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Review

Maternal COVID-19 Vaccine May Reduce the Risk of MIS-C in Infants: A Narrative Review

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Abstract: COVID-19 infection in the pediatric population usually leads to a mild illness, however, a rare but serious complication of MIS-C has been seen in children. MIS-C usually presents 2-4 weeks after COVID-19 infection or exposure, and rare reports have been documented in neonates. Vaccinations for COVID-19 have been approved for children 6 months and above in the United States, and recent reports suggest significantly low prevalence and risk of complications of MIS-C in vaccinated children compared to unvaccinated children. Vaccinations for COVID-19 are safe and recommended during pregnancy and prevent severe maternal morbidity and adverse birth outcomes. Evidence from other vaccine-preventable diseases suggests that through passive transplacental antibody transfer, maternal vaccinations are protective against infections in infants during the first 6 months of life. Various studies have demonstrated that maternal COVID-19 vaccination is associated with the presence of anti-spike protein antibodies in infants, persisting even at 6 months of age. Further, completion of a 2-dose primary mRNA COVID-19 vaccination series during pregnancy is associated with reduced risk for COVID-19–associated hospitalization among infants aged 6 months or less. Therefore, it can be hypothesized that maternal COVID-19 vaccination can reduce the risk of and severity of MIS-C in infants. In this article, we review the literature to support this hypothesis.

Keywords: COVID-19 vaccine; pregnancy; infant; MIS-C

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes relatively mild illness in children as compared to adults, and children usually recover without any adverse clinical course.[1, 2] During this pandemic, an increasing number of Kawasaki-like disease has been seen in otherwise healthy children which is now termed Multiorgan Inflammatory Syndrome (MIS-C). MIS-C is a rare but serious consequence of SARS-CoV-2 infection which occurs after 2-5 weeks after SARS CoV-2 infection or exposure.[3] . Most of the cases are reported in children 8 to 12 years but young children and even neonates are not spared of this severe multi-organ inflammatory disease.[4] Cardiac complications are reported in 50% of the cases and due to the complicated course, most children who develop MIS-C require care in the intensive care unit (ICU). [5, 6] Centers for Disease Control (CDC) started tracking MIS-C cases in May 2020 and since then, 8,210 cases of MIS-C and 66 deaths due to MIS-C have been identified.[7]

An increasing number of MIS-C cases in infants 0-6 months are being reported and most of the data is emerging in the form of case reports and case series. As per the latest systematic analysis, a total 90 cases of MIS-C and MIS-N were identified in 0-6 months

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infants. [8]. However, there is no formal definition of MIS-N, and this term is used by some clinicians for case identification in neonates born to SARS-CoV 2 positive mothers. [8, 9] Both vertical and horizontal transmission of SARS-CoV-2 virus is the proposed etiology for MIS-C in infants.

COVID vaccine is approved for children 6 months and above in the United States and it decreases the severe complications of SARS-CoV-2 infection, hospitalization, and death. [10] There is growing evidence that MIS-C incidence is lower in vaccinated adolescents [11-13] Further, hospitalization rates are lower in vaccinated children, and infants 0-6 months born to vaccinated mothers.[14] COVID-19 vaccines have been approved in pregnant females, and have been proven to be safe and effective in preventing COVID-19 incidence and its complications in mothers.[15] Transfer of IgG antibodies to infants after maternal vaccination has been well documented for other vaccines, and these antibodies can persist in the infant beyond the neonatal period, providing protective effects in the infant. [16] It can therefore be hypothesized that maternal vaccination for COVID-19 can lead to transplacental transfer of IgG antibodies to the infant, and render protection against not only COVID-19 but also its complications such as MIS-C in infants. In this article, we aimed to review the available literature that evaluated (1) transplacental transfer of antibodies to newborn and during early infancy after maternal COVID-19 vaccination, and (2) the risk of COVID-related hospitalization and MIS-C incidence in vaccinated children and infants born to mothers vaccinated during pregnancy.

