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REVIEW

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SARS-CoV-2 in the context of past coronaviruses epidemics: Consideration for prenatal care

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Abstract

Since December 2019, the novel SARS-CoV-2 outbreak has resulted in millions of cases and more than 200 000 deaths worldwide. The clinical course among non-pregnant women has been described, but data about potential risks for women and their fetus remain scarce. The SARS and MERS epidemics were responsible for miscarriages, adverse fetal and neonatal outcomes, and maternal deaths. For COVID-19 infection, only nine cases of maternal death have been reported as of 22 April 2020, and pregnant women seem to develop the same clinical presentation as the general population. However, severe maternal cases, as well as prematurity, fetal distress, and stillbirth among newborns have been reported. The SARS-CoV-2 pandemic greatly impacts prenatal management and surveillance and raise the need for clear unanimous guidelines. In this narrative review, we describe the current knowledge about coronaviruses (SARS, MERS, and SARS-CoV-2) risks and consequences on pregnancies, and we summarize available current candidate therapeutic options for pregnant women. Finally, we compare current guidance proposed by The Royal College of Obstetricians and Gynaecologists, The American College of Obstetricians and Gynecologists, and the World Health Organization to give an overview of prenatal management which should be utilized until future data appear.

1 | INTRODUCTION

In December 2019, multiple cases of pneumonia of unknown origin were reported in the Province of Wuhan, China, and rapidly attributed to a novel coronavirus, closely related to the 2003 severe acute respiratory syndrome (SARS-CoV) and therefore named the SARS 2 (SARS-CoV-2). This new virus spread throughout China and rapidly covered the globe causing over 2 million cases and more than 200 000 deaths within the recent months. The World Health Organization (WHO) declared this outbreak a pandemic on 11 March 2020 (Figure 1).

Although numerous reports have described the clinical course of COVID-19 among nonpregnant patients, data regarding pregnant women remain scarce.[1,2] Recent outbreaks of emerging infections have highlighted their potential impact on pregnant women and/or their fetus, such as the 2009 H1N1 influenza pandemic[3] or more recently, the Zika virus outbreak in the Americas.[4] As information regarding this novel coronavirus is lacking, data on SARS-CoV-1 (2003) and MERS-CoV (Middle East respiratory syndrome, 2012) may help us understand the potential risks for pregnancy in the context of COVID-19. In this narrative review, we described the current knowledge (up to 22 April 2020) about the risks and consequences of SARS-CoV-2 on pregnant women and their babies and compare them to SARS and MERS. Because therapeutic options and clinical management remain unclear, we summarize information about treatments that have been tried or could be considered for COVID-19 affected pregnancies. Finally, we compare current guidelines proposed by the The Royal College of Obstetricians and Gynaecologists (RCOG), The American College of Obstetricians and Gynecologists (ACOG), and WHO to give an overview of prenatal management which should be utilized until future data are available.

2 | METHODS

A PubMed search was carried out using the terms "Coronavirus 2 and pregnancy," "SARS-CoV-2 and pregnancy," "SARS and pregnancy," and "MERS and pregnancy" that identified 447 articles published before 22 April 2020 (Figures 2 and supplementary figure 1). We reviewed all titles and abstracts when available, and limited the search to articles reporting maternal infections, fetal and perinatal outcomes, and clinical management. Guidelines providing recommendations for management of COVID-19 pregnancies were also included. At least two reviewers evaluated the articles and extracted data. Searches were limited to the English language. The process of article selection and the number of articles are described supplementary figure 1.

What is already known about the topic?

The emergence of severe-acute-respiratory-syndrome coronavirus 2 (SARS-CoV-2) and its consequences during pregnancy have led to an increasing volume of data about the maternal and fetal outcomes of SARS-CoV-2 infections.

What does this study add?

This review summarizes maternal and fetal outcomes found in the literature as of 22 April 2020. This review also provides an overview of current candidate therapeutic options during pregnancy and clinical guidelines for prenatal management of COVID-19-affected pregnancies.

