Similarities and differences of Acute Respiratory Distress Syndrome (ARDS) caused by H1N1 versus SARS-CoV-2 in pregnancy: A systematic review of cohort studies

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ABSTRACT

INTRODUCTION The combination of physiological changes that occur during pregnancy and the two major pandemics of the past two decades, have increased the incidence of ARDS during pregnancy. The goal of this systematic review is to assess the occurrence of ARDS in pregnancy in SARS-CoV-2 and H1N1 infections, as well as similarities and differences between them, concerning epidemiology, prognosis, outcomes and others.

METHODS We conducted a literature search on PubMed, Embase and Cochrane databases, for studies published between database inception and March 2022, for SARS-CoV-2 and H1N1 viruses, respectively. We constructed two different flow diagrams for each virus that met the same screening processes of inclusion and exclusion criteria. All prospective and retrospective cohort studies included, focused on severity of disease, as defined by ICU admission. Admission to ICU and ARDS were two independent variables examined separately.

RESULTS Of 8177 records identified for SARS-CoV-2, only 13 cohort studies had completely relevant outcomes to our criteria and were included in the review. Out of 1329 records identified for H1N1 virus, 15 studies were eligible, but 4 were excluded due to poor data quality. Three main parameters were common in these studies: maternal morbidity and mortality, ARDS induced by each virus, and neonatal outcomes. In COVID-19 disease, mortality was associated with higher maternal age which was not evident in H1N1 disease. The average duration of mechanical ventilation was significantly less in the COVID-19 group. Extracorporeal membrane oxygenation (ECMO) seemed to have better results in pregnant patients with COVID-19.

CONCLUSIONS Both respiratory infections were related with preterm delivery, higher rate of cesarean section and neonatal admission to the NICU, however, neonatal mortality was slightly lower in the COVID-19 group.

INTRODUCTION

During the past two decades, two major global pandemics emerged from the mutation and uncontrolled transmission of two already well-known viruses. The first appeared in the USA in April 2009 due to (H1N1) pdm09, a subtype of the influenza virus family and resulted in 18036 deaths within one year[1]. The second is caused by SARS coronavirus 2 (SARS-CoV-2) and first appeared in Wuhan, China in December 2019, already counting millions of deaths[2].

Both H1N1 and SARS-CoV-2, two primarily respiratory viruses, resulted in many cases of patients with Acute Respiratory Distress Syndrome (ARDS). ARDS according to the Berlin Criteria (2012), is defined as respiratory distress of acute onset (within a week of a clinical incident), with diffuse lung infiltrates on chest X-ray, without underlying cardiac failure or abnormally positive fluid balance. The activation and dysregulation of multiple pathways of injury and inflammation, including coagulation, are the main constituents of ARDS pathophysiology[3]. Also, partial pressure of oxygen in the arterial blood to the fraction of inspired oxygen concentration PaO_2/FiO_2 should be ≤300[4]. Causes of ARDS are divided into pulmonary, which could be respiratory tract infection or lung injury, and extrapulmonary, like burns, prior non-thoracic operation, extrapulmonary infection etc. In terms of hospital mortality, it is 34.9% for mild disease, 40.3% for moderate, and 50.4% for severe ARDS5. Finally, ARDS is the primary cause of Intensive Care Unit (ICU) admissions.

According to the World Health Organization (WHO), risk factors for worse prognosis for H1N1 virus disease are young

age, pregnancy, old age and comorbidity[6]. On the other hand, risk factors for SARS-CoV-2 associated with severe disease are still under investigation. So far, it seems that old age and comorbidity are also risk factors for ICU admissions. However, ARDS and death by SARS-CoV-2 have been described in younger patients, children, and parturients[7].

Parturients are considered a high-risk population and are often susceptible to various severe forms of infection such as pneumonia, pyelonephritis, chorioamnionitis and others. The rare occurrence of ARDS in pregnancy makes it relatively difficult to study in a systematic way. Nonetheless, there are a few systematic reviews on the matter. The largest, so far, gathered data from 2006–2012 from Nationwide Inpatient Samples, found the incidence of ARDS in pregnancy to be 0.05%, with the mean age of patients being 28.7 years. Mean hospital mortality was found to be 9%, while in patients undergoing prolonged mechanical ventilation (>96 h) it was 14%. According to Rush et al.[8], improved survival was related to improved mechanical ventilation techniques among parturients in comparison to the past, and younger patients age[8]. Muthu et al.[9] compared ARDS epidemiology in pregnant and non-pregnant women from 2009 to 2016 and found that maternal mortality was 18% with no difference between trimesters, while fetal mortality was 37%. Mortality in non-pregnant women was 20%. Additionally, age in pregnant patients was significantly lower than in non-pregnant women (25 vs 32 years)[9].

The goal of this review is to examine the vulnerability of pregnant women to H1N1 and SARS-CoV-2 infection. Moreover, we investigate the incidence of ARDS and its consequences on perinatal outcomes, as well as similarities and differences between those concerning epidemiology, prognosis, and outcome.

METHODS

In May 2020, we started conducting the literature search on PubMed and Embase, and on PubMed, Embase and Cochrane databases, for studies published between database inception and March 2022, for SARS-CoV-2 and H1N1 viruses, respectively.