2. Materials and Methods

Our search was aimed at identifying studies (1) evaluating transplacental transfer of antibodies to the newborn following maternal COVID-19 vaccination, and (2) evaluating the impact of COVID-19 infection-related hospitalization and MIS-C incidence in vaccinated children and infants born to mothers who were vaccinated during pregnancy. Data for this review were identified by searches of MEDLINE, EMBASE, SCOPUS, Google Scholar, Science Citation Index, and references from relevant articles using the search terms “maternal,” “vaccine,” “vaccination,” “BNT162b2,” “Pfizer-BioNTech,” “mRNA-1273,” “mRNA,” “severe acute respiratory syndrome coronavirus 2,” “SARS-CoV-2,” “COVID-19,” “2019-nCoV,” and “coronavirus.” Only articles published in English from inception to May 18th, 2022 restricted to humans, and directly related to this review were included.

3. Results

This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

3.1. Studies evaluating transplacental transfer of antibodies to newborn and early infancy after maternal COVID-19 vaccination

Our search yielded 19 studies that have thus far evaluated the transplacental transfer of antibodies after maternal vaccine. (Table 1) Most of these case reports/case series and prospective cohort studies are reported from the United States and Israel. After a detailed review, all the studies demonstrated that anti-spike protein (anti-S) IgG antibodies are detected in the umbilical cord samples of neonates at birth after maternal vaccination. Trostel et al found that these antibodies were positive in all the neonates at birth. [17]Interestingly, the fetal titers could reach the maternal level just after 15 days of the first dose of the COVID vaccine, but neonates born to vaccinated parturients have higher antibody titers and prolonged protection compared to those born to infected. [18-21]Vaccination in the third trimester and booster dose in this trimester are also found to be associated with high maternal anti-spike IgG levels.[22] 6 of the studies tested the neutralizing properties of transplacentally transferred maternal antibodies and revealed that the neutralizing

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capacity of neonatal sera is comparable to maternal sera which could protect infants from SARS CoV-2 infection and its complications. [21, 23-26]

The next question relates to the durability of these antibodies. Two of the studies have evaluated the duration for which the transplacentally transferred maternal anti-S IgG antibodies are present in the infant. Shook et al studied 77 vaccinated pregnant women and 12 pregnant women with SARS-CoV-2 infection during pregnancy and tested the durability of these antibodies in both of these groups.[27] Vaccinated parturients had high titers at birth with respective high levels in cord blood samples. Furthermore, these antibodies were positive in 98% of infants at 2 months of age which further declined to 57 % at 6 months but as compared to infants born to parturients with SARS infection in pregnancy as only 8 % of these infants had positive titers at 6 months of age. Mangat et al also reported case reports in which antibodies were persistent positive at 6 months but the tires were declining. [28]

Table 1. Studies showing the transplacental transfer of antibodies to newborns and early infancy after maternal COVID vaccination.