3 | BACKGROUND: VIROLOGY AND EPIDEMIOLOGY OF EMERGING CORONAVIRUSES

Coronaviridae is a large family of single-stranded RNA, non-segmented, and enveloped viruses. Although most of them cause benign disease, we have recently experienced the emergence of three novel coronaviruses associated with alarmingly high mortality rates: the SARS coronavirus 1 (SARS-CoV-1) in 2003, the MERS coronavirus (MERS-CoV) in 2011, and most recently the SARS-CoV-2 in 2020.

These viruses are members of the *Betacoronavirus* genus and have all arisen from animal reservoirs (ie, zoonosis), namely bats for SARS-CoV and SARS-CoV-2 and camels for MERS-CoV. The newly acquired human-to-human transmission allowed for their rapid dispersion, causing epidemics and pandemics among naïve populations.[5] Human-

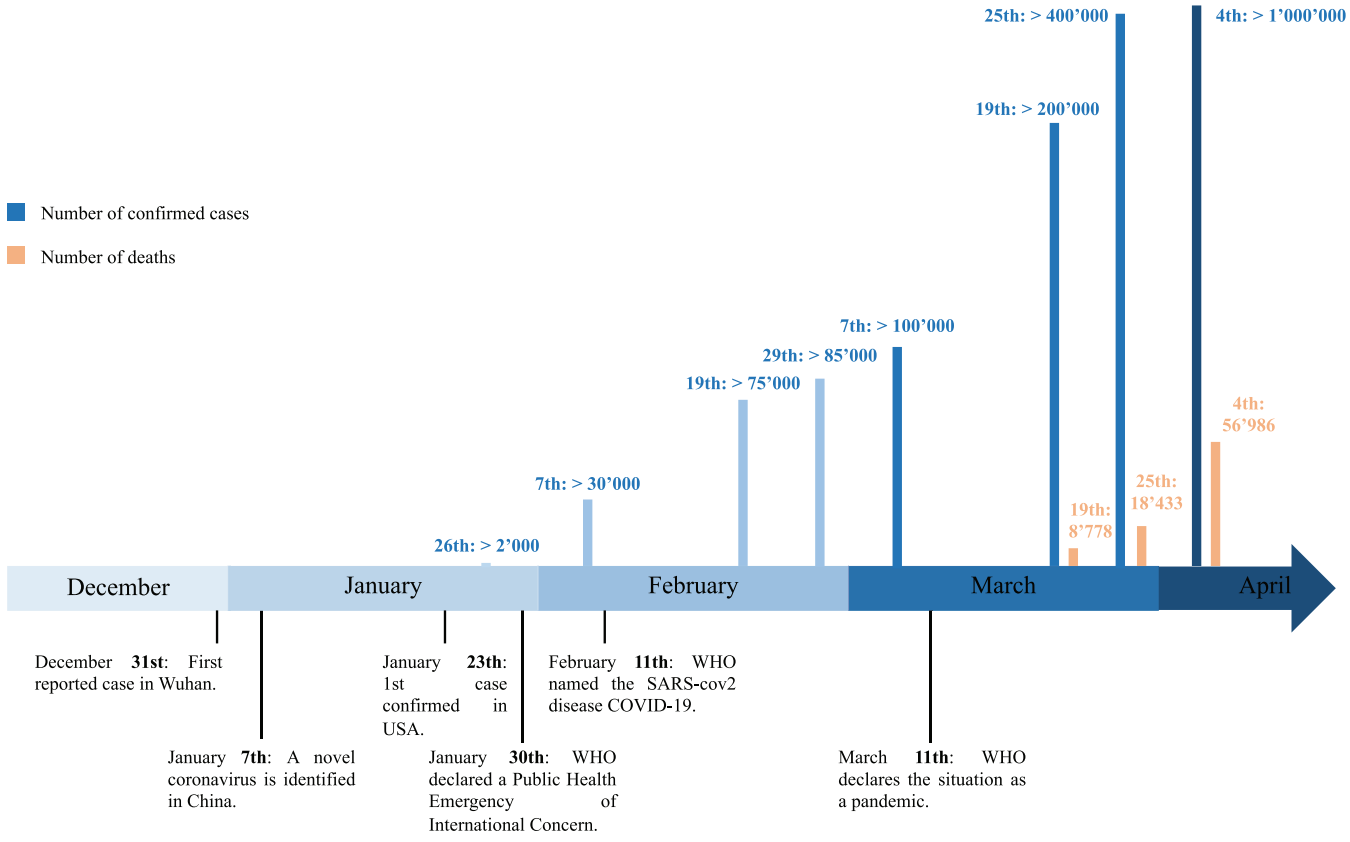

FIGURE 1 Timeline of main events, total number of confirmed cases by WHO, and total number confirmed deaths by WHO from December 2019. WHO, World Health Organization [Colour figure can be viewed at wileyonlinelibrary.com]

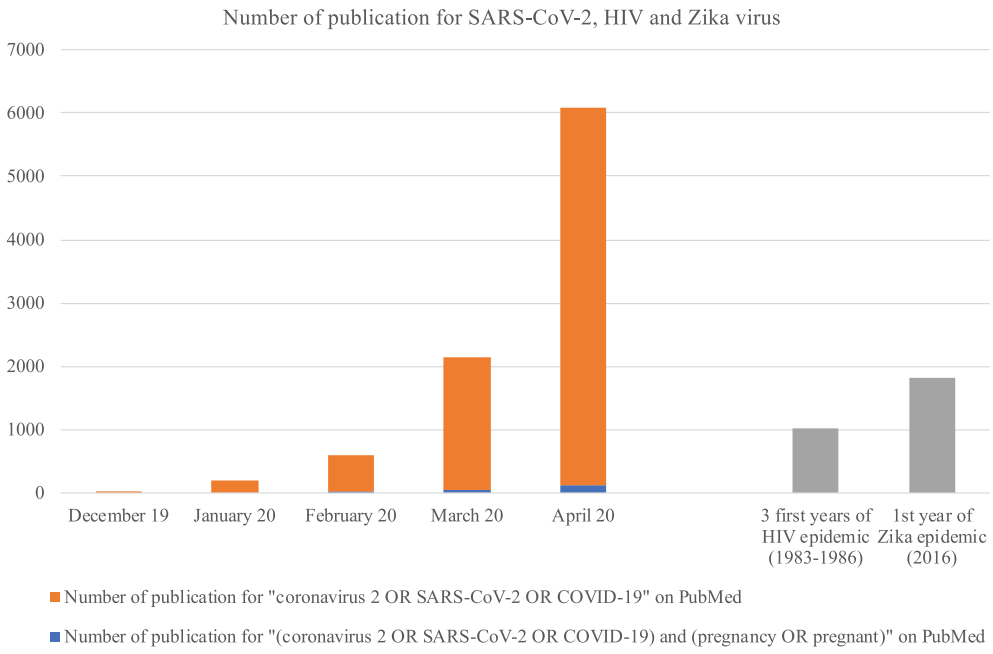

FIGURE 2 Number of publication for SARS-CoV-2 from December 2019, compared with HIV (1983-1986) and Zika virus (2016) [Colour figure can be viewed at wileyonlinelibrary.com]

to-human transmission occurs via droplets and fomites. Although transmission through aerosols has been demonstrated in laboratory conditions,[6] its public health relevance remains highly debated. Recent data have demonstrated the efficacy of contact and droplet protection measures among hospitalized staff, suggesting the lack of significant aerosol transmission.[7]

SARS-CoV-1 presented as a novel atypical pneumonia in Hong Kong in June 2003. More than 8000 individuals were infected around the world and the overall case fatality rate (CFR) was estimated to be around 11% according to the WHO.[8] Drastic infectious disease control measures halted the epidemic, and no cases have been reported since 2004.[5]

Later in 2012, MERS-CoV emerged in the Middle East. Infected individuals exhibited a severe respiratory illness with a high fatality rate of 34.4%. At the end of November 2019, more than 2400 confirmed cases were reported, the majority in Saudi Arabia. This epidemic was marked by a high rate of nosocomial transmission with 19.1% of cases being healthcare workers.[9]

At the end of 2019, the first cases of SARS-CoV-2 were reported in Wuhan, a large city in Southern China, and were linked to the Huanan seafood market. Early Chinese data showed an exponential growth of the number of cases suggesting human-to-human transmission among close contacts.[10] The World Health Organization declared this outbreak a pandemic on 11 March 2020, and strict measures, such as social distancing and public health hygiene protocols, have been taken by many countries to limit the spread of the disease. In many countries, the pandemic is still in its exponential phase as of May 2020.

