The outcome of 216 pregnancies with maternal COVID-19: a fast, systematic review

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This communication consists of two tables from systematic reviews. They are from peer reviewed guidelines in Swedish about COVID-19 (infection with the corona virus SARS-CoV-2), published by www.internetmedicin.se. Their guidelines are not official but highly regarded and much used. My guidelines are compatible with official guidelines, if they exist. Unfortunately, my English is not revised by a translator.

Method

Literature was searched up to April 12, 2020. PubMed was searched for "Covid-19 and pregnancy" and "Covid-19 and child*". Studies that contained clinical data on mothers and/or newborn babies (who 0-10 days old became sick or colonized with SARS-CoV-2) were selected for inclusion in my review. The reference lists of the selected studies and of review articles were also searched. Tables of contents in several journals were searched from 1 January 2020: Acta paediatrica, ADC, AOG, BMJ, JAMA, JAMA Pediatrics, Lancet, Lancet infection diseases, Lancet respiratory diseases, NEJM, Pediatrics, Journal of pediatrics.

In systematic reviews, a second researcher independently should check the extraction of data from the study made by the first researcher. Due to time constrains, it was not possible to ask busy clinicians to do this. Therefore, before submitting the manuscript, I reread all cited studies and checked all data in the tables.

Summary of Table 1: Outcome of pregnancies complicated with maternal COVID-19

In 3 cases, symptoms of maternal COVID-19 didn't appear until the first days after delivery.

Countries: China, Iran, South Korea, Sweden, Turkey.

Number of pregnancies: 216 (vaginal 38, section 155, unknown 3)

Number of live newborns: 214 (3 legal abortions, 2 pairs of twins, 1 miscarriage)

Mode of delivery: vaginal 34, cesarean sections 172, unknown method 6

Length of pregnancy at delivery: 25-41 weeks (most newborns were term)

Seriously ill or dead mothers: One mother was treated with ECMO at time of publication (Liu, Chen et al. 2020). To mothers in Iran died of ARDS after delivery; details were not published (Karimi-Zaorchi 2020).

Seriously ill or dead newborn babies: Data in Table 1 indicate that COVID-19 in pregnant women usually has benign courses for mothers and children, at least after

infections in the third trimester. However, one pregnancy ended with a miscarriage (Liu, Chen et al. 2020).

One boy, born after 34 weeks + 5 days, died when 9 days old of DIC and MODS. The mother caught fever 3 days after delivery and the boy became ill the day before his death, with tachycardia, refractory shock and gastric bleeding. The authors didn't mention any treatment except transfusion of blood components and didn't suggest any diagnosis. They mentioned viremia but it is unclear if it is a finding or a hypothesis. (Zhu 2020)

Vertical transmission: 100 newborns were PCR positive in throat and/or nasal tests for SARS-CoV-2. For most of them, tests were also collected from e.g. amnion fluid, umbilical cord, breastmilk and placenta; these test were also negative. Four nasopharynx swabs were positive for COVID-19-virus at age 2-3 days. These infants had breathing difficulties but both mothers and infants recovered without problems.

A positive COVID was collected from a newborn in London a few minutes after birth but it was not known if virus had infected the baby *in utero* or in the vagina (Murphy 2020; baby not included in Table).

Two of 6 newborns delivered by mothers who were moderately ill in COVIR-19 had high titers of IgM antibodies for COVIR-19-virus. "M" in IgM means "macro", i.e. the molecule is not usually transferred from mother to fetus because of its size. Therefore, it is possible that virus has penetrated the fetus and stimulated its production of IgM. This was supported by an increase of interleukin-6 as a sign of infection. The infants were fine with no sign of illness. (Zeng H 2020) Another infant had also high levels of IgM for COVID-19-virus and interleukins 2 hours after birth (Dong L 2020). It is, however, known that interleukins can cross the placenta barrier and there have been false positive IgM values in other congenital infections. The findings by Zeng and Dong and their coworkers may therefore be artefacts. (Kimberlin 2020)

Limitations

Risk for duplicated publication of pregnancies is a risk. We have read the studies in full if English text has been available and compared the names and addresses of authors. We haven't found any suspicions of redundant publications but duplications cannot be ruled out.