Author & Year	Study type	Location	Type of Vaccine	Study groups	Time of vaccine in pregnancy	Measure	Results
Beharier, 2021[18]	Prospective cohort	Israel	BNT162b2 (2 doses)	a) Vaccinated parturients (n = 86); b) PCR-confirmed SARS-CoV-2 infected during pregnancy (n = 65), c) Unvaccinated non infected parturients (n = 62)	34.5 ± 7.5 weeks	Anti-S and RBD antibodies in maternal blood and in umbilical cord blood (Sera Ig G and Ig M)	1) Vaccination elicits strong maternal humoral IgG response 2) Maternal titers in the fetus attained within 15 days following the first dose.
Collier, 2021 [25]	Prospective cohort	Israel	BNT162b2 or MRNA-1273 (2 doses)	a) 30 pregnant, 16 lactating, 57 neither pregnant nor lactating women who are vaccinated b) 22 pregnant and 6 nonpregnant unvaccinated women with SARS-CoV-2 infection	1st trimester (17%), 2nd trimester (50%), 3rd trimester (33%)	Immunogenicity of the mRNA vaccines in pregnant and lactating women: median RBD and anti-S IgG and Ig A antibody titres	1) Vaccination is immunogenic in pregnant women. 2) Vaccine-elicited antibodies are transported to infant cord blood and breast milk.
Kashani-Ligumsk, 2021[19]	Prospective cohort	Israel	BNT162b2 (2 doses)	a) Women who were vaccinated during pregnancy (n = 29) b) Infected with SARS-CoV-2 during pregnancy (n = 29) c) Women not infected and not vaccinated (n = 21)	3rd-trimester	Titers of anti-S IgG antibodies to SARS-CoV-2 in umbilical cord blood in vaccinated pregnant women	Neonates born to vaccinated parturients have higher antibody titers and prolonged protection compared to those born to infected parturients.
Shook, 2022 [27]	Prospective cohort	United States	BNT162b2 or MRNA-1273	a) 77 vaccinated pregnant mothers b) 12 pregnant women with natural SARS-CoV-2 infection	27 weeks	Persistence of anti-S IgG in infants after vaccine vs natural infection.	Most infants had anti-S IgG persistently positive at 6 months of life.
Nir, 2021 [20]	Prospective cohort	Israel	BNT162b2(2 doses)	a) 64 vaccinated parturient women	33.5 ± 3.2 weeks at	RBD IgG antibodies in maternal blood and	Antibodies detected in cord blood, newborn dried blood spot, and

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				b) 11 parturient women who had COVID-19 during pregnancy	second dosage	in umbilical cord blood	breast milk samples were higher in vaccinated women than in COVID-19-recovered women.
Gray, 2021 [21]	Prospective cohort	United States	BNT162b2 or MRNA-1273 (2 doses)	a) Vaccinated (84 pregnant, 31 lactating, and 16 nonpregnant women) b) Unvaccinated pregnant women (n=37) with natural SARS-CoV-2 infection	23.2 weeks (IQR 16.3–32.1)	Titers of severe acute respiratory syndrome coronavirus 2 spike and receptor-binding domain immunoglobulin G, immunoglobulin A, and immunoglobulin M were quantified in participant sera and breastmilk	1) Robust IgG titers were observed across pregnant, lactating, and nonpregnant women, significantly higher than pregnant women with previous SARS-CoV-2 infection. 2) Immune transfer to neonates occurred via placenta and breastmilk.
Trostle, 2021 [17]	Prospective case series	United States	BNT162b2 or MRNA-1273 (at least 1 dose)	36 vaccinated pregnant women	1st trimester (6%), 2nd trimester (83%), 3rd trimester (11%)	Positive Anti-S IgG antibodies and negative anti-N IgG antibodies in maternal blood and in umbilical cord blood	1) Transplacental antibody transfer following vaccination during pregnancy. 2) 100% of cord blood specimens have high levels of anti-S antibodies.
Rottenstreich, 2021 [29]	Prospective case series	Israel	BNT162b2 (at least 1 dose)	20 vaccinated pregnant women	3rd trimester	Anti-S and RBD IgG antibodies in maternal blood and in umbilical cord blood	1) Vaccination during pregnancy is immunogenic with transplacental antibody transfer 2) A positive correlation between maternal and cord blood antibody concentration was seen.
Mithal, 2021 [30]	Prospective case series	United States	BNT162b2 or mRNA-1273	27 vaccinated pregnant women	33 ± 2 weeks	Transfer of SARS-CoV-2 IgG antibodies to infants	1) Pregnant women vaccinated during the 3rd trimester had transplacental antibody transfer. 2) Infant IgG levels are about equal to maternal levels.
Prabhu, 2021 [31]	Prospective case series	United States	BNT162b2 or MRNA-1273 (at least 1 dose)	122 vaccinated pregnant women	NA	Anti-S IgG antibodies in maternal blood and in umbilical cord blood	1) All women and cord blood samples, except for one, had detectable IgG antibodies by 4 weeks after vaccine dose 1. 1) Timing between vaccination and birth may be an important factor to consider in vaccination strategies of pregnant women.
Yang, 2022 [22]	Retrospective cohort	United States	BNT162b2 mRNA-1273 or Johnson	1359 vaccinated pregnant women	Both in prepregnant state and pregnancy	Transfer of maternal anti-S IgG in cord blood.	1) Maternal anti S-IgG antibodies are detectable at delivery

