Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Evidence summary of placental transfer of antibodies

13 May 2020

Evidence summary for placental transfer of antibodies

Key points

- In total, four studies were identified; two studies included pregnant women with laboratory-confirmed SARS-CoV-2, and one study each with laboratory-confirmed MERS-CoV and SARS-CoV-1.
- Thirteen unique maternal and neonatal pairs were included.
- All included newborn infants tested negative for the presence of laboratory-confirmed coronavirus spectrum infections based on reverse-transcription polymerase chain reaction (RT-PCR) tests of nasopharyngeal or throat swabs.
- Twelve out of 13 newborns had detectable elevated coronavirus-specific antibody levels reported at birth or in the following days. The possibility of cross-reactivity with other respiratory pathogens cannot be ruled out, neither can the possibility of false positives from antibody tests.
- Not all studies included antibody testing of amniotic fluid or placenta. Therefore, the passive transfer of antibodies from mother to infant cannot be confirmed.
- Elevated neonatal immunoglobulin M (IgM) antibody levels reported in two studies, may be suggestive of infection in utero since IgM does not cross the placenta. However, it could potentially be attributable to placental pathology or laboratory error, therefore these results should be interpreted with caution.
- It is unclear if the antibody levels reported in these neonates are sufficiently high enough to achieve immunity.

Introduction

The Health Information and Quality Authority (HIQA) has developed a series of 'Evidence Summaries' to assist the Clinical Expert Advisory Group (EAG) in supporting the National Public Health Emergency Team (NPHET), as well as those developing infection prevention and control guidance in their response to COVID-19. These summaries are based on specific research questions. This evidence summary was developed to address the following research question:

"Is there evidence for placental transfer of antibodies from infected mothers that confers immunity in the newborn in coronavirus spectrum infections?"

The processes as outlined in HIQA's protocol, available on www.hiqa.ie, were followed. Below is the summary of all relevant studies from 1 January 2000 until 23 April 2020.

Results

Five studies were identified, three case series[1-3] and two case reports.[4, 5] Two studies were from mainland China,[3, 4] two from Hong Kong,[1, 2] and one from South Korea.[5] While not explicitly referenced, it is highly likely that the two case series from Hong Kong[1, 2] are reporting on the same five cases, given the similarity of demographic characteristics (see Table 1). Consequently, they are not presented as unique studies in the following results. Overall, 13 unique maternal and neonatal pairs were included. Mothers ranged in age from 27 to 39 years of age. Two studies included pregnant women with laboratory-confirmed SARS-CoV-2,[3, 4] the virus that causes COVID-19. One study included pregnant women with laboratory-confirmed MERS-CoV,[5] which causes Middle East respiratory syndrome (MERS) and the remaining study included pregnant women SARS-CoV-1,[1, 2] the virus that causes Severe Acute Respiratory Syndrome (SARS).

Neonatal laboratory-confirmed coronavirus

Across all included studies, all 13 neonates tested negative for the presence of laboratory-confirmed coronavirus based on reverse-transcription polymerase chain reaction (RT-PCR) tests of nasopharyngeal or throat swabs.[1-5] Samples were collected for testing at time of birth[3, 4] or in the days and weeks following birth.[1, 2, 5]

Placental transfer of coronavirus spectrum infection antibodies

Three original studies reported the presence of antibodies to coronaviruses in neonatal samples.[1-4] Two of these studies comprised mothers with laboratory-confirmed SARS-CoV-2 (n=7) all of whom had detectable anti-SARS-CoV-2 antibodies.[3, 4]

In a case series of six women with SARS-CoV-2, virus-specific antibodies were detected in blood sera samples of all six newborns at birth. However, four of the six infants had virus-specific immunoglobulin M (IgM) concentrations below the threshold for a positive result (<10 AU/mL).[3] Immunoglobulin G (IgG) antibody levels were higher than the reference value in five neonates. No testing of cord blood or amniotic fluid was performed. Delivery was by caesarean section in all cases. All mothers wore face masks, and all medical staff wore protective suits and double masks. The infants were isolated from their mothers immediately after delivery.[3] In a case report of a mother with SARS-CoV-2 from China, the neonate had a SARS-CoV-2 IgG level of 140.32 AU/mL and an IgM level of 45.83 AU/mL two

hours after birth.[4] No testing of amniotic fluid or placenta was performed. Delivery was by caesarean section in a negative-pressure isolation room. The mother wore an N95 face mask and did not hold the infant.[4] The time between the mother's diagnosis of COVID-19 to delivery was 23 days.

