

Original Article: A Brief Study of a Comprehensive Meta-Analysis Study of the Birth Outcomes of Corona Mothers in Iran



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ABSTRACT

Many questions pertaining to the neonates born to the mothers affected by Covid19 have arisen, particularly regarding the likelihood of vertical transmission of the virus, the association between the intensity of disease in mothers and severity of neonatal morbidities. The present systematic review and meta-analysis attempted to deliver the responses to such uncertainties. The Comprehensive Meta-Analysis Software was employed to do the statistical analysis. Overall, 16 studies including 1192 mothers with the average age of 31 years suffering definitive diagnosis of Covid-19 and delivered successfully were assessed with respect to their clinical manifestations as well as pregnancy and neonatal outcome. The median of birth weight was 3080 gr. The pooled cesarean rate was 48.3%. Respecting neonatal outcome, neonatal respiratory distress was overall revealed in 13.1% (95%CI: 10.6% to 16.0%) and in total, 20.1% (95%CI: 17.6% to 20.3%) required NICU admission. Overall, 3.8% (95%CI: 2.6% to 5.7%) of the neonates tested positive for SARS-CoV-2 infection, while no neonatal death was reported in all the studies. The rate of vertical transmission of SARS-CoV-2 infection from mother to neonate is very low and overall outcome reported in these infants is quite favorable. Thus, encouraging immediate bonding, rooming-in and breastfeeding should be considered for all neonates born to infected mothers.

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Introduction

In late 2019, we witnessed the emergence of the Covid-19 pandemic in the world. With the first cases of the infectious disease reported from China, its high prevalence was immediately reported in almost all countries of the world, to the point that in less than a year, the global incidence of the disease was more than 72 million cases and the resulting death toll was 1.6 million cases [1-4]. None of the sections of the society was immune to the disease, and this infection and its adverse consequences were much higher in older patients with high-risk underlying factors [5-8]. In this regard, there were hypotheses as well, such that once infected with the disease, complete immunity to it is created, which was rejected with reports of multiple and repeated cases of the disease [9-12]. It was also initially believed that children were immune to the disease, but there were also reports of infection in even infants and toddlers [13-16]. There are also many ambiguities about the clinical consequences of the disease in pregnant women and their infants. Some have believed that in mothers with Covid-19, enough antibodies are passed on to the baby, so babies are completely immune to the manifestations and consequences of the disease [17-21]. However, some do not believe in this hypothesis, and there are limited reports of symptoms in newborns from infected mothers [22-25]. Therefore, there are fundamental ambiguities regarding the vertical transmission between mothers and their newborn infants as well as there are no complete and comprehensive instructions on how to deal with and manage such neonates. To answer these questions, a comprehensive and systematic review of epidemiological reports of neonatal infection in pregnant women is necessary to examine both the characteristics of mothers and their neonates and to clarify the various aspects of neonatal infection and related risk factors [26-28].

Present systematic review study has pursued such a goal

Disagreements were resolved through discussion and decided by a third reviewer. No

limitation was considered for the country or date of papers published. All English language-based studies were included for initial assessment [29-31]. In this review, all cross-sectional, case-controls and case series were included and thus the abstracts with unavailable full texts or case reports as well as reviews were excluded in first step [32-35]. We also tried to contact authors by letters writing to obtain unpublished data or full texts. The inclusion criterion for retrieved the studies were to describe baseline characteristics, clinical and laboratory findings, as well as clinical outcome of mothers suffering Covid-19 and their neonates affected or not affected by infection. The study quality was evaluated based on the following criteria:

- The systematic review and meta-analysis based on the questions primarily described and formulated;
- Inclusion and exclusion criteria predefined in the studies as eligibility criteria;
- Searching the literature performed on a systematic and comprehensive approach;
- To minimize the bias, the full texts of the article were dually reviewed;
- The quality of included studies were rated independently by the reviewers for appraising internal validity;
- Studies' characteristics and findings were comprehensively listed;
- The publication and risk of bias were listed; and
- Heterogeneity was also assessed. The risk of bias for each study was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions and also according to QUADAS-2 tool [36-39].