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						Assess the association of prior infection and vaccine booster on anti-S IgG levels	regardless of timing of vaccination 2) Highest antibody levels detected with third trimester vaccination. 3) A booster dose in the third trimester was associated with maternal anti-spike IgG levels greater than third-trimester vaccination in women with/without a history of SARS-CoV-2 infection.
Cassaniti, 2021 [24]	Retrospective cohort	Italy	BNT162b2 (2 doses)	a) 2 vaccinated pregnant women b) 7 non-vaccinated controls with SARS-CoV-2 infection during pregnancy	31^{+4} and 27^{+6} weeks	anti-SARS-CoV-2 Spike IgG and IgA antibodies in pregnant women and newborns	1) Transplacental transfer of anti-SARS-CoV-2 IgG at delivery after infection or vaccination. 2) Median neutralizing antibody titer was twofold reduced in newborns with respect to mothers.
Gloeckner, 2021 [26]	Retrospective cohort	Germany	BNT162b2 or MRNA-1273 after a prime vaccination with Oxford–AstraZeneca ChAdOx 1	a) 3 vaccinated pregnant women b) 25 vaccinated non-pregnant controls	NA	anti-Spike immunoglobulin G (IgG) antibody kinetics in pregnant women in comparison to their newborns, as well as to a healthy nonpregnant control group	1) Vaccination-induced immunogenic response in pregnant women showed no significant difference compared with nonpregnant controls 16 weeks after the initial vaccination. 2) Vaccination induces a strong passive humoral immunity in the newborns.
Zdanowski, 2021 [32]	Retrospective case series	Poland	BNT162b2 (2 doses)	16 vaccinated pregnant women	31.8 ± 2.1 weeks	Anti-S IgG antibodies in maternal blood and in umbilical cord blood	1) Maternal immunization provides neonatal protection through the transplacental transfer of antibodies. 2) Antibody transfer is correlated with the time from vaccination to delivery.
Douxfils, 2021 [23]	Case report	Belgium	BNT162b2 (2 doses)	1 vaccinated pregnant woman	25 weeks	anti-S IgG antibodies in umbilical cord blood compared to maternal blood	1) Successful maternal to fetal transfer of neutralizing antibodies 2) Levels of neutralizing antibodies were 5 fold higher in the

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							umbilical cord than in the maternal blood.
Gill, 2021 [33]	Case report	United States	BNT162b2 (2 doses)	1 vaccinated pregnant woman	32^{+6} weeks	IgG SARS-CoV-2 antibodies in maternal blood and in umbilical cord blood	Vaccination in pregnancy produced a robust immune response for the patient, with subsequent transplacental transfer of neutralizing antibodies
Mangat, 2021 [28]	Case report	United States	BNT162b2	1 vaccinated pregnant woman	22 & 26 weeks	Serial anti-S IgG antibody titers in infant	Antibodies in preterm infants are persistently positive at 6 months of age.
Mehaffey, 2021 [34]	Case report	United States	BNT162b2 (2 doses)	1 vaccinated pregnant woman	29 & 32 weeks	IgG SARS-CoV-2 antibodies in maternal and umbilical cord blood	Vertical transmission of IgG SARS-CoV-2 specific antibodies from a vaccinated mother to her son with no evidence of prior infection.
Paul, 2021 [35]	Case report	United States	MRNA-1273 (1 dose)	1 vaccinated pregnant woman	36^{+3} weeks	IgG SARS-CoV-2 in umbilical cord blood after maternal vaccination	SARS-CoV-2 IgG antibodies were detectable in a newborn's cord blood sample after only a single dose of the vaccine.

3.2. Studies evaluating the risk of COVID-related hospitalization and MIS-C incidence in vaccinated children and infants born to mothers vaccinated during pregnancy.