For COVID-19, search keywords were: SARS-CoV-2, COVID-19, Pregnancy, ICU, and ARDS. Two researchers (PD and PT) independently screened articles, by reviewing titles and continued the initial screening process, by reviewing the abstracts of the remaining articles. They discussed inconsistencies and in cases of disagreement they consulted a third reviewer, to obtain a consensus. Only articles in English and with human participants were accepted. No case reports were accepted, only a limited number of cases series. No randomized-control trials were found, so research was focused on prospective and retrospective cohort studies. Abstracts and congress presentations were not included. The final qualitative screening step was again performed by both the reviewers independently and the last studies were excluded, due to being not completely relevant. The

main outcome of the study was severe cases of COVID-19 (the respiratory disease caused by the strain of coronavirus SARS-CoV-2) in pregnancy defined by ICU admission. Admission to ICU and ARDS were two independent variables and they were examined separately. In the ICU period, days of mechanical ventilation were assessed. Moreover, use of ECMO and its outcomes were studied as a support method for severe ARDS. Neonatal outcome data were extracted from all mothers admitted to the ICU. The team also conducted a 'pearl' search in the last months to identify additional studies added in the databases, by searching the citation lists of publications eligible for full-text review.

For influenza A/H1N1, the search was performed by using the keywords: H1N1, Pregnancy, ICU, and ARDS. The search was focused on influenza A/H1N1 and not on other types of influenza. Again, the same screening pattern was followed. The main focus of the study was severe cases of H1N1 in pregnancy, defined as admitted to ICU. The final qualitative screening step was performed by both the reviewers independently and the last studies were excluded due to being not completely relevant or having poor study quality. Neonatal outcome data were examined from all mothers admitted to ICU and not necessarily due to ARDS. Finally, a reverse 'snowball' search was added in the protocol, by using the reference lists of publications eligible for full-text review.

RESULTS

Results for COVID-19 are presented in Figure 1. A total of 13 studies were included examining maternal morbidity and mortality, maternal ARDS caused by SARS-CoV-2, and neonatal outcomes. Data on maternal morbidity are given from 5 studies. Data on maternal SARS-CoV-2 induced ARDS are from 6 studies (Table 1), and neonatal outcome from 5 studies.

Results for influenza A/H1N1 are presented in Figure 2. A total of 11 studies were included examining maternal morbidity and mortality, maternal ARDS caused by H1N1, and neonatal outcomes. Data on maternal morbidity and mortality are from 6 studies. Data on maternal H1N1 induced ARDS are from 4 studies (Table 2), and neonatal outcome from 5 studies.

No eligible studies emerged by using the references or citations of those already examined, in the time period we conducted the search.

Maternal morbidity and mortality

According to the data gathered, maternal morbidity and mortality in H1N1 was more prominent within the second and third trimester[10-13]. Worse prognosis was associated with obesity and history of asthma[9]. Another common component between the studies was that women who eventually died were administered oseltamivir relatively late (>48 h) in contrast to women who survived, to which antiviral agents were administered within 48 h from the onset of symptoms [10-15] (Table 3). Regarding parturients with COVID-19, high

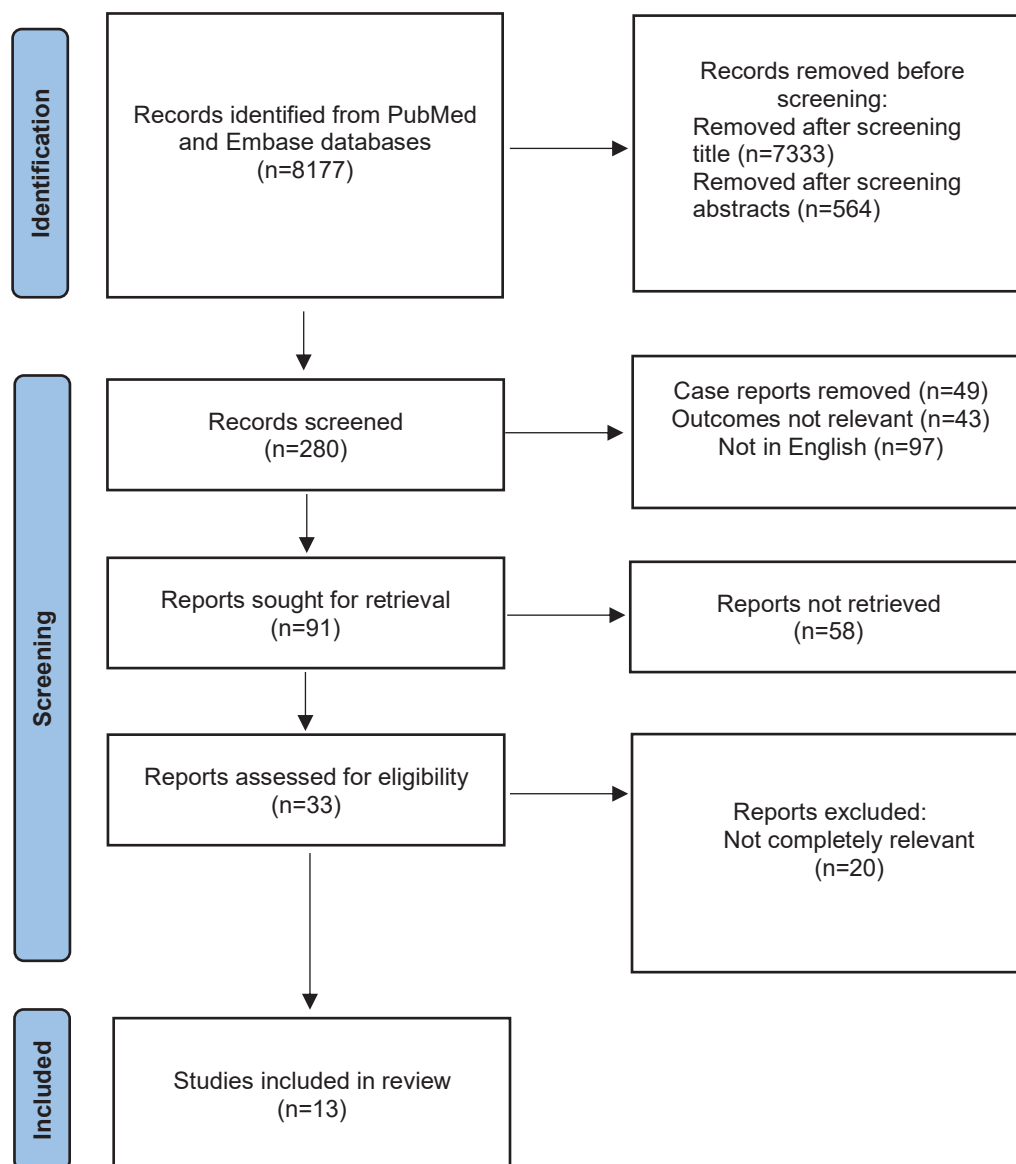## Figure 1. PRISMA flow diagram of SARS-CoV-2 study selection from PubMed and Embase databases