SARS-CoV-2 causes an illness quite similar to the other emerging coronaviruses and was renamed "COVID-19" by the WHO on 11 February 2020. Typical symptoms of COVID-19 pneumonia include fever, dry cough, anosmia, and fatigue. These mild presentations represent 81% of cases according to a large Chinese report of 72 134 cases,[11] whereas 14% and 5% of cases present with severe or critical disease such as respiratory failure, septic shock, and multiple organ dysfunction, respectively. Similar data have been reported in the United States, with 14.3% of patients requiring intensive care management and a mortality rate that has reached 21% among hospitalized patients.[12] The most frequent complications during hospitalization are acute respiratory distress syndrome (ARDS), arrhythmia and shock, as well as thromboembolic diseases.[13,14] Atypical SARS-CoV-2 symptoms, such as diarrhea and nausea, have been frequently reported[15] along with neurological symptoms and complications such as Guillain-Barré.[16] In addition, there are increasing reports of asymptomatic infections.[17,18] This further complicates the calculation of exact mortality rates.[19,20] In a recent model-based analysis, the CFR was estimated to be 0.32% (0.27%-0.38%) in patients <60 years old (yo), 6.4% (5.7%-7.2%) in older patients, and reaching up to 13.4% (11.2%-15.9%) in those >80 yo.[21] Comorbid conditions, such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer, have been shown to be associated with increased mortality (10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer).[11]

4 | IMPACT OF EMERGING CORONAVIRUSES IN PREGNANCY

Current data regarding emerging coronaviruses and their impact in pregnancy are mostly based on case reports and small case series. As these are often biased by worse maternal and fetal outcomes, the subsequent section should be interpreted with caution.

4.1 | Maternal outcomes

Respiratory infections are known to be associated with an increased risk of maternal complications. This was observed during the Influenza A pandemic in 2009, where up to 23% of affected women required admission to intensive care and 8.2% of them died.[3,22] The relative immunosuppressed state as well as the restricted respiratory capacity of pregnancy account for such outcomes.[23] Current data regarding emerging coronaviruses, based mostly on case series, are summarized below.

4.1.1 | SARS-CoV-1

A total of 25 cases of SARS-CoV-1 infection among pregnant women were identified in the literature.[24-30] Infections were observed in the first trimester (n = 7), second trimester (n = 4), and third trimester (n = 14). Among the 25 cases of SARS-CoV, 3 maternal deaths (12%) were recorded, 10 patients required intensive care unit (ICU) admission (40%) with or without mechanical ventilation. Compared with nonpregnant women, the rates of ICU admission and maternal death were significantly higher and independent of the trimester of infection, including two patients in their first trimester. In one case, SARS-CoV-1 RNA was amplified within the cerebrospinal fluid and associated with seizures suggesting encephalitis.[26]

4.1.2 | MERS-CoV

Twelve cases of MERS-CoV infection among pregnant women were identified in the literature. Infections occurred in all trimesters of pregnancy (n = 2 for first trimester, n = 3 for second trimester, and n = 6 for third trimester). Three (40%) maternal deaths were identified, seven (58.3%) required ICU admission, and two (16.7%) patients remained asymptomatic. Complications were only observed among patients in their late second or third trimester. No severe adverse maternal outcomes were observed among patients infected earlier in pregnancy. The fatality rate of MERS-CoV in pregnancy (36%) was similar to nonpregnant adults (35%).[31-37]

4.1.3 | SARS-CoV-2

As of 22 April 2020, more than 150 cases have been reported. We identified four cohort studies, including 118[38] and 116[39] Chinese patients, 42 Italian patients,[40] and 43 American patients,[41] respectively. Almost all infections occurred in the third trimester or close to delivery. In general, pregnant women experienced symptoms similar to those of nonpregnant patients, developing mild clinical symptoms in the majority of cases with mainly fever, cough, and myalgia. Interestingly, among the American cohort, 32.2% (n = 14 of 43) of patients were asymptomatic at the time of diagnosis. Six patients remained asymptomatic after positive testing, suggesting the possibility of completely asymptomatic disease, which supports the eventual need for routine screening.[41]