Our search yielded 10 studies in this section, that includes, 5 case-control studies, 3 population-based surveillance studies, 1 prospective cohort, and 1 patient registry. Most of the studies are case-control studies from the United States.

Between June 1-September 30, 2021, during Delta variant predominance, 2 doses of BNT162B2 were effective in reducing 93% of COVID-19-related hospitalizations among patients aged 12-18. [36] Comparison of the data during Delta and Omicron predominance showed that COVID-19 vaccine decreased the hospitalization rate during the Omicron surge from 93% to 79% in 12-18 age group, whereas vaccine effectiveness (VE) against hospitalization among children 5 to 11 years of age was 68% for which the data is available only during Omicron surge. [37] From April 2021-January 2022, VE against hospitalization in 5-11 group was 78 % but VE was reduced in older children when 2nd dose of vaccine was >150 days from infection.[38] Furthermore, completion of 2 doses of mRNA COVID-19 vaccine during pregnancy, showed VE of 61% against hospitalization in infants 0-6 months [14]. On the other hand, an increased hospitalization rate was noted in children 1-4 years during Omicron surge as the vaccination was not available for this age group during that time.[39]

Receipt of 2 doses of BNT162b2 vaccine showed protection against MIS-C, which is a life-threatening complication of SARS-CoV-2 infection in children aged 12-18 years (July -December 2021) with estimated effectiveness of 91% vaccine against MIS-C and along with this, MIS-C complications were also decreased in vaccinated children and all MIS-C patients requiring life support were unvaccinated. [11] Studies from France also reported similar findings where decreased MIS-C likelihood was noted after the first dose of the COVID vaccine (From September 1, 2021, to October 31, 2021,) the HR for MIS-C was 0.09 after the first vaccine dose compared with unvaccinated adolescents.[12] Oduldali et al reported that MIS-C reporting rate was significantly low in vaccinated children in France, they found that MIS-C was 1.5 per 1,000,000 doses of COVID vaccine as compared to 113 MIS-C cases occurred per 1,000,000 infected by SARS-CoV-2 in children 12-17-years.[13]

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However, no study is available to date which examined the MIS-C in vaccinated younger children 5-11 although the vaccine has been available for this group since November 2021 in the United States. Risk of MIS-C has also not been examined yet in infants born to the vaccinated mothers.

Approved vaccine for children 12-18 is available in USA since May 2021 and for 5-11 years it is available since November 2021. [40] Vaccine is found safe and effective it's being administered under the most intensive vaccine safety surveillance effort in history. Based on benefit-risk assessment, it's estimated that approximately 1,000 COVID-19 hospitalizations may have been prevented during the Omicron surge among fully vaccinated children ages 5-11 years. [41].

There is growing evidence that among vaccinated children, hospitalization rates and complication rates are low in children 12-18 years and 5-11 years. [36, 41] Table 2 However, the highest hospitalization rate among children was noted in 0-4 years during Omicron surge. [43]. Furthermore, maternal vaccination is associated with a reduced risk for COVID-19–associated hospitalization among infants 0-6 months due to passive transfer of vaccine-induced antibodies during pregnancy.[14]

Table 2. Studies showing the decrease in COVID-related hospitalization and MIS-C incidence in vaccinated children and infants born to mothers vaccinated during pregnancy.