Table 1. SARS-CoV-2 induced ARDS

First author	Year of publication	Study type	Number of women admitted to ICU	Number of women with ARDS	Number of women on ECMO	Days of mechanical ventilation	Mortality n (%)
Marwal[29]	2021	Case series	4	4	0	1	0
Scheler[26]	2021	Cross-sectional	5660	5660	Unknown	Unknown	377 (7.8)
Bamasood[27]	2022	Retrospective cohort	18	10	10	3	1 (5.0)
WAMP[31]	2020	Retrospective cohort	43	7	2	Unknown	3
Pierce-Williams[28]	2020	Retrospective cohort	20	14	0	3	0
Yan[30]	2020	Retrospective cohort	6	6	1	Unknown	0

Figure 2. PRISMA flow diagram of H1N1 study selection from PubMed, Embase and Cochrane databases
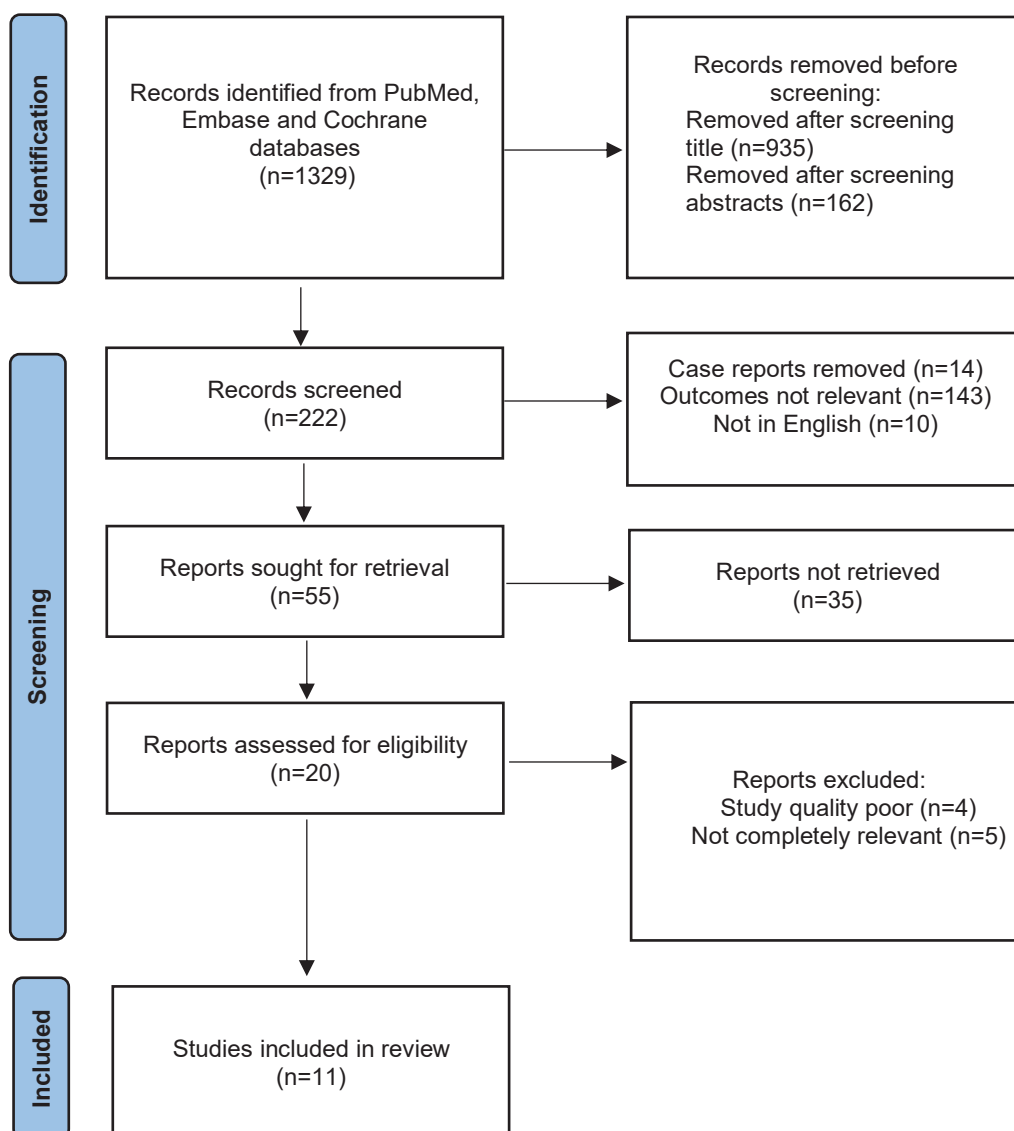

Table 2. H1N1 induced ARDS

First author	Year of publication	Study type	Number of women admitted to ICU	Number of women with ARDS	Number of women on ECMO	Days of mechanical ventilation	Mortality n (%)
Anzic[20]	2011	Retrospective cohort	64	44	9	9	7 (10.9)
Nair[22]	2011	Retrospective cohort	12	12	9	25	4 (33.33)
Handyal[23]	2015	Case series	3	3	0	12	1 (33.33)
Dubar[24]	2010	Prospective cohort	40	20	11	13	3 (7.5)

morbidity and mortality rates were associated with various comorbidities, with the most important being obesity and hypertensive disorders of pregnancy. Moreover, higher maternal age (>30 years) was another important risk factor, while that was not the case in H1N1 positive parturients. Overall death rate was higher in the H1N1 pandemic compared to COVID-19 pandemic in the pregnant population [16-19] (Table 4). A significant difference between the two viruses is that in the case of influenza, a specific antiviral agent was discovered and administered as it seemed to improve the prognosis in parturients, as it did for the general population, while for COVID-19, a specific antiviral agent was not found by that time[16-20].