For statistical analysis, the Comprehensive Meta-Analysis Software (CMA, version 3.0) was employed [40-45]. We presented dichotomous data related to pooled prevalence of each procedural complication as prevalence rate and its 95% Confidence Interval (CI). Data were assessed by both fixed effects and random effect models; however, the random effect analyses were reported if the heterogeneity was

significant evaluated by the I2 statistic. Reported values were two-tailed, and hypothesis testing results were considered statistically significant at $p = 0.05$. The publication bias was assessed by drawing the funnel plot [46-50].

Special Comparison for the Obtained Results

From the end of December 2019, when the coronavirus appeared in Wuhan, China, until it became a pandemic, the epidemic situation progressed alarmingly, and consequently pregnant women were no exception. Due to physiological changes in the immune, cardiovascular and respiratory systems during pregnancy (especially weakened immune system), their tolerance to hypoxia decreases; Therefore, respiratory problems are expected to increase in pregnant women and increase the risk of more severe forms of the disease. Therefore, this study was performed to investigate the consequences of Covid 19 on pregnancy and childbirth [51-54]. This study is a review study that was done by searching the databases of pubmed, A total of 20 studies were found on the purpose of the study [55-58]. So far, there is no evidence that the risk of coronary artery disease in vaginal delivery is higher than cesarean section, but due to the longer stages of vaginal delivery, the risk is higher, and this time is so important that even in the case of delayed umbilical clamp [59-62]. There is disagreement about the possibility of transmitting coronary heart disease. Therefore, coronary heart disease should not be an indication for labor induction and cesarean section, but the time and manner

of delivery should be determined for each patient individually and based on the usual symptoms of obstetrics and gynecology. According to studies, the common clinical manifestations of Covid 19 in pregnant women include fever, cough, and muscle aches; And the most common laboratory manifestations include decreased blood lymphocytes and increased blood CRP [63-65]. Of course, the range of clinical manifestations varies from asymptomatic to severe. There is no documented case of vertical transmission of other coronaviruses (MERS and SARS); However, due to the limited studies on vertical transmission of COVID_19, its vertical transmission from mother to infant is unclear, although the results of most studies are in favor of not vertical transmission from mother to fetus and infant. The disease can be transmitted through direct maternal contact with the baby (the virus is not found in amniotic fluid, placenta, and milk) and is often transmitted after delivery [66-69]. Therefore, temporary separation of newborns from their mother is necessary for at least two weeks. Direct breastfeeding is not recommended during this time. The most common reported complications of labor were increased preterm delivery, cesarean section rate and abortion. Discussion and Conclusion: According to studies, clinical and laboratory manifestations and radiographs in pregnant women were similar to non-pregnant patients [70-74].

The flow diagram of the study selection is summarized in Figure 1.

