19-exposed
(N = 32)
High-throughput sera proteome multiplexing
(1440 proteins)

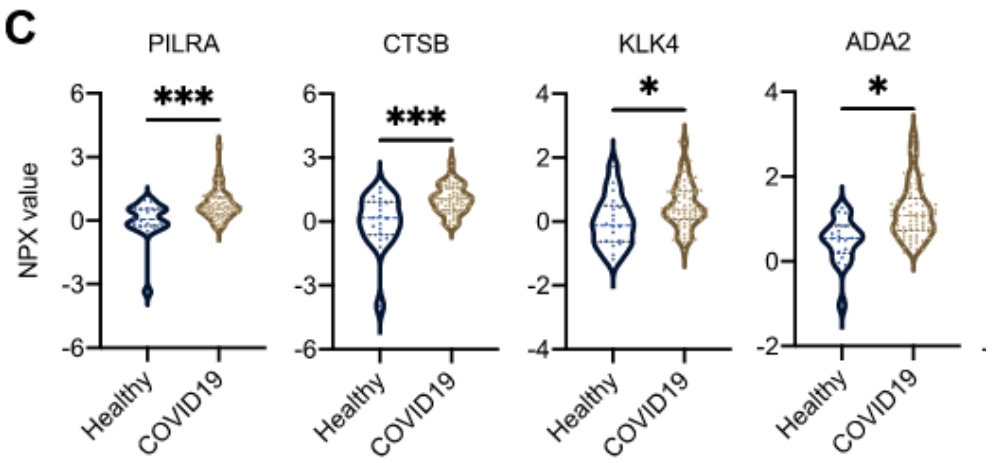

B
-Log(P-value)
Fold change
WARS
CCL2
TNFRSF6
PRELP
LDLR
KRT5
HLRA
CTSB
IFNG
IL13
IL1RA2
TNFRSF4
KLK4
ADGRB3
APOM
FABP4
CST6
HSPG2
SOD2
FGF21
CASA
TEK
KLK13
SSC5D
Significantly altered (Total: 171 cytokines; P < 0.05)
Highly upregulated (48 cytokines; 10 < FC < 300)
Upregulated (121 cytokines; 2 < FC < 10)
Downregulated (2 cytokines; FC < -2)


A
Mild/
Moderate
Healthy
Asymptomatic
Severe/
Critical
Healthy
Asymptomatic
Mild
Moderate
Severe
Critical

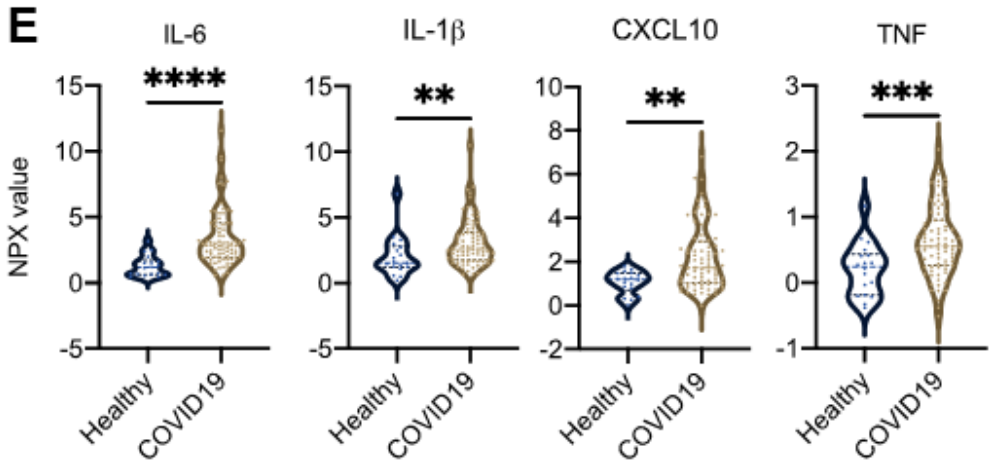

A
Healthy and COVID19-exposed infants
Maternal COVID19 status
Healthy
Asymptomatic
Mild
Moderate
Severe
Critical
Mild/
Moderate
Healthy
Asymptomatic
Severe/
Critical


B
Canonical pathways: Symptomatic COVID19
Neuroinflammation Signaling Pathway
Hepatic Fibrosis Signaling Pathway
Cardiac Hypertrophy Signaling (Enhanced)
NF-κB Signaling
Regulation Of The EMT By GF Pathway
p38 MAPK Signaling
Role of PKR in IFN Induction and Antiviral Response
Production of NO and ROS in Macrophages
Type I Diabetes Mellitus Signaling
Coronavirus Pathogenesis Pathway
Crosstalk between DCs and NK Cells
Colorectal Cancer Metastasis Signaling
Osteoarthritis Pathway
IL-15 Production
STAT3 Pathway
Mild/Moderate
Severe/Critical
z-score