ARDS

ARDS caused by H1N1 infection was more common in the third trimester and post-partum[21-24]. The average days of mechanical ventilation varied from 8 to 25 days[21-24]. Better outcomes were associated with early onset antiviral agent administration. Prone position was used in one study in some patients[23]. ECMO was used in some patients who had severe ARDS from which 66% survived[22]. Dubar et al.[24] noted that 25% of women developed secondary infection (Table 2).

Secondary bacterial infection was not extensively studied in the SARS-CoV-2 cases during pregnancy, nevertheless, according to a review by Lachana et al.[25], risk factors for secondary infection admitted to ICU is hospitalization for >48 h in the ICU, COVID-19 disease severity, number of lymphocytes (0.7×10^9/L) and lower values of PaO_2/FiO_2

ratio. ARDS induced by COVID-19 was also more common in the third trimester and post-partum[26-28]. There was no anti-viral agent that seemed to improve maternal outcomes; however, mortality rate could not be assessed since results were published prior to maternal discharge or death[20]. Ten patients were placed on ECMO and 9 survived[27]. Thus, present evidence shows that ECMO had better results in survival in ARDS induced by SARS-CoV-2 compared to H1N1. Nevertheless, it is not clear whether this is related to the experience gained in the last two years. The average ventilator days for parturients with ARDS caused by COVID-19, was 1 to 3 days (Table 1)[26-31].

Thus, one major difference between H1N1 and COVID-19 is the average of ventilator days was much higher in the H1N1 induced ARDS. Lung mechanics were only assessed in one study, that of Bamasood et al.[27], and those patients were all placed on ECMO, and had Murray scores of 3–4, which indicate severe ARDS (Murray score includes 4 criteria for the development of ALI/ARDS from 0 to 4 according to the severity of the condition). The mean value of their static compliance (Cstat) was 23.5 mL/cmH$_2$O (stiff lung) and the average positive end expiratory pressure (PEEP) placed 16.4 cmH$_2$O[27].

Perinatal outcomes

Perinatal outcomes were assessed only in women admitted to the ICU. Neonatal outcomes, however, were assessed in COVID-19 and H1N1 infected women regardless of disease severity. Neonatal outcomes of women in those groups

Table 3. Maternal morbidity and mortality attributed to H1N1

First author	Year of publication	Study type	Country	Number of women	Hospitalizations n (%)	Deaths n (%)
Da Silva[10]	2014	Prospective cohort	Brazil	163	70 (43)	18 (11)
Doyle[11]	2013	Retrospective cohort	USA	187	163 (87)	8 (4)
Jamieson[12]	2009	Prospective cohort	USA	34	14 (41)	1 (2.9)
Siston[13]	2010	Prospective cohort	USA	788	115 (22.6)	30 (3.8)
Al Husban[14]	2019	Retrospective cohort	Jordan	27	19 (70)	1 (3)
Kim[15]	2010	Retrospective cohort	Korea	150	12 (8)	0 (0)

Table 4. Maternal morbidity and mortality attributed to COVID-19

First author	Year of publication	Study type	Country	Number of women	Hospitalizations n (%)	Deaths n (%)
Epelboin[16]	2021	Retrospective national cohort	France	874	874	2 (0.23)
Qeadan[17]	2021	Retrospective cohort	USA	1609	974 (60)	4 (0.2)
Villar[18]	2021	Retrospective multinational cohort		706	706	11 (1.6)
Asalkar[19]	2021	Cross-sectional	India	871	871	9 (1.03)

Table 5. Perinatal outcomes of ICU admitted women (H1N1)

First author	Year of publication	Study type	Number of women admitted to ICU	Total number of neonates born	Number of liveborn neonates
Dubar[24]	2010	Prospective cohort	40	33	33
Nair[22]	2011	Retrospective cohort	12	12	10
ANZIC[21]	2011	Retrospective cohort	64	60	56
Al-Husban[14]	2019	Retrospective cohort	2	2	2
CDC[32]	2009–2010	Retrospective cohort	168	160	148

Table 6. Perinatal outcomes of ICU admitted women (COVID-19)

First author	Year of publication	Study type	Number of women admitted to ICU	Total number of neonates born	Number of liveborn neonates
Pierce-William[38]	2020	Retrospective cohort	20	18	18
Bamasood[27]	2022	Retrospective cohort	10 (ECMO)	9	9
Dileep[34]	2022	Retrospective cohort	Unknown 53 (severe disease)	53	53
Hantoushzadeh[35]	2020	Case series	9	5	4
Asalkar[19]	2021	Cross-sectional	Unknown (9 deceased)	3	3

admitted to the ICU are still very heterogeneous (Tables 5 and 6). In general, neonates born from H1N1 positive mothers were premature, delivered by cesarean section and were admitted to the neonatal ICU (NICU) to a large extent due to prematurity. Even in patients who had to be placed on ECMO treatment, 7 livebirths were after the initiation of ECMO treatment, and from 12 neonates delivered, 10 were alive despite the extreme prematurity (mean gestational age of 31 weeks)[22]. Data from the Center for Disease Control (CDC) showed that from a cohort of 168 women being admitted to the ICU, neonatal survival was 88%[32]. Concerning neonatal outcomes of SARS-CoV-2 positive mothers admitted to the ICU, results were slightly better than H1N1[33,34]. From the study in which women were placed on ECMO, 9 of 10 neonates were liveborn and the one undelivered fetus was of the deceased mother[31] (Table 1). In another study by Hantoushzadeh et al.[35] in which 7 out of 9 women died, there were 4 liveborn neonates (Table 6). In general, the incidence of preterm delivery due to maternal deterioration, cesarean delivery and admission to NICU was high. Nevertheless, adverse neonatal outcomes in terms of mortality were not very common in COVID-19 cases. From the present data, results on perinatal outcomes between the two groups are comparable with slightly better survival being in the COVID-19 group.