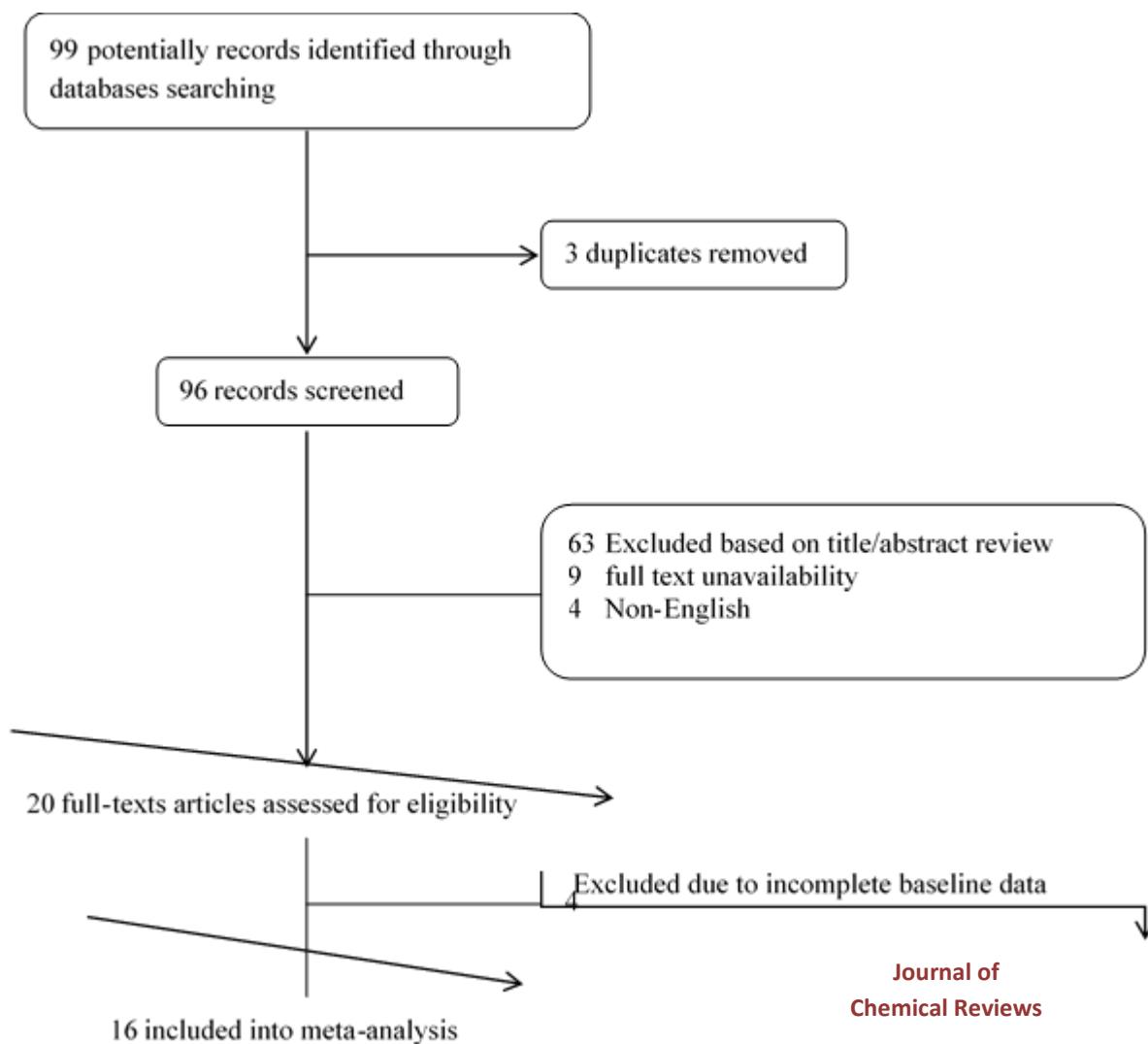


Figure 1. The flowchart of screening the eligible studies

Primarily, 99 articles were collected by database searching and other sources. After removing 3 articles due to evidences of duplication, 96 records were primarily under-screened. Based on the titles and abstracts, 76 records were excluded and the remaining 20

citations were assessed for further eligibility. Of those, 4 were also excluded due to incompleteness of the data and contents. In final, 16 articles were eligible for the final analysis [75-79] (Table 1).

Table 1. Characteristics of mothers infected by Covid-19

Author	Country	Number	Median age	Fever	Cough	Dyspnea	Asymptomatic
Ayed (9)	Kuwait	185	31.0	105	90	22	21
Biasucci (10)	Italy	15	31.0	4	4	2	11
Chen (11)	China	4	29.0	3	2	2	0
De Luca (12)	France	7	32.7	4	2	0	1
Dumitriu (13)	USA	101	28.5	---	---	---	67
Farghaly (14)	USA	15	33.4	1	4	2	9
Flaherman (15)	USA	179	31.5	---	---	---	---
Gabriel (16)	Spain	42	33.6	25	28	10	4
Hu (17)	China	6	30.3	3	2	1	2
Liu (18)	China	19	31.1	11	5	5	5
Liu (19)	China	15	32.0	10	6	3	0
Liu (20)	China	51	31.9	4	4	4	3
Mascio (21)	Italy	388	---	171	202	60	94
Oncel (22)	Turkey	125	---	---	---	---	40
Yang (23)	China	7	---	5	1	0	0
Zeng (24)	China	33	---	8	10	0	0