Author	Country	Type of study	n: study group vs control group (if any)	Age	Intervention	Study period	Measure	Results:
Olson, 2022 [36]	United States	Case-control	179 cases (SARS-CoV-2 test positive) vs 285 controls (SARS-CoV-2 test negative)	12-18	2 Doses of BNT162b2	June to September, 2021	• Vaccine effectiveness (VE) against COVID-19 associated hospitalization	• VE = 93% (95% CI = 83%-97%); predominant variant: Delta
Klein, 2022 [38]	United States	Case-control	9640 cases (SARS-CoV-2 test positive) vs 31276 controls (SARS-CoV-2 test negative)	5-17	2 Doses of BNT162b2	April 2021–January 2022	• Vaccine effectiveness against COVID-19 associated hospitalizations (ED/UC encounters)	• Age 5–11 years; VE= 46%. • Age 12–17 years; VE = >90% (protection within 149 days of second dose administration.)
Price, 2022 [37]	United States	Case-control	1185 cases (SARS-CoV-2 test positive) vs 1627 controls (SARS-CoV-2 test negative)	5-18	2 Doses of BNT162b2 messenger RNA vaccine	July -Feb 2022	• Vaccine effectiveness against COVID-19 associated hospitalization, critical COVID-19 and non-critical COVID-19	• Age 12 to 18; VE = 93% (95% CI, 89 to 95) at 2 to 22 weeks following vaccination and VE = 92% (95% CI, 80 to 97) at 23 to 44 weeks., Predominant variant: Delta • Age 12 to 18 VE = 40% (95% CI, 9 to 60) against Covid-19 associated hospitalization, 79% (95% CI, 51 to 91) against critical Covid-19, and 20% (95% CI, −25 to 49) against noncritical Covid-19. (median interval of 162 days following vaccination) Predominant variant: Omicron

								• Age 5 to 11 years, VE = 68% (95% CI, 42 to 82; median interval of 34 days since vaccination). predominant variant: Omicron
Halasa, 2022 [14]	United States	Case-control	176 cases (SARS-CoV-2 test positive) vs 203 controls (SARS-CoV-2 test negative)	0-6 month	Maternal 2-dose mRNA vaccination	July 2021-January 2022	• Vaccine effectiveness against COVID-19 associated hospitalization	• infants aged <6 months; VE = 61% (95% CI = 31% to 78%). • VE = 32% (95% CI = –43% to 68%), (vaccination in first 20 weeks), and VE = 80% (95% CI = 55% to 91%), (vaccination later in pregnancy: 21 weeks through 14 days before delivery)
Zambrano, 2022 [11]	United States	Case-control	102 cases (diagnosed with MIS-C) vs 181 controls (no evidence of SARS-CoV-2 infection)	12-18 years	2 doses of Pfizer-BioNTech vaccine in 12-18 years	July 2021-January 2022	• Vaccine effectiveness against MIS-C	• VE = 91% (95% CI = 78%–97%)
Fowlkes, 2022 [42]	United States	Prospective cohort	1,364 participants	5–15 Years	2-Doses of BNT162b2	July 2021–February 2022	• Vaccine effectiveness against COVID-19 associated hospitalization	• Age 5-11, VE = 31% (95% CI = 9%–48%). (14–82 days after dose 2 administration) ; against Omicron infection • Age 12-15, VE = 87% (95% CI = 49%–97%) (14–149 days after dose 2 administration), variant: Delta infection, and 59% (95% CI = 22%–79%), variant: Omicron infection.
Shi, 2022 [43]	United States	Population-based surveillance	1,475 (laboratory confirmed COVID-19)	5-11 years	1-2 Doses of BNT162b2	March 2020-February 2022	• COVID-19 associated hospitalizations in unvaccinated children	• Cumulative hospitalization rates among unvaccinated children were 2.1 times that of (19.1)vaccinated.
Ouldali, 2022 [13]	France	Population-based surveillance	NA	12-17	2 Doses of mRNA vaccine	June 15th, 2021 and January 1st, 2022	• Vaccine effectiveness against MIS-C	• MIS-C Incidence = 2.9 per 1,000,000 in vaccinated children • MIS-C Incidence = 113 per 1,000,000 in children infected with SARS-CoV-2
Marks, 2022 [39]	United States	Population-based Surveillance	2818 (laboratory confirmed COVID-19)	12-17	1-2 Doses of BNT162b2	July 2021–January 2022	• Vaccine effectiveness against COVID-19 associated hospitalization	• Monthly hospitalization rates in unvaccinated adolescents aged 12-17 years (23.5) was six times as much as

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								fully vaccinated adolescents (3.8). ● Increased rate of hospitalization in 0-4 years among unvaccinated
Levy, 2021 [12]	France	Patient Registry	107 (diagnosed with MIS-C)	12-18 years	1-2 Doses of mRNA vaccine	September 2021 and October 2021.	● Vaccine effectiveness against MIS-C	● HR for MIS-C = = 0.09 (95% CI, 0.04-0.21; *P* < .001)