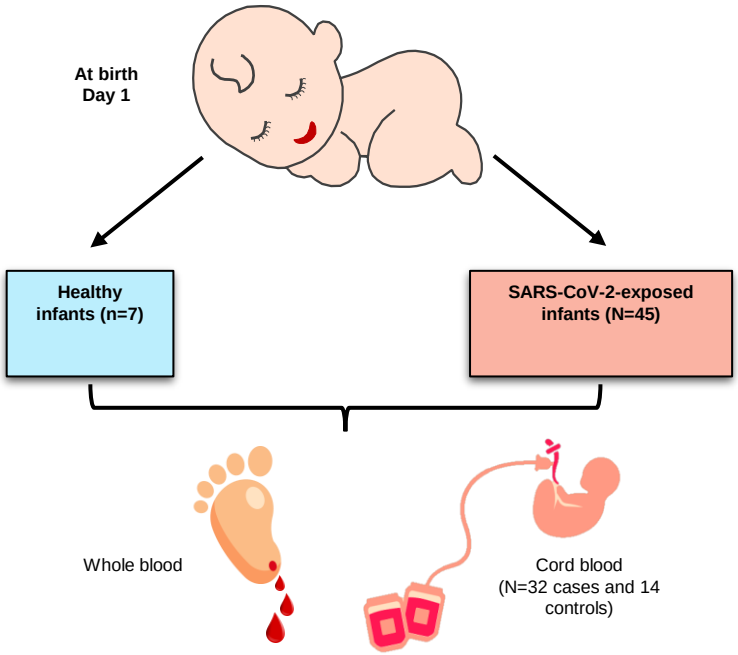
Highly upregulated cytokines

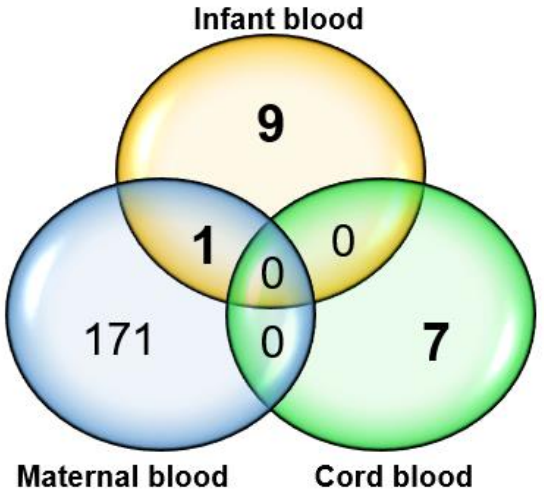


Proinflammatory cytokines significantly altered in COVID19-affected pregnancies



COMP Study – First 45 case infants





Comparison of proteomic profiles of neonatal blood at day 1 of life compared to cord blood and maternal blood. Very little overlap. Cytokines do not cross the placenta.

Respiratory Distress in Neonates Exposed to Maternal SARS-CoV-2 Infection *In Utero*

Jessica S. Cranston [1], Sophia Finn Tiene [1], Mary Catherine Cambou [1], Sophia Paiola [1], Thalia Wong [1], Jenny Mei [1], Vivianna Fajardo [1], Debika Bhattacharya [1], Grace Aldrovandi [1], Tara Kerin [1], Rashmi Rao [1], Trevon Fuller [1,2], Patricia Brasil [2], Karin Nielsen-Saines [1]

[1] University of California Los Angeles, CA, United States [2] Fiocruz, Rio de Janeiro, Brazil

Background

- Respiratory Distress is one of the most common causes of admission to the NICU
- Neonates with respiratory distress have 2-4 times higher fatality rate than those without respiratory distress
- Respiratory Distress affects approximately 1-2% of term infants, with a higher incidence among pre-term infants
- Studies have shown a high prevalence of respiratory distress in infants born to mothers with COVID-19 during pregnancy

Objective

- To characterize the multifactorial associations leading to Respiratory Distress (RD) in neonates born to mothers diagnosed with Covid-19 during pregnancy

Methods

- The COVID-19 Outcomes in Mother-Infant Pairs (COMP) study is a longitudinal cohort of mother-infant dyads diagnosed with SARSCoV-2 during pregnancy in Los Angeles, California and Rio de Janeiro, Brazil
- Respiratory Distress was defined as at least 2 of the following: RR>60/min, retractions, nasal flaring, central cyanosis
- Sera proteomics profiling was performed using Olink Explore 1536, a high-multiplex, high-throughput protein biomarker platform that utilizes Proximity Extension Assay (PEA) technology coupled with next generation sequencing for readout of >1400 cytokines
- Normalized protein expressions (NPX) values for all proteins were received from Olink after sequencing and validated using real-time PCR

Results

Table 1. Maternal/Infant Demographics and Clinical Findings

	Respiratory Distress (+) (N=20)	Respiratory Distress (-) (N=43)	
	Median (Range)	Median (Range)	P Value
Age	34 (19-42)	32 (16-42)	0.094
	N (%)	N (%)	
Ethnicity			0.63
- Latina	6 (30%)	21 (49%)	
- White	4 (20%)	13 (30%)	
- Black/African American	3 (15%)	4 (9.3%)	
- Asian/Other	3 (15%)	5 (11.6%)	
Trimester of Covid Diagnosis			0.97
- First Trimester	0	2 (5%)	
- Second Trimester	6 (30%)	11 (15%)	
- Third Trimester	14 (70%)	30 (70%)	
Medical History Prior to Covid			
- Any Comorbidities	11 (55%)	22 (51%)	0.78
- Obesity (Pre- Pregnancy)	8 (40%)	14 (33%)	
- Diabetes (not GDM)	1 (5%)	2 (5%)	
- Pulm. Art. Hypertension	0	0	
- Congenital Heart Disease	0	4 (9%)	
- Asthma	3 (15%)	5 (12%)	
- Autoimmune Disorder	0	2 (5%)	
- HIV	0	1 (2%)	
Covid Severity			0.012
- Critical	4 (25%)	0	
- Severe	2 (12.5%)	0	
- Mild	6 (30%)	29 (67%)	
- Asymptomatic	4 (25%)	9 (21%)	
Covid Symptoms			
- Asymptomatic	4 (25%)	9 (21%)	
- Fever	5 (25%)	3 (7%)	0.035
- Cough/Sore Throat/Rhinorrhea	5 (25%)	6 (14%)	0.28
- Dyspnea	3 (15%)	4 (9%)	0.5
- Abdominal pain/ Nausea/Emesis/Diarrhea	0	6 (14%)	0.29
- Anosmia/Dysgeusia	2 (10%)	6 (14%)	0.66
- Fatigue/Myalgia/Arthralgias	6 (30%)	13 (30%)	0.99
Cytokine Storm/Release Syndrome	3 (15%)	1 (2%)	0.025
Pregnancy Complications			
- Gestational Diabetes	5 (25%)	6 (14%)	0.28
- Hypertensive Disorder	10 (50%)	11 (26%)	0.56
- Fetal Growth Restriction	2 (10%)	6 (14%)	0.66
- Chorioamnionitis	0	3 (7%)	0.4
- Preeclampsia/HELLP	7 (35%)	4 (9%)	0.012
- Preterm Rupture of Membranes	1 (5%)	3 (7%)	0.77
Mode of Delivery			
- Vaginal Delivery	3 (15%)	30 (70%)	0.00005
- C-Section	13 (65%)	13 (30%)	0.0091
Infant Outcomes			
- Parity (Median (Range))	1 (1-3)	1 (1)	<0.00001
- Preterm	14 (70%)	3 (7%)	<0.00001
- Small for Gestational Age	3 (15%)	5 (12%)	0.73
- Low Birth Weight (<2500g)	14 (70%)	3 (7%)	<0.00001
- Fetal Sex (M)	10 (50%)	25 (58%)	0.55