The studies included were assessed qualitatively by the QUADAS-2 tool (Table 2)

Table 2. Neonatal outcome

Author	Country	Number	M/F	GA at delivery	Neonatal death	Cesarean	Birth weight	5-Apgar	Positive for COVID	Fetal distress	NICU admit
Ayed	Kuwait	185	---	38	0	99	3006	9	3	9	---
Biasucci	Italy	15	9/6	39	0	6	3245	10	2	0	---
Chen	China	4	3/1	37	0	3	3400	9	0	1	1
De Luca	France	7	6/1	38	0	6	3331	9	1	0	0
Dumitriu	USA	101	47/54	39	0	46	3295	9	0	12	19
Farghaly	USA	15	3/12	37	0	10	2800	8	1	6	10
Flaherman	USA	179	137/42	38	0	76	3211	10	2	11	31
Gabriel	Spain	42	18/24	38	0	20	3082	10	3	10	9
Hu	China	6	5/1	34	0	5	2155	9	1	1	2
Liu	China	19	13/6	38	0	18	3293	9	0	0	19
Liu	China	15	9/6	37	0	14	3001	9	0	0	15
Liu	China	51	24/27	38	0	48	3080	10	0	0	---
Mascio	Italy	388	---	37	5	136	2919	---	1	---	69
Oncel	Turkey	125	69/56	37	1	89	2802	9	4	26	26
Yang	China	7	4/3	36	0	7	2962	9	0	2	5
Zeng	China	33	19/14	37	0	26	---	8	3	1	1

According to our risk of bias assessment, all 7 studies yielded good quality and none of the citation was determined to have high risk of bias

and therefore the pooled results should be persuasive (Figure 2) [80-85].

Authors	Patient selection	Index test	Outcomes measuring	Flow and timing
Ayed	+	+	+	+
Biasucci	+	+	+	+
Chen	+	+	+	+
De Luca	+	+	+	+
Dumitriu	?	?	+	+
Earghaly	+	+	+	+
Elaherman	?	?	?	+
Gabriel	+	+	+	+
Hu	+	+	+	+
Liu	+	+	+	+
Liu	+	+	+	+
Liu	+	+	+	+
Mascio	+	?	+	+
Oncel	+	?	?	+
Yang	+	?	+	+
Zeng	+	?	+	+



Figure 2. The Assessment of the risk of bias

Overall, 16 studies including 1192 mothers with the average age of 31 years suffering definitive diagnosis of Covid-19 and delivered successfully were assessed with respect to their clinical manifestations as well as pregnancy and neonatal outcome [80-85]. Regarding clinical symptoms on admission, the pooled prevalence

of mothers' fever was 47.0% (95%CI: 43.3% to 50.6%), the prevalence of cough was 47.5% (95%CI: 43.9% to 51.2%), and the prevalence of dyspnea was 15.1% (95%CI: 12.7% to 17.9%), while 28.4% (95%CI: 25.3% to 31.6%) remained asymptomatic (Figure 3) [86-89].