In a case series from Hong Kong of mothers with a laboratory-confirmed diagnosis of SARS-CoV-1, three of the five maternal participants had anti-SARS-CoV-1 antibodies confirmed.[1, 2] Four of the five deliveries were by caesarean section. While the authors report that SARS-CoV-1 was not detected using RT-PCR in any of the infants, all five infants had detectable anti SARS-CoV-1 antibody titres present at birth.[1] No rise in paired serologic (acute and convalescent) titres was found. RT-PCRs and viral cultures of cord blood and placenta tissues were all negative for SARS-CoV-1. The class of antibody detected was not specified as a test detecting a mixture of IgM and IgG was used. It is not stated whether the levels found were sufficient to provide clinical protection.[1, 2] Duration from diagnosis of SARS to delivery ranged from 0 to seven weeks.

In the remaining case report of a mother with MERS-CoV from South Korea, anti-MERS-CoV IgG, but not IgM and IgA, was detected (weakly) in the mother's serum. Antibody tests performed with umbilical cord blood, placenta, and newborn blood were all negative for specific anti-MERS-CoV IgG, IgM, and IgA.[5] Delivery was by emergency caesarean and after delivery, the baby was immediately moved to an airborne infection isolation room. The time between the mother's diagnosis of MERS-CoV to delivery was approximately two weeks.

Study quality and quality of the evidence

The included studies were of low to moderate quality for their design (case series and case reports). The majority of studies had small sample sizes and the identification and selection of cases for inclusion was not always adequately described. Specific details regarding the antibody test (e.g. test type, assay method) were poorly reported across studies, as was the exact timing of the specimen collection.

Discussion and conclusion

The overall level of evidence is low. The limited number of case reports and case series identified in this review included pregnant women with laboratory-confirmed SARS-CoV-2, MERS-CoV and SARS-CoV-1. Overall, 13 unique maternal and neonatal pairs were included.

Detection of coronavirus spectrum antibodies in newborns was reported. In total, 12 out of 13 newborns had detectable coronavirus-specific antibody levels reported. Seven newborns were delivered to mothers with laboratory-confirmed SARS-CoV-2 and five to mothers infected with SARS-CoV-1. Of note, IgG was only weakly detected in the serum of the mother whose infant tested negative for anti-MERS

antibodies. It is possible that antibodies in the neonatal sample were below the limit of detection of the test.

Although antibodies were present in newborn serum within hours of delivery and at later follow-up in some cases, a lot of uncertainty remains. Firstly, it is unclear if the levels reported are sufficiently high to achieve immunity in the infants, or at what point maternal antibodies in the infant may begin to decline. Secondly, it is unclear if antibodies from coronavirus spectrum-infected mothers were actually transmitted to the foetus during pregnancy. Elevated IgM antibody levels may be suggestive of a neonatal immune response (that is, the body's response against infection) to infection in the womb,[3, 4] since IgM does not cross the placenta. SARS-CoV-2 or SARS-CoV-1 was not detected by RT-PCR in any of the newborns, although as the duration between onset of maternal illness and delivery was up to seven weeks in some cases, this may have been sufficient time to develop a primary antibody response to the virus and clear the virus in utero. However, it is possible that placental vascular damage or abnormalities could have resulted in the passage of larger substances than normal such as IgM into the foetal circulatory system. Placental assessment would be necessary to rule out the possibility of transfer of maternal IgM antibodies through placental lesions. Zeng et al.[3] did not report results of placental assessment in the six women. It is also noted that IgM antibodies usually do not appear until 3 to 7 days after infection,[4] so it unlikely that elevated IgM levels detected in one newborn 2 hours post-delivery was as a result of infection during birth. Repeated RT-PCR tests for SARS-CoV-2 were only undertaken up to 16 days post birth in one newborn, and for other newborns a single RT-PCR test was taken at birth (SARS-CoV-2) or within the first five weeks of life (SARS-CoV-1). Therefore, it is not known if the infants remained RT-PCR negative. Lastly, studies did not include antibody testing of amniotic fluid, cord blood or placenta. Therefore, the passive transfer of antibodies from mother to infant cannot be confirmed in these studies. A limited number of studies have reported the presence of antibodies in umbilical cord samples, but these were not confirmed in clinical samples from the newborns, so have not been included in this review.[6, 7]