Figure 1. Respiratory Distress in Term and Pre-Term Infants

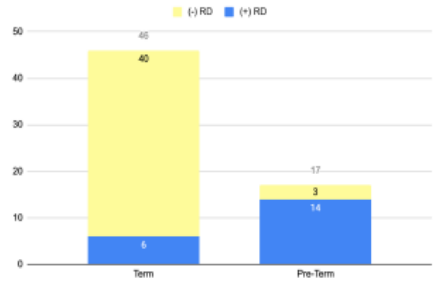


Figure 2. Cytokines Associated with Respiratory Distress

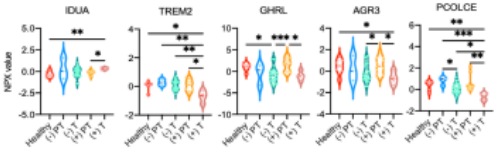


Figure 2: Serum cytokines specifically altered in (+) RD: term COVID-19-exposed infants. Data presented as means ± SEMs, using 1-way ANOVA Kruskal-Wallis with uncorrected Dunn's test. *p < 0.05, **p < 0.01, ***p <0.001.

- A total of 215 mother-infant dyads were enrolled in the study
- RD status of the neonate was known in 63 of the cases
- 31.7% of these infants suffered from neonatal RD
- Of these, 15% of term infants suffered from RD without a clear etiology (Figure 1)
- Maternal Covid severity (p=0.012), maternal fever with Covid (p = 0.035), presence of maternal cytokine storm with Covid (p=0.025), maternal preeclampsia/HELLP (p=0.012), method of delivery (p=0.00005), term (p<0.00001), parity (p<0.00001) and low birth weight (p<0.00001) were all found to be significantly associated with a neonatal diagnosis of RD (Table 1)
- Preterm COVID-19-exposed infants with RD exhibited the most significant immune alterations of 36 cytokines
- 5 specific cytokines that were affected in COVID 19- exposed term birth infants with RD, including iduronidase (IDUA), TREM2, ghrelin and obestatin prepropeptide (GHRL), anterior gradient 3, protein disulfide isomerase family member (AGR3), and procollagen C-endopeptidase enhancer (PCOLCE) (Figure 2)

Conclusions

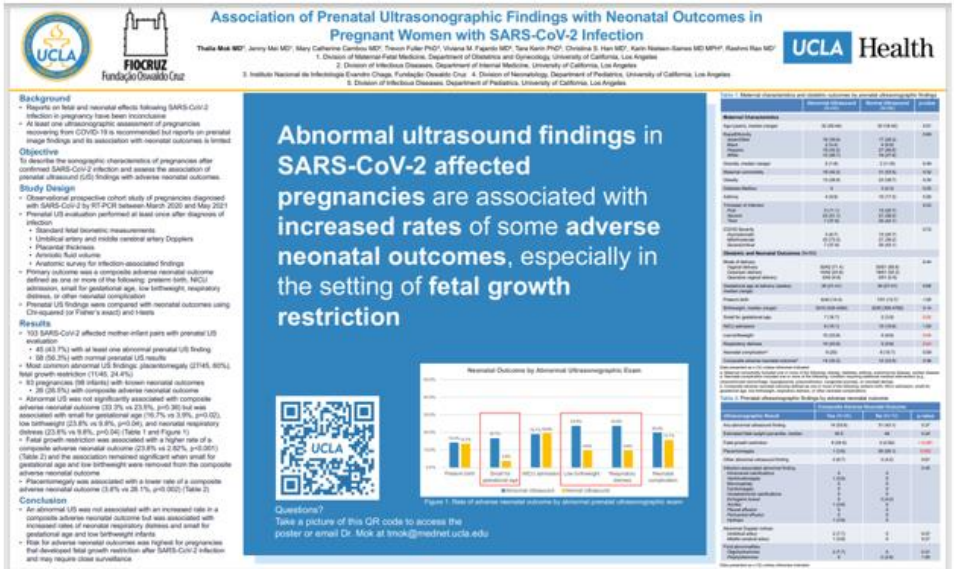
- Overall, infants born to COVID-19 mothers with more severe/critical disease and cytokine storm exhibited more pronounced immune alterations as compared to infants born to mothers with asymptomatic disease
- The rate of RD in infants born to COVID-19 mothers was higher than baseline
- In addition, several serum factors were identified as potential biomarkers for prenatal SARS-CoV-2 infection and neonatal RD
- Immunological evaluations of term COVID-19 exposed infants who developed RD identified:
  - ➢ High levels of IL-18, IL-1B, and CASP1, indicative of an activated NLRP3 inflammasome pathway
  - ➢ High levels of TREM2, known to promote macrophage survival and viral-induced lung pathogenesis
  - ➢ Increased IDUA levels that degrade glycosaminoglycans, and decreased AGR3, which is essential in regulating ciliary beat frequency in the airway
- Therefore, these proteins are potential pathogenic factors implicated in RD associated with prenatal COVID-19-exposure in term infants and should be further explored
- Infants exposed to COVID-19 in utero should be carefully assessed for RD at birth

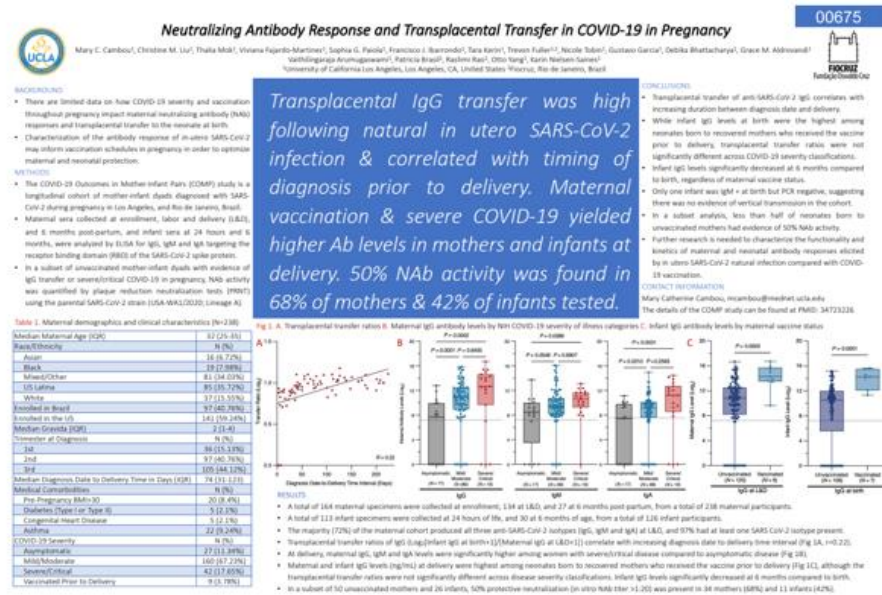
The details and resources of the COMP study can be found at PMID: 34723226