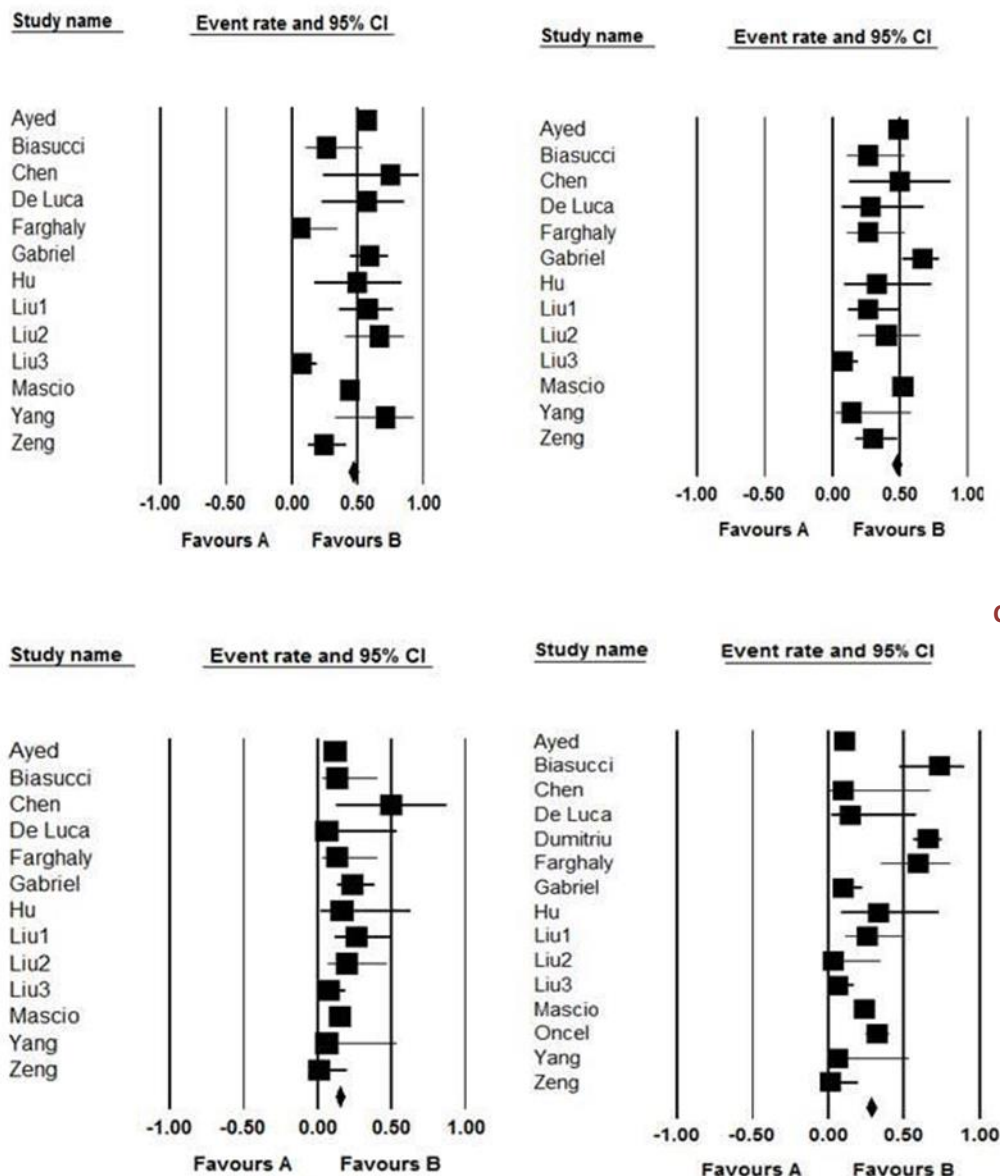


Figure 3. The pooled prevalence of Fever (A), cough (B), dyspnea (C) and asymptomatic condition (D) in mothers' studies

The gestational age at delivery ranged 34 to 39 weeks. Regarding neonates' characteristics, the median of birth weight was 3080gr ranged 2155gr to 3400gr. With regard to mode of delivery, the pooled cesarean rate was 48.3% (95%CI: 45.3% to 51.4%) [90-95]. Respecting neonatal outcome (Figure 4), neonatal respiratory distress was overall revealed in 13.1% (95%CI: 10.6% to 16.0%) and in total, 20.1% (95%CI: 17.6% to 20.3%) required NICU

admission. Overall, 3.8% (95%CI: 2.6% to 5.7%) of the neonates tested positive for SARS-CoV-2 infection, while no neonatal death was reported in all the studies (Figure 4). The heterogeneity across the studies in the pointed measurements including maternal symptoms and neonatal morbidities was significantly relevant with the I² values ranged 43.114 to 86.456 ($p < 0.05$). But the egger test detected no significant publication bias [96-100].