Table 1. Outcome of pregnancies complicated with maternal COVID-19

Reference (country)	Number of pregnancies /CS	Gestational age at illness onset (weeks+ days)	Complications during pregnancy (in addition to maternal COVID-19)	Deaths in mother or child; complications after delivery	Vertical transmittance of virus to newborns
Chen H (China)	9/9	36-39	Fetal distress, PROM, hypertonia, pre-eclampsia, influenza	0/0; no complications	No (amniotic fluid, cord blood, babies' throat swab, and breastmilk from 6 patients were tested)
Chen S, Huang B et al. (China), cited by RCOG (2020:2)	3/?	?	?	?	No (three placentas of infected mothers were swabbed and tested negative)
Chen S, Liao E et al. (China)	5/2	38-41	Gestational diabetes (2 mothers), preeclampsia (1), fetal tachycardia (1)	0/0; excellent clinical course	No (probably throat and/or nasal swab)
Dong L (China)	1/1	34+2 (CS 37+4)	No	0/0	Yes? 2h after birth, the baby's blood contained IgM for SARS-CoV-2 and cytokines
Fan (China)	2/2	37, 36	No	0/0	No (7 different tissues examined in each baby)
Gidlöf (Sweden)	1/1 (twins)	36+2; CS the same day	Severe preeclampsia; gestational diabetes (BMI 38 at first antenatal visit)	0/0	No (PCR mother's nasal swab +, breastmilk -, vaginal secretions -; infant's nasal swab -)
Kalafat (Turkey)	1/1	35+3 (day 0, first day with symptoms)	Day 1: PCR- (nasal and throat swabs); day 3: US lungs+; day 5:US lungs+, CT lungs+, PCR+, CS due to hypoxemia	?/0 The mother was still in the ICU at time of writing	No (blood from umbilical cord, swabs from placenta, infant's nose and throat, and breastmilk were all -)
Khan (China)	17/17	35-41	3 preterm deliveries	0/0; pneumonia in 5 newborns	No(?) (All 17 throat swabs were – at delivery but 2 swabs were + within 24 hours. Conflicting data if cord blood was analyzed.)
Lee (South Korea)	1/1	36+2	CS at 37+6 due to obstructed labor	0/0	No (PCR- for nasal swab (x2), placenta, amniotic fluid, and cord blood)

Li N (China)	34/32 (18 of them were PCR- but CT lung+)	No data	Significantly increased numbers of preterm deliveries; gestational diabetes and hypertension	No severe maternal or neonatal complications	No ("COVID-19 infection was not found in the newborns" but only 3 babies were tested (throat swabs))
Li Y (China)	1/1	35	Emergency CS due to fetal bradycardia. No other complication.	0/0	No. The infant's throat swab, blood, feces, and urine samples were - at 7 different times. On the delivery day, the woman's sputum was + but serum, urine, feces, amniotic fluid, umbilical cord blood, placenta, and breast milk were -.
Liang (China) cites anonyme researchers	18/2 (i.e. 16 PN)	?	?	?	No (methods not specified)
Liu D (China)	11/10 (15 pregnancies; 4 still pregnant)	12-38 (delivered at 34-38 weeks)	All 15 mothers had mild COVID-19 and recovered	0/0	No? (The study says "No SARS-CoV-2 infection was found in the neonates"; methods not specified)
Liu W (China)	3/2	38-40	One fetus had fetal distress and chorioamnionitis	0/0	No
Liu Y	10 CS; 3 healthy, on-going pregnancies	25-38	5 emergency CS due to fetal distress (3 cases), PROM (1), stillbirth (1). The 9 live born babies had Apgar 1' =10.	0?/1. One mother in ECMO at time of publication, after MODS, ARDS and septic shock.	No
Tasnim Agency, cited by Karimi-Zarchi (Iran)	3/?	?	?	2/0 two mothers died of ARDS	No ("their neonates were negative when tested for COVID-19")
Wang	1/1	30	Severe maternal pneumonia; pathological CTG	0/0 (mother and baby well after delivery)	No
Wen	0/0 (ongoing pregnancy)	30	No complications so far. COVID-19 healed after treatment with interferon.	The baby was not born at time of publication	Unknown