Severe cases of COVID-19 infection in pregnant women are not frequent as with the previous coronavirus infections described above. Nevertheless, 9 (2.7%) maternal deaths have been reported among 11 Iranian patients with third trimester infections.[42-44] All women presented with typical symptoms, including dyspnea. They were previously healthy except two patients known for hypothyroidism and one patient with suspected gestational diabetes. Maternal age was between 22 and 49 yo and two women had dichorionic/diamniotic twin gestations. All women were admitted to the ICU, intubated and ventilated, and died from cardiopulmonary collapse or multiple organ failure (MOF). One had septic shock and disseminated intravascular coagulation (DIC) before progressing to heart failure. Intrauterine fetal death was described among four patients (4 of 9) with gestational ages between 24 and 30 weeks gestation (WG). CS was performed in other cases (5 of 9) with gestational age between 30 and 38 WG.

Cohort studies have reported a rate of severe disease requiring ICU admission of 6.9% to 8% (n = 9 of 118; n = 8 of 116), including three requiring mechanical ventilation among Chinese patients. In the Italian cohort, a total of 17% of pregnant women (n = 7 of 42) required either oxygen supplementation through continuous positive airway pressure or ICU admission, whereas in the American cohort, four (9.3%) presented with severe disease and two (4.7%) required ICU admission without mechanical ventilation.

Severe complications in pregnant women are similar to what has been described in the general population and include MOF, respiratory failure requiring mechanical ventilation, and even extracorporeal membrane oxygenation, as described in a patient at 35 WG.[45] In the latter, the patient required an emergency Cesarean section for maternal resuscitation and the newborn unfortunately died due to an intrauterine asphyxia. The mother had MOF, needed mechanical ventilation before extracorporeal membrane oxygenation for a total of 7 days. She was discharged from hospital 6 weeks later.

Two cases of cardiomyopathy related to COVID19 were reported by Juusela et al.[46] The first pregnant woman was 45 yo, had a BMI of 44.6 m^2/kg, and was diagnosed with diet-controlled gestational diabetes. She delivered via Cesarean at 39 WG for severe preeclampsia and tested positive to SARS-CoV-2 on postpartum day 1 with evidence of fever, tachypnea, and suspicious chest imaging. She was then diagnosed with acute heart failure after an echocardiogram was performed, showing a moderately reduced left ventricular ejection fraction (LVEF) of 40% with global hypokinesis. On day 5 postpartum, the mother required mechanical ventilation and was still intubated at the time of publication. The second patient was a 26 yo women with no relevant medical history. She was admitted for respiratory symptoms necessitating nasal oxygen support. Due to the previous experience, an echocardiogram was completed and showed a moderately reduced LVEF of 40% to 45% with global hypokinesis. She rapidly developed severe features leading to a Cesarean section at 34 WG.

At the time of publication, she was postpartum day 1 and did not require oxygen support.

Although current data suggest that most pregnant women with COVID-19 will have an uncomplicated clinical course, severe complications must be anticipated. Nevertheless, the observed rates appear similar to those for nonpregnant patients between 20 and 40 yo. In a recent analysis based on a Chinese cohort, the actual rate of severe disease was 173 of 1170 (9.8%) among 20 to 39 yo patients; after adjusting for demographic factors, the expected rate of severe disease was 0.6% to 8.6%.[21]

Breslin et al also reported a similar rate of complications in pregnant women compared with nonpregnant adults[41]: 86% vs 80% with mild clinical symptoms, 9.3% vs 15% with severe symptoms, and 4.7% vs 5% requiring ICU admission, respectively. We should point out, however, that complications in the general population mainly impacted the elderly and patients with comorbidities. When comparing pregnant woman to their typical age group, they qualify as a high-risk group for adverse maternal outcomes.[47]

Therefore, although the majority of infected pregnant women seem to demonstrate a mild clinical course, pregnancies should be approached with caution considering the potential critical complications reported in several cases published so far report. More exhaustive data, however, are needed to understand the additional risk pregnancy may pose to women with a COVID-19 infection.