PAS 2022 IN PERSON & ON DEMAND
APRIL 21-25,2022 | DENVER, CO

Gross motor function in Infants exposed to Prenatal SARS-CoV-2 infection using the General Movement Assessment Tool

		Trimester Maternal Dx			
	N = (57/51)	1st (7/7)	2nd (19/17)	3rd (31/27)	Mean
Severity	**Asymptomatic** (10/8)	19 (1/1) -	- (0/0) -	10 - 28(9/7) *20.67(22)*	**20.50**
	Mild/Moderate (39/37)	12 - 24 (5/5) *20.4(22)*	17 - 28 (14/14) *23.29(24)*	9 - 28 (20/18) *21.65(22)*	**22.08**
	Severe/Critical (8/6)	21 (1/1) -	18 - 24 (5/3) *20.80(21)*	24 - 24 (2/2) *24*	**21.63**
	Mean	**20.29**	**22.63**	**21.52**	***21.74***



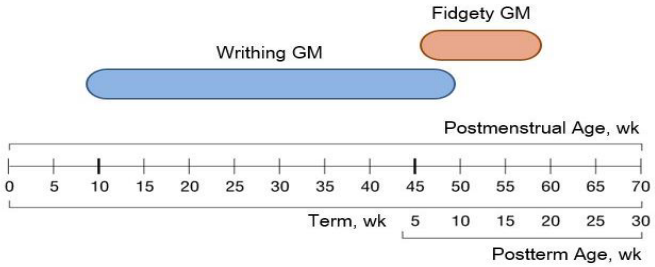


Maternal immune profiles of abnormal prenatal ultrasonographic findings following SARS-CoV-2 infection

Thalia Mok, MD
Society for Maternal Fetal Medicine's 42nd Annual Pregnancy Meeting
February 3, 2022

General Movement Assessment (GMA)

- Non-invasive, video-based assessment
- Identify neurological deficits
- Enables referral of infants at risk
- Long term relevance for the later development of cognitive, speech-language and motor function.



General movement assessments (GMA) at 3 to 5 months identify poor neurodevelopment at 12 months, specificity 96%, sensitivity 70% in infants exposed to maternal Zika

Einspieler et al.
Jama Netw Open 2019

Christa Einspieler

Peter Marschik

There are tools for early identification of children at risk for poor neurodevelopment

Neuromotor function in infants exposed to Prenatal SARS-CoV-2 infection using the General Movement Assessment Tool

Viviana Fajardo-Martinez[1], Dajie Marschik[2], Sophia Paiola[1], Thalia Mok[1], Mary C. Cambou[1], Rashmi Rao[1], Patricia Brasil[3], Fatima Ferreira[3], Trevon Fuller[3], Debika Bhattacharya[1], Christa Einspieler[4], Peter Marschik[2], Karin Nielsen-Saines[1]

[1] University of California Los Angeles, Los Angeles, CA, United States, [2]Georg-August University of Göttingen, Germany, [3]Fiocruz, Rio de Janeiro, Brazil, [4]Medical University of Graz, Austria

Background

- The long-term neurodevelopmental impact of the SARS-CoV-2 pandemic on prenatally exposed infants is still unknown.
- Early life is a critically important and vulnerable period for neurodevelopment.
- Studies have shown an association between acute respiratory virus infections such as SARS CoV-1 and Influenza and increased risk of neurodevelopmental disorders in offspring including cerebral palsy, autism spectrum disorder and schizophrenia.
- The Prechtl General Movement Assessment (GMA) is a reliable screening tool for identifying infants at risk for neuromotor deficits. GMA was Introduced in 1990 and has been increasingly utilized in the screening of motor dysfunction. It is non-invasive, cost effective and highly reliable tool.
- Between 3 to 5 months post-term age, GMAs appear as fidgety movements, small movements of the neck, trunk, and limbs in all directions and of variable acceleration indicating a normal neurological development. Abnormal fidgety movements with exaggerated amplitude, speed and jerkiness may point to neurological deficits, but it is the absence of fidgety movements that is strongly related to the development of severe neurological deficits.

Objectives

- To assess the integrity of the developing nervous system by analyzing the neuromotor repertoire at 3-5 months postterm age in infants exposed to SARS-CoV-2 infection *in utero* using GMA.

Methods

- The COVID-19 outcomes in Mother-Infant Pairs (COMP) study is a longitudinal cohort where infants prenatally exposed to SARS-CoV-2 during any trimester in pregnancy were recruited in Los Angeles, and Rio de Janeiro, Brazil between March 2020 to the present.
- Infants exposed to SARS CoV-2 *in utero* were matched 1:1 by gestational age, gender, and age at video recording to normal, pre-pandemic neurotypical controls from the Univ Graz database.

Results

- 114 SARS CoV-2 exposed infants were evaluated using the general movement assessments (GMAs) by video recordings, lasting 2-3 minutes, of active wakefulness lying in supine position without manipulation.
- Motor Optimality score (MOS) were generated for each infant, based on age-specific movement repertoire, postural patterns, and movement character.
- The reported median MOS for typically developing infants (neurotypical infants) is 26.
- Among the 114 infants, MOS ranged from 9-28,with a median of 23, and IQR 21-24.
- 8 infants (7%) scored between 9-16 points
- 8 infants (7%) scored between 17-19 points
- 79 infants (69%) scored between 20-24 points
- 20 infants (17%) scored between 25-28 points.
- 29 preterm infants (born before 37 weeks) had a median MOS score of 23 (IQR 21-24). There were 4 multiple-births (10 infants).
- An average MOS of 20 points or higher is seen as non-pathological. This was the case in most infants within the cohort.
- 14.0% of babies had scores lower than 20 and should be closely followed.