SARS-CoV-2 has been shown to demonstrate a high degree of similarity to other common human coronaviruses, many of which occur frequently in early childhood.[8] The possibility of cross-reactivity with these coronaviruses or other common human respiratory pathogens cannot be ruled out; data on cross-reactivity for other infections in infants was not reported in any of the studies. Therefore, a positive result from an antibody test may indicate infection from another coronavirus infection, rather than SARS-CoV-2. Additionally, there is currently no reference antibody test for SARS-CoV-2 so the sensitivity and specificity of the tests used is uncertain. More studies with collection of samples including amniotic fluid, placenta, and umbilical cord and neonatal samples such as serum and clearer reporting of the tests used are required.

Cases of vertical transmission (passage of infection from mother to baby during pregnancy and during the period immediately before and after birth) of coronavirus spectrum infection have not been reported previously in the literature.[9, 10] All

included newborns tested negative for the presence of laboratory-confirmed coronavirus spectrum infections based on reverse-transcription polymerase chain reaction (RT-PCR) tests of nose or throat swabs. However, since IgM does not cross the placenta and could represent a neonatal immune response to in utero infection, vertical transmission cannot be ruled out.

Table 1 Summary of identified studies

Author Country Study design	Population setting Maternal characteristics	Test characteristics	Primary outcome results
Dong (2020)[4] **China (Wuhan)** **Case report** **DOI:** **10.1001/jama.2020.4621**	**Population setting:** 1 pregnant female with laboratory-confirmed SARS-CoV-2, confirmed at 34 weeks gestation, Renmin Hospital. **Maternal demographics:** *Age:* 29-year-old *Gravidity:* primiparous **Delivery details** *Gestation:* 37 weeks *Mode:* caesarean in a negative-pressure isolation room. The mother wore an N95 mask and did not hold the infant. **Neonate demographics** *Gender:* Female *Weight:* 3,120g	**Diagnostic Test** RT-PCR *Sample site(s)* *Maternal:* Nasopharyngeal swab *Neonate:* Nasopharyngeal swab (repeated swabs taken from 2 hours to 16 days) **Immunoassay** *Assay test type:* not reported *Assay method:* not reported *Nature of test result:* not reported *Measure target:* IgG and IgM *Type of specimen:* blood *Cross-reactivity:* Not reported	**Coronavirus spectrum infection antibodies** *Maternal* One day prior to delivery: IgG level: 107.89 AU/mL IgM level: 279.72 AU/mL *Neonate* At 2 hours of age: IgG level: 140.32 AU/mL IgM level: 45.83 AU/mL **Neonatal laboratory-confirmed coronavirus (PCR)** Negative (from five RT-PCR tests on nasopharyngeal swabs taken from 2 hours to 16 days). **Pregnancy related material laboratory-confirmed coronavirus (PCR)** Not reported
Jeong (2017)[5] **South Korea** **Case report** **DOI:** **10.3346/jkms.2017.32.10.1717**	**Population setting:** 1 pregnant female with laboratory-confirmed MERS-CoV, confirmed at 35 weeks gestation. **Maternal demographics:** *Age:* 39 years *Gravidity:* not reported **Delivery details** *Gestation:* 37 weeks	**Diagnostic Test** RT- PCR tests *Sample site(s)* *Maternal:* peripheral blood and nasopharyngeal swab, umbilical cord blood and placenta *Neonate:* Nasopharyngeal swab **Immunoassay**	**Coronavirus spectrum infection antibodies** *Maternal* ELISA (IgG): weakly positive, (0.302) IIFT (IgG): the titre of 1:100 IgM and IgA were not detected through ELISA and the PRNT test *Neonate* ELISA and IIFT both negative