Wu	23/18 (2 vaginal, 3 legal abortions)	3 ≤12 weeks, 20 ≥28 weeks	No	21 healthy babies (1 pair of twins)	4 PCR-, 17 clinically healthy
Xiong	1/0	33+1	PN at 38+4	No	No, inclusive neonatal IgG and IgM antibodies to SARS-CoV-2 were both negative
Yu	7/7	37-41	Influenza, Legionella	0/0; no complications except SARS-CoV-2 (see right)	3 infants tested; 1 had SARS-CoV-2 virus and mild respiratory signs when 36 hours old; follow-up uneventful
Zeng H	6/6	3rd trimester		0/0, healthy	2 neonates had IgM for SARS-CoV-2
Zeng L	33/26	4 preterm babies	No	0/0; 2 term infants had lethargy, fever and pneumonia; one preterm (31w+2d) had fetal distress, RDS, DIC and sepsis. Follow-up was uneventful.	The 3 sick infants (see left) had SARS-CoV-2 in nose and anus when 2 days old. No data on virus in the other 30 infants.
Zhang, cited by Schwartz	16/16	35-41	Normal rate of complications		No (negative throat swabs in 10 babies)
Zhu	9/7 (10/7 babies). 3 mothers became sick in COVID-19 1-3 days pp.	31-39; 6 babies were preterm	Fetal distress (6 cases).	0/1 One child died of MODS at 9 days of age.	No (negative throat swabs in 9 babies)
Sum	**216 CS: 172 PN: 34 Stillbirth: 1 Legal abortions: 3 Unknown mode of delivery: 6**			**2 mothers dead in ARDS; 1 infant dead of MODS**	**100 PCR-, 3 IgM+, 4 PCR+ 24-36 h PP**

Abbreviations: ARDS, acute respiratory distress syndrome; CS, cesarean section; ECMO, extracorporeal membrane oxygenation; IgM, immunoglobulin M; MODS, multiple organ dysfunction syndrome; PCR, polymerase chain reaction for detecting SARS-CoV-2; PP, post partum (after delivery); PN, partus normalis (normal, vaginal delivery); PROM, premature rupture of membranes; US, diagnostic ultrasound.

*In most cases, the pregnant woman delivered within one week after the beginning of COVID-19 symptoms.

Deleted studies

Liu H 2020: Very few clinical data.

Review which have been reviewed for missed primary studies

Dashraath (2020)

Fretheim A. Barns rolle i spredning av SARS-CoV-2 (Covid-19) – en hurtigoversikt. Hurtigoversikt, 2020. Oslo: Folkehelseinstituttet, 2020. *No relevant reference.*

Panahi (2020)

Parazzini (2020)

RCOG 2020:8

Table 2. Case– fatality rate (%) for reported COVID–19 cases, by age group, in 5 countries in the year 2020. Data were collected up to the following dates: China 11 February, Italy 9 April, Japan 12 April, South Korea 11 April, Sweden 13 April and the USA 16 March.

Age (years)	**0-9**	**10-19**	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**≥80**	**Total**
China*	0	1	7	18	38	130	309	312	208	1023**
	0	0,2	0,2	0,2	0,4	1,3	3,6	8,0	14,8	2,3
Italy	1	0	7	36	153	638	1957	5366	8495	16654
	0,1	0	0,1	0,4	0,9	2,4	9,0	23,4	29,8	12,2
Japan	0	0	0	0	2	6	9	37	47	101
South Korea	0	0	0	1	3	14	29	63	101	211
	0	0	0	0,1	0,2	0,7	2,2	9,1	21,3	2,0
Sweden	0	0	3	2	4	35	66	236	573	919
Age (years)	**0-19**		**20-44**		**45-54**	**55-64**	**65-74**	**75-84**	**≥85**	**Total**
USA	3***									
			0,1		0,5	1,4	2,7	4,3	10,4	1,8

Source: CCDC; ISS; Ogiwara; KCDC; FHM; CDC-MMWR. *For each country, total numbers of deaths are shown on the first line and CFR (case fatality rates) on the second line. **The number of COVID deaths in China was 2611 on March 27, 2020 (National Health Commission of the People's Republic of China). ***CDC declared on April 6 that 3 children (<18 years old) were reported dead by COVID-19.

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