Conclusions

- Compared to controls, COVID-exposed infants had lower MOS scores, less frequent age adequate repertoires, a higher frequency of abnormal movement patterns and abnormal postural patterns, and more frequent alterations in movement character. Associations between MOS score and maternal disease severity or with trimester of maternal infection were not statistically significant.
- Lower median scores could reflect heightened stress caused by infection during pregnancy and the deviance may be transient, with normal outcomes for most infants, but this remains to be seen.
- SARS *CoV-2 in utero* exposed infants require long term follow-up.

Table 1. Motor Optimality Scores (MOS) of 114 infants grouped by maternal Covid-19 disease severity and trimester of maternal infection in pregnancy. Numbers indicate the range of MOS in the cell. Italic formatted number indicate the cell mean and (median). p = 0.09.

	N = (114)	1st (n=17)	2nd (n=36)	3rd (n=61)	Mean
Severity	Asymptomatic (n=16)	19 (1) -	21 (1) -	10 – 28 (14) *21.8 (22)*	**21.81**
	Mild/Moderate (n=77)	12 - 28 (15) *21.8 (23)*	12 - 28 (23) *21.8 (23)*	9 - 28 (39) *21.9 (23)*	**21.86**
	Severe/Critical (n=21)	21 (1) -	17 - 28 (12) *22.1 (23)*	20 - 24 (8) *21.9 (23)*	**22.0**
	Mean	**21.86**	**21.98**	**21.89**	**21.9**

Table 2. Clinical Characteristics and Motor Behavior at 3-5 Months Post-term age

	Covid-19 Exposed	Controls	p-value
Male, No. (%)	59 (51.7)	63 (54.8)	0.69
Preterm birth, No. (%)			
<34 wk gestation	12 (10.5)	12 (10.4)	0.999
34-36 + 6 wk gestation	17 (14.9)	16 (13.9)	0.999
Weeks of gestation at the time of infection, wk, No. (%)			
≤13	17 (14.9)	NA	NA
14-28	36 (31.6)	NA	
>=29	61 (53.5)	NA	
Age at GMA, wk, No. (%)			
9-12	39 (33.9)	39 (33.9)	NA
13-16	46 (40.0)	46 (40.0)	
17-20	30 (26.1)	30 (26.1)	
Fidgety movements, No. (%)			
Normal	107 (93.0)	115 (100)	
Abnormal exaggerated	8 (7.0)	0	
Absent	0	0	0.007
Motor Optimality Score			
Median (IQR) [range]	23 (21-24) [9-28]	25 (24-26) [20-28]	<0.001
Optimal range of 25-28, No. (%)	20 (17.4)	63 (54.8)	
Reduced ≤24, No. (%)	95 (82.6)	52 (45.2)	<0.001
Repertoire, No. (%)			
Age adequate	32 (27.8)	48 (41.7)	
Not age adequate	83 (72.2)	67 (58.3)	0.038
Movement patterns, apart from fidgety movements, No. (%)			
More normal than abnormal	102 (88.7)	115 (100)	
Normal equals to or less than abnormal	13 (11.3)	0	<0.001
Postural patterns, No. (%)			
More normal than abnormal	33 (28.7)	86 (74.8)	
Normal equals to or less than abnormal	82 (71.3)	29 (25.2)	<0.001
Movement character, No. (%)			
Smooth and Fluent	25 (21.7)	55 (47.8)	
Abnormal but not cramped-synchronized	90 (78.3)	60 (52.2)	<0.001
Cramped-synchronized	0	0	NA

UCLA Mattel Children's Hospital
Children's Discovery & Innovation Institute

FIOCRUZ Fundação Oswaldo Cruz

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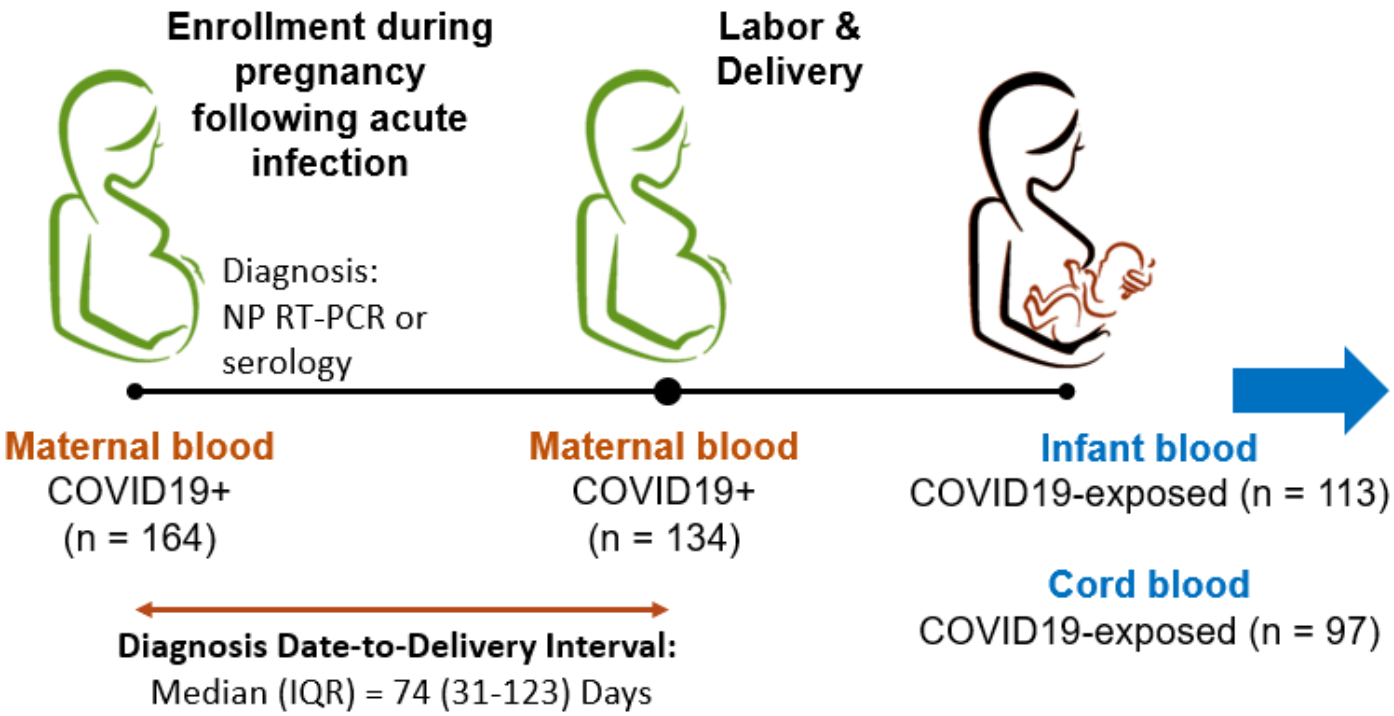
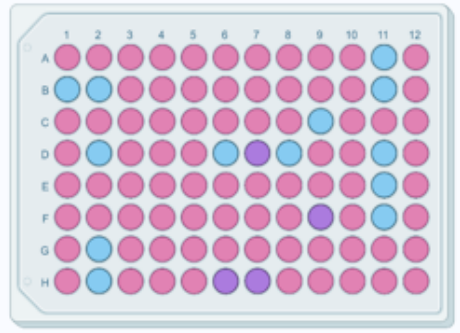
Details of the COMP study can be found at PMID34723226