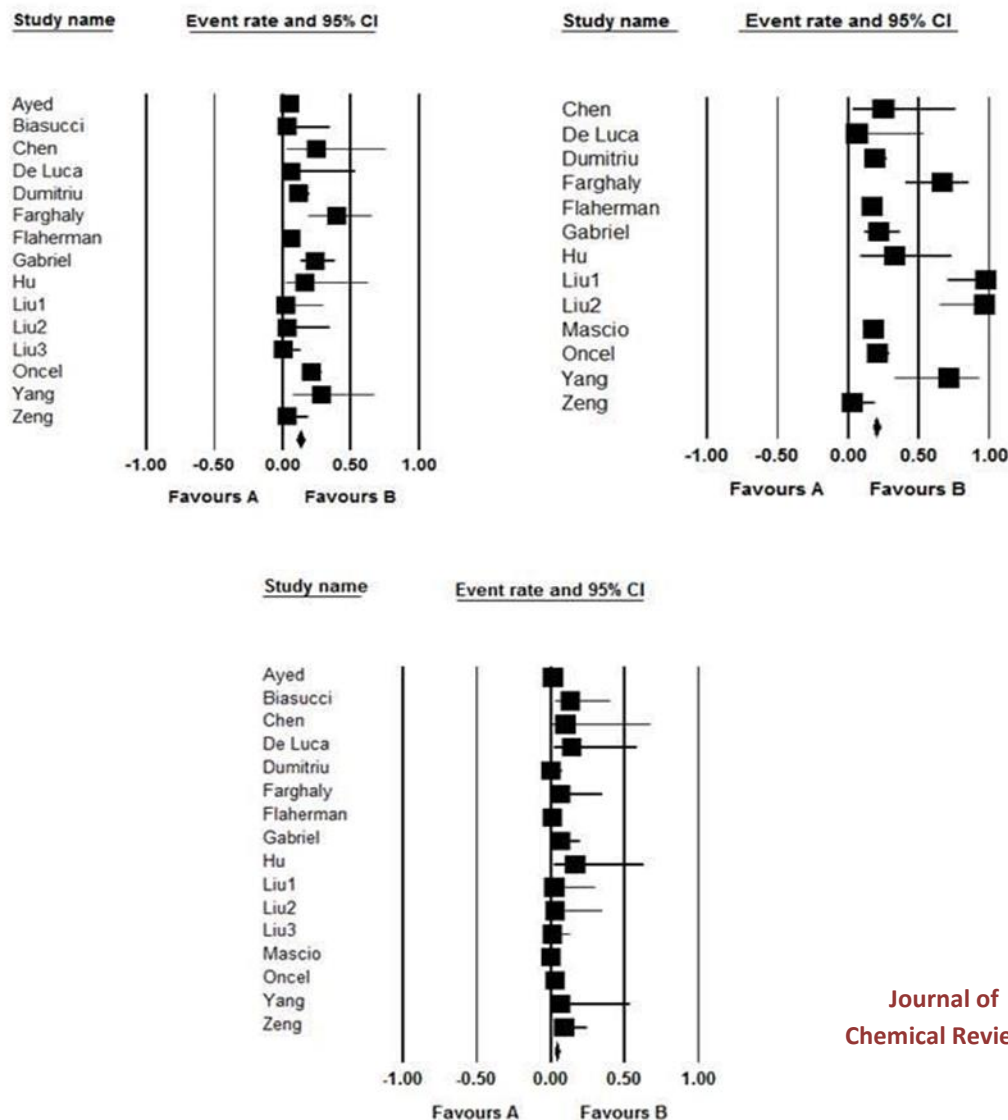


Figure 4. The pooled prevalence of neonatal distress (A), NICU admission (B), and positivity for SARS-CoV-2 infection (C) in neonates studied