Vaccination status and efficiency was not assessed to a great extent, since many studies were performed prior to approval of vaccination to pregnant women for both H1N1 and SARS-CoV- 2. Vaccination was found to reduce the incidence of polymerase chain reaction (PCR) proven maternal infection by 50% in H1N1 infection[36]. The risk of congenital malformations, preterm birth, and miscarriage was not found to be increased compared to non-vaccinated individuals[37]. However, evidence as to whether the disease impact to neonate is reduced, is still inadequate[38]. As far as neonatal outcomes are concerned, various studies have demonstrated that vaccination reduces hospitalization in the first months of life, which is attributed to both placental crossing of maternal antibodies and to possible decreased disease severity[38]. According to Pratama et al.[39], mRNA vaccines for immunization against COVID-19 potentially reduces the risk of SARS-CoV-2 infection in pregnancy. Antibody placental transfer was reported since neonates of vaccinated mothers had higher levels of IgG antibodies. Finally, it is worth mentioning that even though vaccination against influenza has not scientifically proved a reduction in COVID-19 severity, according to a large cross-sectional epidemiological study performed in Greece by Kopsidas et al.[40], people who regarded themselves more susceptible to severe COVID-19 infection were more likely to get vaccinated against influenza, even if they had not been vaccinated against the virus in the past.

DISCUSSION

Multiple physiological changes occur during pregnancy which, admittedly, change the state of women making them

high-risk for increased severity of infections, and certain autoimmune diseases. One of those changes is weight gain. The higher the pre-pregnant body mass index (BMI) the lower the weight encouraged to be gained in order for maternal and fetal well-being[41]. Nevertheless, remaining within the recommended limits is not very common. In fact, more than 50% of parturients in the US are obese and 8% are extremely obese (BMI >40 kg/m^2)[42]. Regarding the cardiorespiratory system, there is a progressive increase in total blood volume and cardiac output, reduction of systemic vascular resistance and pulmonary vascular resistance.

Moreover, there is a decrease in vascular colloid pressure, which leads to pulmonary edema formation susceptibility. Oxygen consumption is increased by approximately 15% and minute ventilation by approximately 40–50%[43]. The main mechanical changes parturients undergo are diaphragmatic elevation due to abdominal distention leading to reduction of functional residual capacity (FRC) and extension of the anteroposterior diameter of the chest wall, caused by the relaxation of rib fibrocartilage joints[41]. Consequently, vital capacity is generally sustained throughout pregnancy so that it matches increased oxygen consumption[41]. Therefore, previous assumptions that dyspnea of pregnancy is attributed to declining vital capacity are probably false. In fact, a possible explanation for this phenomenon is a disproportionate increase in minute ventilation needs and actual increase in vital capacity[41]. Additionally, some evidence has shown that even airway resistance increases during pregnancy[44]. All the previous changes occur in order to increase the delivery of oxygen to peripheral tissues and particularly to the fetus.

Evidence shows that oxygen consumption increases during pregnancy[45]. Thus, deterioration of parturients with community acquired pneumonia (CAP) that would not have the same effect had not they been pregnant, is partly explained. Furthermore, immunological changes are also crucial for infection in pregnancy. It has been shown that there is increased leukocyte number with increased number or polymorphonuclear cells (PMCs), and particularly immature granulocytes[41]. It has also been shown that there is impaired chemotaxis gradually, with a peak on the 26th week of gestation, partly explaining higher incidence of symptomatic infections on the second, and mainly third, trimester of pregnancy[46].

Evidence is rich concerning epidemiological data of both infections and particularly COVID-19 disease. Nevertheless, data concerning severe disease and ARDS are not yet adequate.

Pregnancy outcomes from the COVID-19 pandemic have been widely studied during the past two years. According to Hantoushzadeh et al.[35] who performed a systematic review and meta-analysis on perinatal outcomes of COVID-19 infection, the most common comorbidities in positive parturients were hypertension and diabetes, while among the non-obstetric comorbidities was asthma. Furthermore, concerning perinatal outcomes, around 30% of parturients experienced pre-term delivery. Premature rupture of

membranes and fetal distress were developed by 2% of the studied cases. Mean birth weight was 2855 g and prevalence of small-for-gestational age was 17.4%. Apgar scores were 8.8 and 9.2 at 1 and 5 min, respectively[47].

Furthermore, Pathirathna et al.[48] performed a systematic review (21 observational studies) on perinatal outcomes in COVID-19 infected parturients. Maternal death was found to be significantly increased in infected individuals (p<0.05), and pre-eclampsia was found to be significantly incident in infected parturients (p<0.05). Moreover, cesarean section was found to be significantly increased as a method of delivery in infected patients compared to non-infected individuals (p<0.05). No statistical significance was found in miscarriages/abortions, and in premature rupture of membranes (PROM), between infected and non-infected individuals. Regarding fetal outcomes, fetal distress was found to be increased in infected women (p<0.05) but no increase in neonatal death was found. Preterm birth, low birth weight, APGAR score of <7, and admissions to the NICU, were all found to be increased in infected individuals (p<0.05). Neonatal death was not found to be statistically significant[48].