Maternal & infant antibody responses and placental antibody transfer at labor & delivery to SARS-CoV-2 infection / vaccination in pregnancy



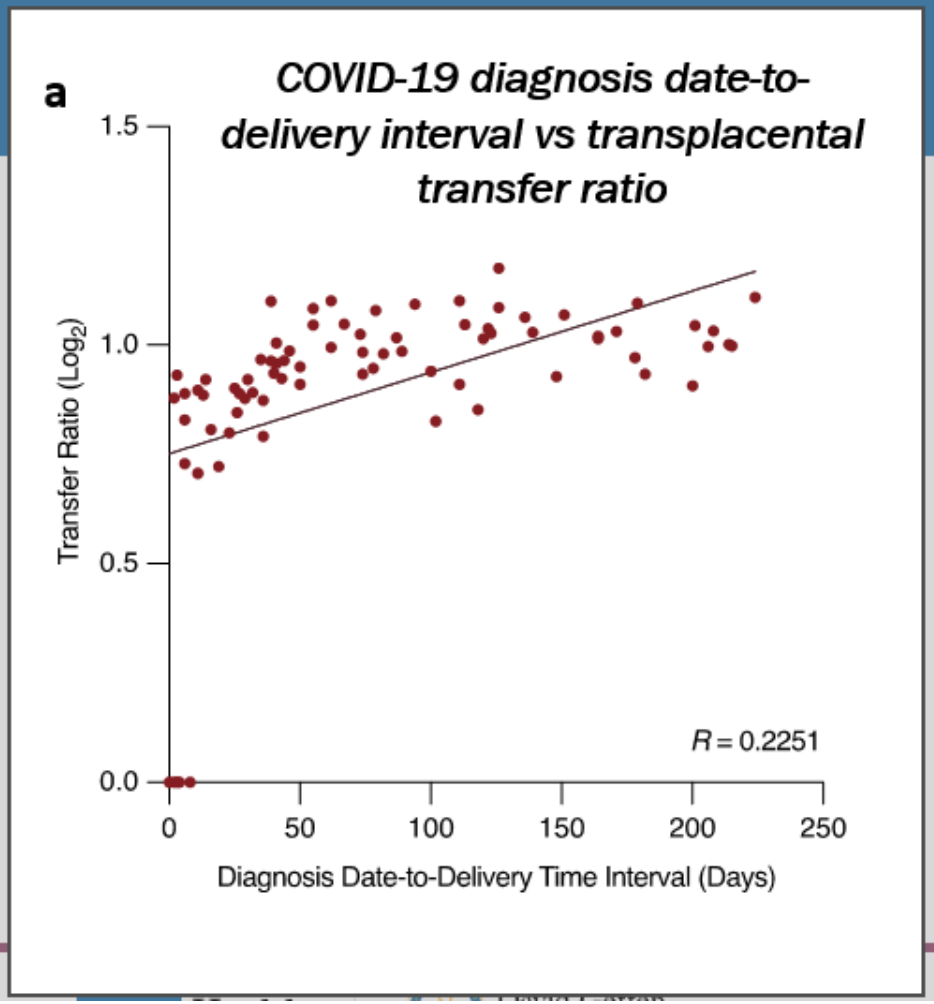
ELISA:
Anti-SARS-CoV-2 IgA, IgG, and IgM