Many questions pertaining to the neonates born to the mothers affected by Covid-19 have arisen, particularly with regard to the likelihood of vertical transmission of the virus, the association between the intensity of disease in mothers and severity of neonatal morbidities, and also the best way for neonatal respiratory caring [15]. The present systematic review and meta-analysis attempted to deliver the responses to such uncertainties. As the first finding and with regard to SARS-CoV2 infection positivity among neonates, the overall rate of such infection among neonates of mothers suffering definitive Covid-19 was revealed to be 3.8% (95%CI: 2.6% to 5.7%) that although the

number obtained is relatively small, it can be very important in terms of neonatal care and complications from infection. Also, although cases of premature infant mortality have not been reported in any of the studies, longer follow-up will be required to achieve more reliable results regarding the complications of infection in infants. Overall, the results of neonatal outbreaks of maternal vertical transmission disease have not necessitated intensive neonatal care [10]. Thus, as the first conclusion, the rate of vertical transmission of SARS-CoV-2 infection from mother to neonate is very low. As previously pointed by early reports [15], vertical transmission in utero is rare

including an initial report of pregnant infected women in China whose infants all tested negative for the virus. But, even low prevalence rate of SARS-CoV-2 positivity (mainly based on detecting immunoglobulin (Ig)-M antibodies in new born infants) propose a possibility of vertical transmission mainly due to their immature immune system [116-120]. Such neonates should be intensively managed to minimize the likelihood of Covid-19 related morbidities. In this regard, the important question arises as to whether such infants can be breastfed and routinely cared for during infancy. As the new recommendations of World Health Organization [15], encouraging immediate bonding, rooming-in and breastfeeding should be considered for all neonates born to infected mothers. In this line, although there is a risk for contracting SARSCoV-2 from the infected mother, they are not likely to develop serious symptoms [16].

Conclusion

Coronaviruses are a large family of viruses and a subset of coronaviruses that range from the common cold virus to the cause of more serious illnesses such as SARS, Mers, and Covid. The virus is naturally prevalent in mammals and birds; however, seven human-transmitted coronaviruses have been identified so far. Coronaviruses are zoonotic in the sense that they are transmitted between animals and humans. The last of these, the New Corona, became widespread in humans in December 2019 in Wuhan, China, and the results of studies indicate the animal origin of the disease, which was first transmitted from animal to human and then through human-to-human transmission. It has spread pandemically in many countries. Given the large number of people in contact with the Wuhan Marine Animal Market, it is likely that this market is the covid-19 zoonotic zone. Many studies have been performed to identify the main source of this disease, but so far it has not been precisely determined and only the results show that mammals are the most likely link between COVID-19 and humans. Based on the results of virus genome sequencing and evolutionary analysis, bats are suspected of being natural hosts of virus origin (4), and

COVID-19 may be transmitted from bats through unknown intermediate hosts to infect humans. And protein sequence alignment and phylogenetic analysis have shown that it provides a more likely host for alternative mediators, such as turtles, anteaters, and snakes. The discovery of the original origin and how it originated will help scientists decide which types of wildlife meat to ban in order to prevent the spread of these dangerous epidemics. This seems to be the most basic way to stop the disease and prevent dangerous epidemics, although some hypotheses have been put forward about the anthropogenicity of the virus, which the results of the study by Menachery et al. Have made this hypothesis more serious. However, a recent Andersen study published in the journal Nature rejected the hypothesis that COVID-19 was handmade. According to statistics provided by China, the rate of corona deaths was higher in people over the age of 50. A small number of patients quickly develop acute respiratory symptoms, organ failure, and even death, and some adults and children with coronary heart disease may not have severe symptoms but can transmit the virus to adults as carriers.

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