Recent data have been gathered mainly after the 2009 Influenza A/H1N1 pdm09 and have variable results. Hansen et al.[49] gathered data from July 2008 to May 2010 from a sample of 109015 pregnancies, from which 959 (0.9%) were diagnosed with H1N1. Firstly, increased incidence of influenza related adverse outcomes were associated in parturients suffering from asthma (8.1% vs 3.9%), neurologic disease (3.6% to 0.9%) or obesity (29.8% to 22%)[49]. Moreover, women who were diagnosed with H1N1 or seasonal influenza were commonly non-Caucasian and aged 20–29 years[49]. Hospitalization within 30-days of diagnosis was more common in parturients infected with H1N1 (15%) compared to seasonal influenza virus (4%). Antiviral treatment was administered in 553 parturients infected with H1N1, early (within 2 days of diagnosis), and in 34 women late (3–7 days after diagnosis), and the rate of 30-day hospitalization was three times higher in women who received late antiviral treatment[49].

A systematic review performed by Meijer et al. (100 studies-observational and randomized control mostly) concerning perinatal outcomes of H1N1 infection[50], found that women from second trimester onwards are at increased risk of hospitalization. Up to 55% was found to have underlying conditions. The range of hospitalized women classified as severe cases was 2–64%, and median duration of hospitalization was 3–9 days. Maternal mortality rate ranged from 0–33%[50]. Fell et al.[51] assessed the risk of perinatal abnormalities in a systematic review (21 comparative studies) and found that parturients not suffering from influenza had a risk of preterm birth ranging from 5.2% to 11.5%, while women who were positive to influenza A/H1N1 pdm had an incidence ranging from 4 to 25.8%. The range of results is relatively wide due to the fact that studies were heterogeneous, especially in disease severity. Among

women who had severe disease, the risk of preterm birth was found to be 24%.

Nonetheless, in epidemiological studies of parturients of variable disease severity, no significant risk of preterm birth was found[51]. The incidence of fetal death, miscarriages/abortions and PROM were not meaningfully interpreted since evidence was very heterogeneous[51]. Another national cohort study, assessing the same matter[38], found that the stillbirth rate in 2009/H1N1 pandemic in UK was 27 (95% CI: 11–56) per 1000, showing an association between H1N1 infection and perinatal mortality. Moreover, H1N1 positive parturients had higher incidence of delivering preterm (<37 weeks of gestation) and 72% of those deliveries were by cesarean section due to deteriorated maternal state. Mean birth weight was lower in neonates of H1N1 positive mothers compared to negative mothers. Nevertheless, this was attributed to lower gestational age of those neonates. Congenital abnormalities were found to be 32 (95% CI: 14–62) per 1000. Incidence of neonatal NICU admission was 33%[38].

All the above data referred mainly to the general effects of SARS-CoV-2 and H1N1 in the pregnant population. Nonetheless, the goal of this study was to assess the effects of severe disease on pregnancy. Data about this are still very inhomogeneous both in H1N1 and SARS-CoV-2.

CONCLUSIONS

Maternal mortality was associated with comorbidities such as obesity, hypertensive diseases of pregnancy, asthma and others, for both infections. In COVID-19 disease mortality was associated with higher maternal age (>30 years), which was not evident in H1N1 disease. H1N1 disease was associated with better outcomes when antiviral agent (oseltamivir) was administered within the first 48 hours of symptoms, while for COVID-19 there were no specific antiviral agents to be administered. The average days of mechanical ventilation were significantly different between the groups, since in the COVID-19 group they were significantly fewer. ECMO seemed to have better results in pregnant patients with COVID-19. Finally, both infections were related with preterm delivery, higher rate of cesarean section and neonatal admission to the NICU; however, neonatal mortality was slightly lower in the COVID-19 group.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for disclosure of Potential Conflicts of Interest and none was reported. N. Rovina reports receiving payments for presentations from GSK, Astra Zeneca, Menarini, Chiesi, Baxter and Pfizer. She also reports receiving support for attending meetings and/or travel from Astra Zeneca, GSK and Guidotti, participating on a Data Safety Monitoring Board or Advisory Board of GSK, Astra Zeneca, Menarini, Chiesi, Guidotti and ELPEN. Furthermore, she reports having a leadership role in the Hellenic Thoracic Society Pharmacovigilance Committee, National Organization for Medicines.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed

DISCLAIMER

A. Koutsoukou and N. Rovina report that they are Editorial Board Members of Pneumon. They had no involvement in the peer-review or acceptance of this article, and had no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to a handling editor of the journal.

REFERENCES

1. Pandemic (H1N1) 2009 - update 105. World Health Organization. June 18, 2010. Accessed October 21, 2022. https://www.who.int/emergencies/disease-outbreak-news/item/2010_06_18-en

2. 14.9 million excess deaths associated with the COVID-19 pandemic in 2020 and 2021. World Health Organization. May 5, 2022. Accessed October 21, 2022. https://www.who.int/news/item/05-05-2022-14.9-million-excess-deaths-were-associated-with-the-covid-19-pandemic-in-2020-and-2021

3. Bos LDJ, Ware LB. Acute respiratory distress syndrome: causes, pathophysiology, and phenotypes. Lancet. 2022;400(10358):1145-1156. doi:10.1016/S0140-6736(22)01485-4

4. McCormack V, Tolhurst-Cleaver S. Acute respiratory distress syndrome. BJA Educ. 2017;17(5):161-165. doi:10.1093/bjaed/mkx002

5. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA. 2016;315(8):788-800. doi:10.1001/jama.2016.0291

6. Van Kerkhove MD, Vandemaele KAH, Shinde V, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. PLoS Med. 2011;8(7):e1001053. doi:10.1371/journal.pmed.1001053