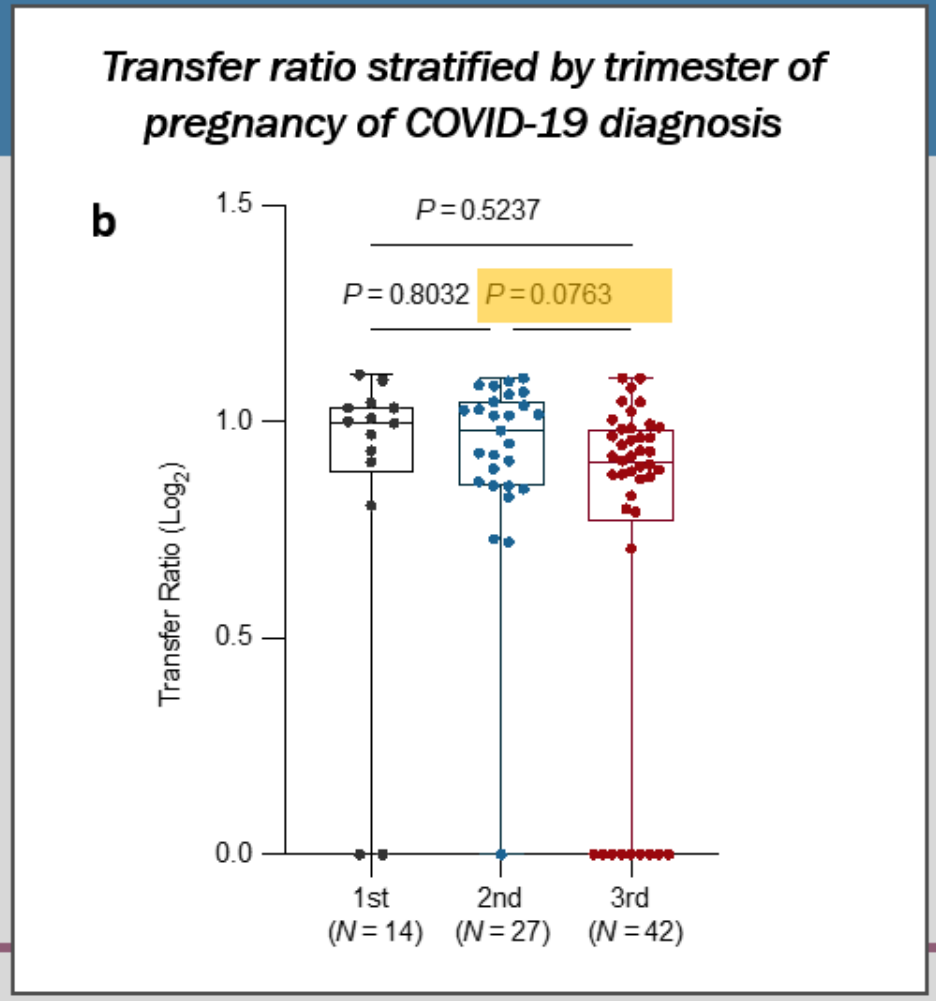


Serology of Mother-Infant Dyads Infected with SARS-CoV-2 During Pregnancy

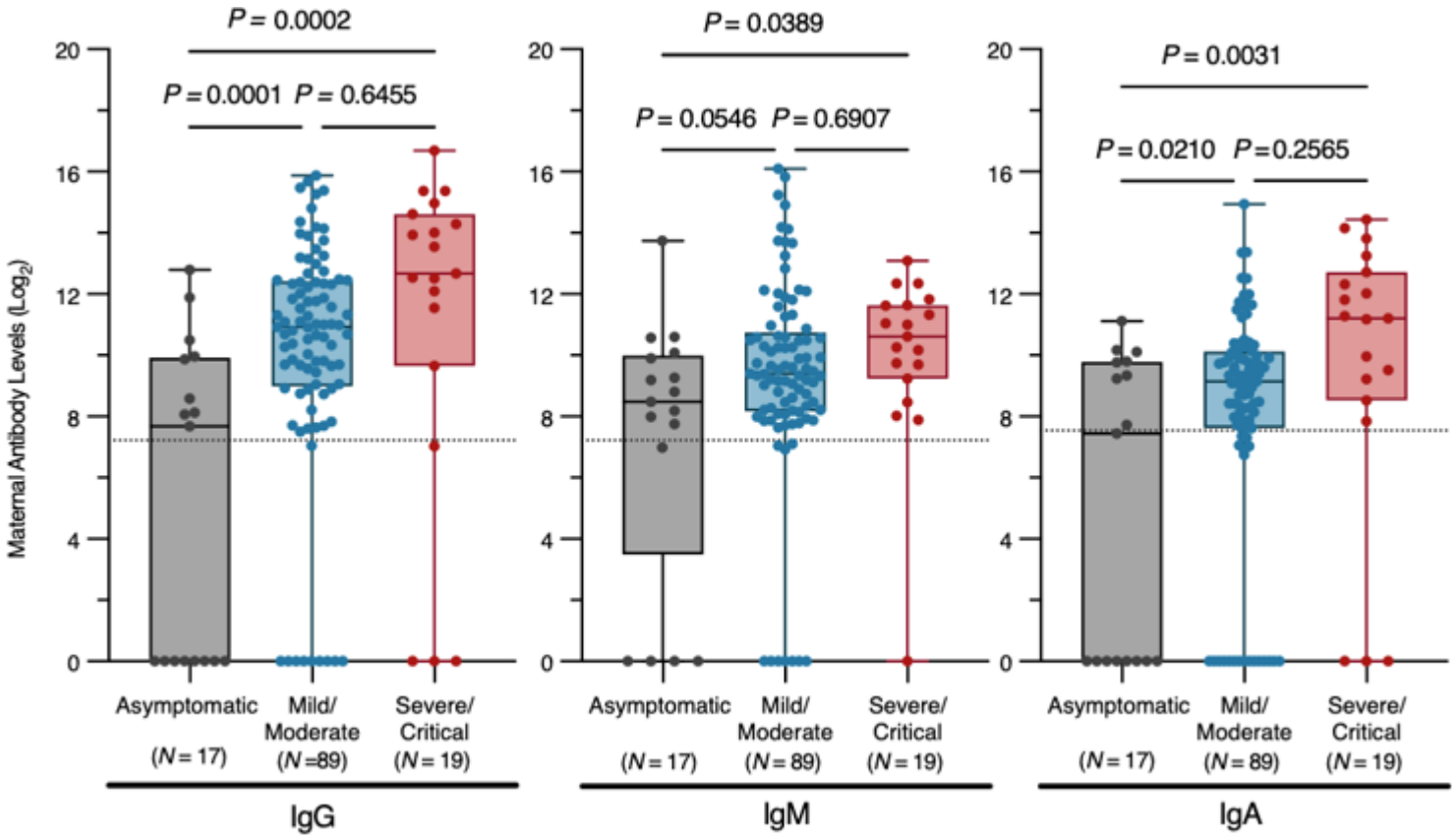
	Maternal Serum at L&D	Cord Blood	Infant Serum at Birth
Anti-SARS-CoV-2 IgG, IgM, and IgA	N = 134	N = 97	N = 113
	N (% of Total)	N (%)	N (%)
IgG + Total	114 (85)	81 (98)	87 (77)
IgM+ Total	120 (90)	10 (12)	1 (1)
IgA+ Total	108 (81)	10 (12)	1 (1)
IgG (+) / IgM (+)/ IgA (+) (all 3 present)	97 (72)	6 (7)	1 (1)
Seronegative	6 (4)	13 (13)	26 (23)

Transplacental IgG transfer was high following natural in utero SARS-CoV-2 infection correlating with timing of infection prior to delivery. Maternal vaccination & severe COVID-19 yielded higher Ab levels in mothers and infants at delivery. 50% NAb was present in 68% of mothers & 42% of infants tested