	Mode: emergency caesarean (placental abruption). After delivery, the baby was immediately moved to an airborne infection isolation room. **Neonate demographics** *Gender:* Male *Weight:* 3,140g	*Assay test type:* not reported *Assay method:* enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence test (IIFT), plaque reduction neutralisation test (PRNT) *Nature of test result:* not reported *Measure target:* IgG, IgM, IgA *Type of specimen:* umbilical cord blood, placenta, blood (serum) *Cross-reactivity:* Not reported	**Neonatal laboratory-confirmed coronavirus (PCR)** Negative (test conducted 5 days after birth) **Pregnancy related material laboratory-confirmed coronavirus (PCR)** Umbilical cord blood: negative Placenta: negative
Shek (2003)[1] and Wong (2004)[2] **Hong Kong** **Case series** **DOI Shek: doi.org/10.1542/peds.112.4.e254** **DOI Wong: 10.1016/j.ajog.2003.11.019** **Note:** While not explicitly referenced, it is highly likely that these two case series are reporting on the same five cases, given the similarity of demographic characteristics	**Population setting:** 5 pregnant females with laboratory-confirmed SARS-CoV-1. **Maternal demographics:** *Age:* 27 to 34 years *Gravidity:* Not reported **Delivery details** *Gestation:* 26 to 32 weeks *Mode:* 4 (80%) caesarean section, 1 (20%) spontaneous preterm labour **Neonate demographics** *Gender:* 3 Male, 2 female *Weight:* 975g to 1,985g	**Diagnostic Test** RT-PCR *Sample site(s)* *Maternal:* maternal stool samples (n=2); nasopharyngeal aspirates (n=1); maternal stool, cerebrospinal fluid, and peritoneal fluid (n=1); throat and nasal swabs (n=1). Cord blood, placenta tissue, and amniotic fluid at or after delivery. *Neonate*: Throat swab, rectal, serum, (taken in the first 5 weeks of life) **Immunoassay** *Assay test type:* not reported *Assay method:* ELISA paired acute (days 1–9) and convalescent (days 21–23) titres for maternal and neonatal samples *Nature of test result*: Qualitative	**Coronavirus spectrum infection antibodies** *Maternal* SARS-CoV antibody titre >100: 3/5 (60%) 2/5 (40%) not reported Rise in paired acute and convalescent SARS-CoV antibody titre: 2/5 (40%) Patient 1: Acute antibody titres: <1:25 Convalescent antibody titres: 1:400. Patient 2: Acute antibody titres: <1:25 Convalescent antibody titres: 1:600. *Neonate* Paired acute and convalescent titres: Patient 1 to 3 = <1:25/<1:25 Patient 4: 1:50/1:50 Patient 5: 1:200/1:200 Rise in paired acute and convalescent SARS-CoV antibody titre: 0/5 (0%)