7. Coronavirus disease (COVID-19): Similarities and differences between COVID-19 and Influenza. World Health Organization. Updated January 3, 2024. Accessed October 21, 2022. https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-covid-19-similarities-and-differences-with-influenza

8. Rush B, Martinka P, Kilb B, McDermid RC, Boyd JH, Celi

LA. Acute Respiratory Distress Syndrome in Pregnant Women. Obstet Gynecol. 2017;129(3):530-535. doi:10.1097/AOG.0000000000001907

9. Muthu V, Agarwal R, Dhooria S, et al. Epidemiology, lung mechanics and outcomes of ARDS: A comparison between pregnant and non-pregnant subjects. J Crit Care. 2019;50:207-212. doi:10.1016/j.jcrc.2018.12.006

10. da Silva AA, Ranieri TMS, Torres FD, et al. Impact on pregnancies in south Brazil from the influenza A (H1N1) pandemic: cohort study. PLoS One. 2014;9(2):e88624. doi:10.1371/journal.pone.0088624

11. Doyle TJ, Goodin K, Hamilton JJ. Maternal and neonatal outcomes among pregnant women with 2009 pandemic influenza A(H1N1) illness in Florida, 2009-2010: a population-based cohort study. PLoS One. 2013;8(10):e79040. doi:10.1371/journal.pone.0079040

12. Jamieson DJ, Honein MA, Rasmussen SA, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet. 2009;374(9688):451-458. doi:10.1016/S0140-6736(09)61304-0

13. Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA. 2010;303(15):1517-1525. doi:10.1001/jama.2010.479

14. Al-Husban N, Obeidat N, Al-Kuran O, Al Oweidat K, Bakri F. H1N1 Infection in Pregnancy; A Retrospective Study of Feto-Maternal Outcome and Impact of the Timing of Antiviral Therapy. Mediterr J Hematol Infect Dis. 2019;11(1):e2019020. doi:10.4084/MJHID.2019.020

15. Kim BN, Kwak YG, Moon CS, et al. Pandemic Influenza (H1N1 2009) among pregnant Korean women. Infection and Chemotherapy. 2011;43(1):55-59. doi:10.3947/ic.2011.43.1.55

16. Epelboin S, Labrosse J, De Mouzon J, et al. Obstetrical outcomes and maternal morbidities associated with COVID-19 in pregnant women in France: A national retrospective cohort study. PLoS Med. 2021;18(11):e1003857. doi:10.1371/journal.pmed.1003857

17. Qeadan F, Mensah NA, Tingey B, Stanford JB. The risk of clinical complications and death among pregnant women with COVID-19 in the Cerner COVID-19 cohort: a retrospective analysis. BMC Pregnancy Childbirth. 2021;21(1):305. doi:10.1186/s12884-021-03772-y

18. Villar J, Ariff S, Gunier RB, et al. Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection: The INTERCOVID Multinational Cohort Study. JAMA Pediatr. 2021;175(8):817-826. doi:10.1001/jamapediatrics.2021.1050

19. Asalkar M, Thakkarwad S, Rumani I, Sharma N. Prevalence of Maternal Mortality and Clinical Course of Maternal Deaths in COVID-19 Pneumonia-A Cross-Sectional Study. J Obstet Gynaecol India. 2022;72(3):208-217. doi:10.1007/s13224-021-01545-3

20. Gajbhiye RK, Mahajan NN, Waghmare RB, et al. Clinical characteristics, outcomes, & mortality in pregnant women with COVID-19 in Maharashtra, India: Results from PregCovid registry. Indian J Med Res. 2021;153(5-6):629-636. doi:10.4103/ijmr.ijmr_1938_21

21. ANZIC Influenza Investigators and Australasian Maternity Outcomes Surveillance System. Critical illness due to 2009 A/H1N1 influenza in pregnant and postpartum women: population based cohort study. BMJ. 2010;340:c1279. doi:10.1136/bmj.c1279

22. Nair P, Davies AR, Beca J, et al. Extracorporeal membrane oxygenation for severe ARDS in pregnant and postpartum women during the 2009 H1N1 pandemic. Intensive Care Med. 2011;37(4):648-654. doi:10.1007/s00134-011-2138-z

23. Handyal H, Sanchez L, Babu R, Mekala J. Pregnancy with severe influenza A (H1N1) related acute respiratory distress syndrome: Report of three cases from a rural critical care unit in India. Indian J Crit Care Med. 2015;19(12):747-750. doi:10.4103/0972-5229.171416

24. Dubar G, Azria E, Tesnière A, et al. French experience of 2009 A/H1N1v influenza in pregnant women. PLoS One. 2010;5(10):e13112. doi:10.1371/journal.pone.0013112

25. Lachana A, Chrysanthopoulou E, Vakiarou F, Dimopoulos G. Secondary bacterial infections in patients with COVID-19. Pneumon. 2021;34(2):6. doi:10.18332/pne/136152

26. Scheler CA, Discacciati MG, Vale DB, Lajos GJ, Surita F, Teixeira JC. Mortality in pregnancy and the postpartum period in women with severe acute respiratory distress syndrome related to COVID-19 in Brazil, 2020. Int J Gynaecol Obstet. 2021;155(3):475-482. doi:10.1002/ijgo.13804

27. Mohammed Bamasood O, Shamsah M, Alfoudri H, et al. Extracorporeal Membrane Oxygenation in Pregnant Women With COVID-19. ASAIO J. 2022;68(4):471-477. doi:10.1097/MAT.0000000000001646

28. Pierce-Williams RAM, Burd J, Felder L, et al. Clinical course of severe and critical coronavirus disease 2019 in hospitalized pregnancies: a United States cohort study. Am J Obstet Gynecol MFM. 2020;2(3):100134. doi:10.1016/j.ajogmf.2020.100134