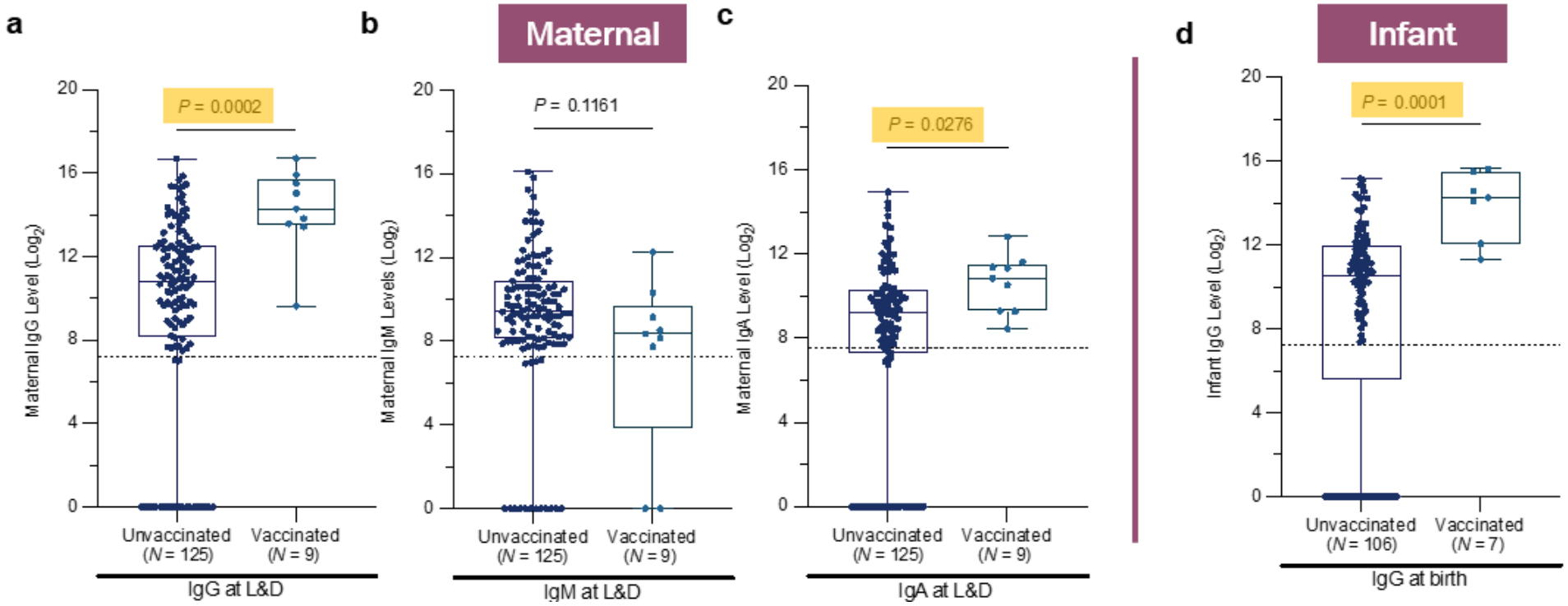

a
COVID-19 diagnosis date-to-delivery interval vs transplacental transfer ratio
Transfer Ratio (Log2)
1.5
1.0
0.5
0.0
R = 0.2251
0
50
100
150
200
250
Diagnosis Date-to-Delivery Time Interval (Days)


Transfer ratio stratified by trimester of pregnancy of COVID-19 diagnosis
b
P = 0.5237
P = 0.8032
P = 0.0763
Transfer Ratio (Log2)
1.5
1.0
0.5
0.0
1st (N = 14)
2nd (N = 27)
3rd (N = 42)

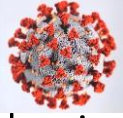
Maternal antibody levels at L&D stratified by COVID-19 Disease Severity



Comparison of mother-infant antibody responses at L&D to maternal vaccination and SARS-CoV-2 natural infection



Conclusions



- Pregnancy confers an increased risk of infection due to dynamic immunologic changes that facilitate fetal growth
- COVID-19 in pregnancy may be associated with increased risk of maternal ICU admissions, ARDS, and adverse pregnancy outcomes
- Minority and disenfranchised pregnant women are disproportionately impacted by COVID-19 as a result of systemic inequities.
- Pregnant women with severe/critical COVID-19 exhibit distinct immune signatures that may explain clinical manifestations.
- Nearly all clinical trials excluded pregnant women, although remdesivir, dexamethasone, monoclonal antibodies and convalescent plasma are still recommended when appropriate.
- SARS-CoV-2 vaccines were not tested in pregnant women, but should be offered to all pregnant individuals.
- Low risk of SARS CoV-2 MTCT, but long term infant follow-up recommended.

COMP Study

Pregnant women in this cohort with severe/critical disease were more likely to be Latina, have public insurance, and have at least one underlying medical condition, reflective of systemic racism/inequities

SARS-CoV-2 infection re-shaped maternal immunity at delivery, potentially promoting late pregnancy- and postpartum-related complications

SARS-CoV-2 infection in pregnancy appears to trigger NF-κB-dependent proinflammatory immune activation

Cytokines do not appear to cross the placenta.

Neonates with in-utero exposure to severe/critical COVID-19 maternal disease exhibited dysregulated Wnt signaling, which may impact immunity and neurodevelopment.

Take home points

- ❑ Pregnant women are at higher risk of developing COVID-19 related complications and their infants are at risk of being premature and having respiratory distress at birth, even if not infected.
- ❑ Mother to child transmission of SARS CoV-2 is rare.
- ❑ Infants born to women who had COVID-19 in pregnancy should be followed closely for neurodevelopment, regardless of whether the mother has severe illness.
- ❑ Maternal antibodies to COVID-19 cross the placenta and protect the fetus when the mother was vaccinated or had moderate to severe illness. Vaccination confers the highest antibody levels to the infant.
- ❑ By six months of age, maternal antibodies to SARS CoV-2 transferred to the infant have waned.

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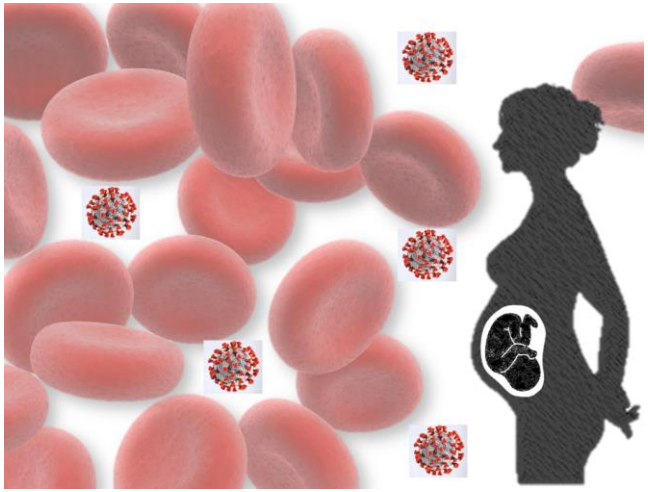

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Any questions?