4. Discussion

CDC defines MIS-C as an individual aged less than 21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with more than two organ involvement with no alternative plausible diagnoses, and with current or recent SARS-CoV-2 infection or COVID-19 exposure within the 4 weeks prior to the onset of symptoms. [44] Most of the cases of MIS-C are clustered in age 8-11 and number of cases in neonates and infants reported thus far has been low.[45] In a systematic meta-analysis, DeRose et al analyzed 48 studies which include 29 case reports, 6 case series and 13 cohort studies.[8] They identified 25 papers which included a total 32 cases of MIS-C in the form of case studies in infants aged 0- 6 months. Additionally, 31 infants 0-6 months with MIS-C were identified in existing 12 cohort studies which included total 1062 children 0-18 years old. The youngest case of MIS-C reported was in a 7-day-old infant. [46] MIS-N is the proposed definition for infants born to mothers with SARS Cov-2 infection by some clinicians but there is no formal definition of MIS-N. Based on this proposed definition, Del Rose et al identified 33 neonates with MIS-N and interestingly only 18.2% had fever as compared to fever as a major criterion in diagnosis of MIS-C in children. [8] The true incidence of MIS-C is not known. Based on a multicenter study of a large cohort in the United States, the cumulative incidence of MIS-C in those younger than 21 years of age was 2.1 per 100,000 persons, with a mortality rate of 1.4%. [4] Incidence in newborns and infants is unknown due to scarcity of data and difficulty in diagnosis as newborns could be afebrile and due to many overlapping symptoms, it can be difficult to differentiate MIS-C from sepsis in early infancy.[8]Although there are only a few cases reported so far, risk of cardiac complications and critical illness is high in this population, with very high mortality of 12.5% reported in infants 0-6 months. [4, 8]

MIS-C is temporally associated with current or prior SARS-Cov-2 infection, but the exact pathogenesis of MIS-C is not fully understood. Available literature proposes the multilineage activation of the immune system which include both innate and adaptive signatures.[47] Viral load at the time of MIS-C diagnosis is lower, and it has been hypothesized to be an autoimmune and hyperinflammatory response to the initial infection. High levels of inflammatory cytokines, including interferons alpha and gamma, and interleukin (IL) 1β, IL-6, IL-8, IL-10, and IL-17 are reported but no pathognomonic marker has been identified yet. [48, 49] Decreased expression of angiotensin convertase enzyme (ACE) receptors in early infancy and predominantly stronger innate immune response with less adaptive immune development are the proposed reasons behind the decreased incidence of severity of COVID-19 infection and eventually the development of MIS-C in infants.

The safety and efficacy of COVID-19 vaccination in children >5 years has been well documented. Further, a multistate study from the US hospital network by Zambrano et al revealed that receipt of 2 doses of the Pfizer- BioNTech vaccine was associated with protection against MIS-C in patients aged 12- 18 years. The likelihood of developing MIS-C was 91% less in vaccinated children and vaccinated children who developed MIS-C were less likely to develop respiratory or cardiac complications. [11] Similar studies from France also revealed a lower incidence of MISC- in vaccinated children. [12, 13]

Our review identified several studies that have documented transplacental transfer of antibodies following maternal COVID-19 vaccination, and a reduced risk of

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hospitalization related to COVID-19 in infants 0-6 months of age. Further, these antibodies can persist in infants up to 6 months of age, after which, a decline in their titers were reported. [14, 28]. It is unknown if the risk of COVID-19 and its complications increases corresponding to the decline in titers of these antibodies after 6 months or not. The risk of MIS-C in infants born to vaccinated mothers has not been extensively evaluated. Maternal vaccination leads to anti-spike protein IgG antibody production in maternal circulation which then gets passively transferred to the fetus through transplacental transport and is detected in newborns after birth and early infancy and has neutralizing effect against COVID-19 infection and its complications including MIS-C.[17, 23, 28, 31] (Figure 1)