		Measure target: immunoglobulin M and G *Type of specimen:* blood (serum) *Cross-reactivity:* Maternal viral serology for adenovirus, influenza A and B, parainfluenza type 1 to 3, and respiratory syncytial virus were negative.	**Neonatal laboratory-confirmed coronavirus (PCR)** Negative in all samples. **Pregnancy related material laboratory-confirmed coronavirus (PCR)** Umbilical cord blood: negative Placenta: negative Amniotic fluid: negative **Other findings of relevance:** Wong et al.[2] reported on 12 pregnant females admitted to 5 public hospitals with suspected SARS-CoV-1. 5/12 (41.7%) resulted in live deliveries with 7/12 early pregnancy losses. For the full 12 cases the following outcomes were reported: Maternal deaths: 3/12 (25%) Early pregnancy loss: 1 Spontaneous miscarriages: 4 Abortions: 2
Zeng (2020)[3] **China (Wuhan)** **Case series** **DOI:** **10.1001/jama.2020.4861**	**Population setting:** 6 pregnant women with laboratory-confirmed SARS-CoV-2, Zhongnan Hospital. **Maternal demographics** *Age range:* Not reported *Gravidity:* Not reported **Delivery details** *Gestation:* Not reported *Mode:* 6 (100%) caesarean section. All mothers wore masks, and all medical staff wore protective suits	**Diagnostic Test** RT-PCR Sample site(s) Maternal: Blood at delivery Neonate: Blood and throat swab at birth **Immunoassay** *Assay test type:* not reported *Assay method*: not reported *Nature of test result*: not reported	**Coronavirus spectrum infection antibodies** *Maternal* Antibodies detected: 6/6 (100%) IgM: 1.39 to 236.6 AU/mL IgG: 8.12 to 136.7 AU/mL *Neonate* Antibodies detected: 6/6 (100%) IgM range: 0.16 to 39.6 AU/mL IgG range: 7.25 to 125.5 AU/mL IgG and IgM higher than the normal level (<10 AU/mL): 2

	and double masks. The infants were isolated from their mothers immediately after delivery. **Neonate demographics** *Gender:* Not reported *Weight:* Not reported	*Measure target:* IgG and IgM *Type of specimen:* blood (serum) *Cross-reactivity:* not reported	**Neonatal laboratory-confirmed coronavirus (PCR)** Negative in all samples. **Pregnancy related material laboratory-confirmed coronavirus (PCR)** Not reported

References

1. Shek CC, Ng PC, Fung GPG, Cheng FWT, Chan PKS, Peiris MJS, et al. Infants Born to Mothers With Severe Acute Respiratory Syndrome. Pediatrics. 2003;112(4):e254-e.

2. Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, Shek CC, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol. 2004;191(1):292-7.

3. Zeng H, Xu C, Fan J, Tang Y, Deng Q, Zhang W, et al. Antibodies in Infants Born to Mothers With COVID-19 Pneumonia. Jama. 2020:e204861.

4. Dong L, Tian J, He S, Zhu C, Wang J, Liu C, et al. Possible Vertical Transmission of SARS-CoV-2 From an Infected Mother to Her Newborn. Jama. 2020:e204621.

5. Jeong SY, Sung SI, Sung JH, Ahn SY, Kang ES, Chang YS, et al. MERS-CoV Infection in a Pregnant Woman in Korea. J Korean Med Sci. 2017;32(10):1717-20.

6. Jiang X, Gao X, Zheng H, Yan M, Liang W, Shao Z, et al. Specific immunoglobulin g antibody detected in umbilical blood and amniotic fluid from a pregnant woman infected by the coronavirus associated with severe acute respiratory syndrome. Clin Diagn Lab Immunol. 2004;11(6):1182-4.

7. Robertson CA, Lowther SA, Birch T, Tan C, Sorhage F, Stockman L, et al. SARS and pregnancy: a case report. Emerg Infect Dis. 2004;10(2):345-8.

8. Dijkman R, Jebbink MF, Gaunt E, Rossen JWA, Templeton KE, Kuijpers TW, et al. The dominance of human coronavirus OC43 and NL63 infections in infants. J Clin Virol. 2012;53(2):135-9.

9. Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of Coronavirus spectrum infections (SARS, MERS, COVID 1 -19) during pregnancy: a systematic review and meta-analysis. American Journal of Obstetrics & Gynecology MFM. 2020:100107.

10. Schwartz DA. An Analysis of 38 Pregnant Women with COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2: Maternal Coronavirus Infections and Pregnancy Outcomes. Archives of Pathology & Laboratory Medicine. 2020;0(0):null.