29. Marwah S, Kanwar R, Naghma S, Dabral A, Gupta N. A Clinical Study on Initial Experience of COVID-19 ARDS in Obstetric Patients at a Tertiary Care Centre in India. Case Rep Obstet Gynecol. 2021;2021:5591041. doi:10.1155/2021/5591041

30. Yan J, Guo J, Fan C, et al. Coronavirus disease 2019 in pregnant women: a report based on 116 cases. Am J Obstet Gynecol. 2020;223(1):111.e1-111.e14. doi:10.1016/j.ajog.2020.04.014

31. WAPM (World Association of Perinatal Medicine) Working Group on COVID-19. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection. Ultrasound Obstet Gynecol. 2021;57(2):232-241. doi:10.1002/uog.23107

32. Maternal and infant outcomes among severely ill pregnant and postpartum women with 2009 pandemic influenza A (H1N1) --- United States, April 2009--August 2010. Centers for Disease Control and Prevention; 2011. Accessed October 21,

2022. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6035a2.htm

33. Cheng SO, Khan S, Alsafi Z. Maternal death in pregnancy due to COVID-19. Ultrasound Obstet Gynecol. 2020;56(1):122. doi:10.1002/uog.22111

34. Dileep A, ZainAlAbdin S, AbuRuz S. Investigating the association between severity of COVID-19 infection during pregnancy and neonatal outcomes. Sci Rep. 2022;12(1):3024. doi:10.1038/s41598-022-07093-8

35. Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, et al. Maternal death due to COVID-19. Am J Obstet Gynecol. 2020;223(1):109.e1-109.e16. doi:10.1016/j.ajog.2020.04.030

36. Conlin AMS, Bukowinski AT, Sevick CJ, DeSciscolo C, Crum-Cianflone NF. Safety of the pandemic H1N1 influenza vaccine among pregnant U.S. military women and their newborns. Obstet Gynecol. 2013;121(3):511-518. doi:10.1097/AOG.0b013e318280d64e

37. Irving SA, Kieke BA, Donahue JG, et al. Trivalent inactivated influenza vaccine and spontaneous abortion. Obstet Gynecol. 2013;121(1):159-165. doi:10.1097/aog.0b013e318279f56f

38. Pierce M, Kurinczuk JJ, Spark P, Brocklehurst P, Knight M; UKOSS. Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study. BMJ. 2011;342:d3214. doi:10.1136/bmj.d3214

39. Pratama NR, Wafa IA, Budi DS, Putra M, Wardhana MP, Wungu CDK. mRNA Covid-19 vaccines in pregnancy: A systematic review. PLoS One. 2022;17(2):e0261350. doi:10.1371/journal.pone.0261350

40. Kopsidas I, Chorianopoulou E, Kourkouni E, et al. COVID-19 pandemic impact on seasonal flu vaccination: A cross-sectional study. Pneumon. 2021;34(2):8. doi:10.18332/pne/136173

41. Chestnut DH, Polley LS, Wong CA, Tsen LC. Chestnut's Obstetric Anesthesia: Principles and Practice. 4th ed. Mosby; 2009.

42. Stüber TN, Künzel EC, Zollner U, Rehn M, Wöckel A, Hönig A. Prevalence and Associated Risk Factors for Obesity During Pregnancy Over Time. Geburtshilfe Frauenheilkd. 2015;75(9):923-928. doi:10.1055/s-0035-1557868

43. Soma-Pillay P, Nelson-Piercy C, Tolppanen H, Mebazaa A. Physiological changes in pregnancy. Cardiovasc J Afr. 2016;27(2):89-94. doi:10.5830/CVJA-2016-021

44. Harirah HM, Donia SE, Nasrallah FK, Saade GR, Belfort MA. Effect of gestational age and position on peak expiratory flow rate: a longitudinal study. Obstet Gynecol. 2005;105(2):372-376. doi:10.1097/01.AOG.0000152303.80103.69

45. Pernoll ML, Metcalfe J, Schlenker TL, Welch JE, Matsumoto JA. Oxygen consumption at rest and during exercise in pregnancy. Respir Physiol. 1975;25(3):285-293. doi:10.1016/0034-5687(75)90004-3

46. Krause PJ, Ingardia CJ, Pontius LT, Malech HL, LoBello TM, Maderazo EG. Host defense during pregnancy: neutrophil chemotaxis and adherence. Am J Obstet Gynecol. 1987;157(2):274-280. doi:10.1016/s0002-9378(87)80150-3

47. Yee J, Kim W, Han JM, et al. Clinical manifestations and perinatal outcomes of pregnant women with COVID-19: a systematic review and meta-analysis. Sci Rep. 2020;10(1):18126. doi:10.1038/s41598-020-75096-4

48. Pathirathna ML, Samarasekara BPP, Dasanayake TS, Saravanakumar P, Weerasekara I. Adverse Perinatal Outcomes in COVID-19 Infected Pregnant Women: A Systematic Review and Meta-Analysis. Healthcare (Basel). 2022;10(2):203. doi:10.3390/healthcare10020203

49. Hansen C, Desai S, Bredfeldt C, et al. A large, population-based study of 2009 pandemic Influenza A virus subtype H1N1 infection diagnosis during pregnancy and outcomes for mothers and neonates. J Infect Dis. 2012;206(8):1260-1268. doi:10.1093/infdis/jis488

50. Meijer WJ, van Noortwijk AGA, Bruinse HW, Wensing AMJ. Influenza virus infection in pregnancy: a review. Acta Obstet Gynecol Scand. 2015;94(8):797-819. doi:10.1111/aogs.12680

51. Fell DB, Savitz DA, Kramer MS, et al. Maternal influenza and birth outcomes: systematic review of comparative studies. BJOG. 2017;124(1):48-59. doi:10.1111/1471-0528.14143