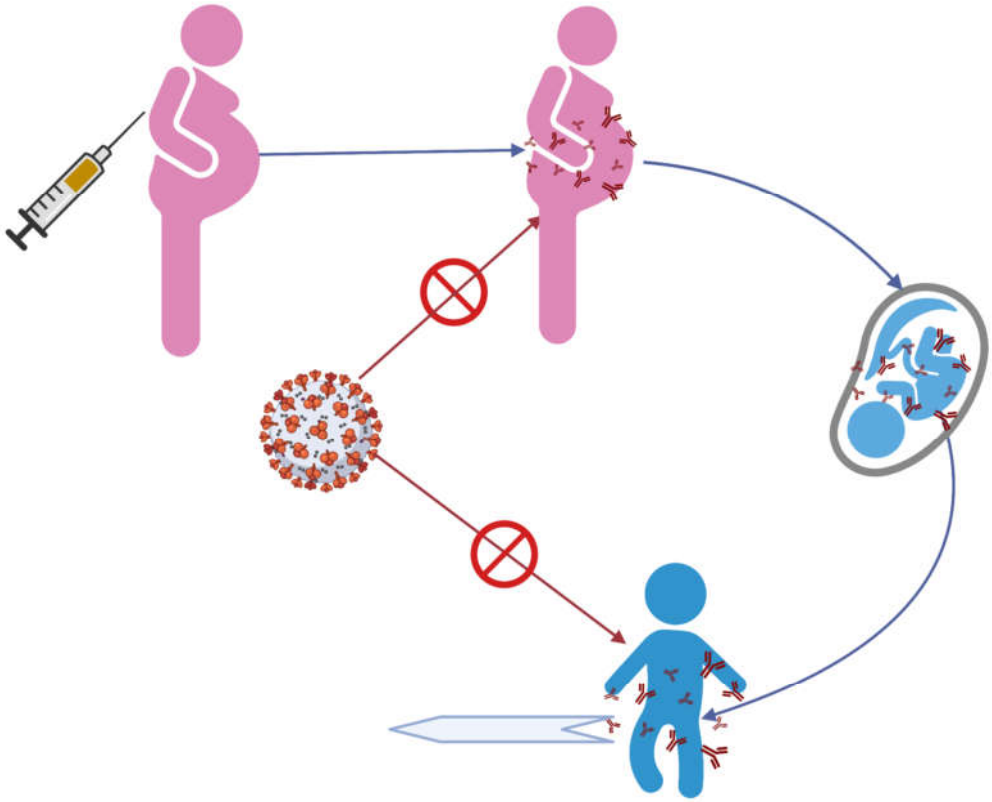

Figure 1. Figure showing proposed hypothesis on reducing the risk of MIS-C in infants after material COVID vaccine. (Created with BioRender.com.").

Vaccine for children in the 6 months through 4 years age group was recently approved but so far, it is unknown if and when a vaccine for infants 0-6 months will be available. Our review supports the evidence that maternal COVID-19 vaccination could provide protection to the infant in the first 6 months of life as seen with other recommended Tdap and influenza vaccines during pregnancy which have been successful in reducing the morbidity and mortality associated with these infections in infants. [16].

Our review has many limitations. Due to heterogeneity of the available studies, a quantitative analysis could not be performed. Since the search was limited to English only and was not systematic, some studies could have been missed. Most of the available studies were case reports or case series, and thus, the level of evidence is low. Further, well-conducted randomized clinical trials can strengthen the evidence and provide clearer information about the risk of MIS-C in infants following maternal vaccination for COVID-19.

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5. Conclusions

Maternal vaccination for COVID-19 may be effective in rendering passive immunity to infants under 6 months of age. There is emerging evidence that it can prevent SARS-CoV-2 infection, its complications and hence the life-threatening consequence of MIS-C in infants < 6 months. The data is still premature, and further studies can elicit the exact impact and timing of vaccination in pregnancy on the risk of MIS-C in infants.

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