4.2 | Fetal and neonatal outcomes

SARS-CoV-1 and MERS-CoV infections during pregnancy were associated with adverse fetal and neonatal outcomes.

4.2.1 | SARS-CoV-1

A report on 12 pregnant women suffering from SARS-CoV-1 (2002-2003 pandemic) was published,[29] and the rate of adverse fetal/neonatal outcomes was 66% (8 of 12) in this series. Four of the seven patients (57%) infected during the first trimester experienced miscarriages. Two others decided to terminate their pregnancy after recovering from SARS, and the last had an uncomplicated pregnancy. Among the five patients infected during the second or third trimester, four (four of five, 80%) had a preterm delivery, including one for fetal distress (one of five, 20%). Two neonates exhibited respiratory distress syndrome and other complications related to prematurity (necrotizing enterocolitis). All placentas of these patients (five of five, 100%) weighed below the fifth percentile, of which two had abnormal anatomo-pathology results (thrombotic vasculopathy with avascular fibrotic villi and/or placental infarct).[48] When the infection occurred during the week before birth, no fetal growth restriction (FGR) was noted (zero of two). When the infection occurred 1 month or more before birth, two fetuses (two of three, 33%) had FGR with oligohydramnios, related to the abnormal placentas presented above. Another Chinese series[24] reported fetal demise in one of five (20%) fetuses exposed to SARS-CoV-1 during the second or third trimester of pregnancy.

4.2.2 | MERS-CoV

Eleven fetuses/neonates from mothers infected with MERS-CoV have been described.[36,49,34] Among them, three (3 of 11, 27%) had fetal or neonatal demise: two intra-uterine fetal deaths at 20 and 34 weeks, and one neonatal demise at 24 weeks due to extreme prematurity.[34,31] Abruption was identified on placental examination from these fetuses and from another liveborn neonate who presented with fetal distress at 37 weeks.[35]

4.2.3 | SARS-CoV-2

With regards to SARS-CoV-2 infection during pregnancy, several case-series and case reports show that similar adverse fetal and neonatal outcomes could occur. Overall, we included 142 cases with fetal and/or neonatal outcomes available at the time of this review. Among them, 40 (28%) were born prematurely (<37 weeks) and 20 (14%) had adverse outcomes (FGR, fetal or neonatal demise, severe symptoms at birth). Congenital or perinatal transmission was suspected in 6 of 115 (5%) newborns tested. Details of all cases available are presented in Table 1.

In a case-control study,[51] among 17 fetuses from SARS-CoV-2 infected mothers, 3 exhibited FGR (3 of 17, 18%), 2 had fetal distress (2 of 17, 12%), and 4 were born prematurely (4 of 17, 24%) due to PROM or placental bleeding. The rates of low birth weight and premature birth were significantly higher when compared with the control groups. One of these fetuses also exhibited sinus tachycardia that persisted after birth. Zhu et al[50] described the outcomes of 10 neonates from SARS-CoV-2 infected mothers. Two of them were small for gestational age (2 of 10, 20%), and six had a Pediatric Critical Illness Score below 90 with shortness of breath (6 of 10, 60%), fever (2 of 10, 20%), thrombocytopenia accompanied by abnormal liver function (2 of 10, 20%), tachycardia (1 of 10, 10%), vomiting (1 of 10, 10%), and pneumothorax (1 of 10, 10%). Neonatal radiography showed abnormalities in seven of them (7 of 10, 70%): four had signs of infection, two respiratory distress syndrome, and one pneumothorax. Among these neonates, two (2 of 10, 20%) had DIC and one (1 of 10, 10%) refractory shock with MOF leading to death at day 8 of life. Liu et al[56] presented the outcomes of 10 other newborns exposed during pregnancy: none which were positive for SARS-CoV-2 at birth, 6 (6 of 10, 60%) were premature (for fetal distress in three cases, 3 of 10, 30%), and 1 was stillborn (1 of 10, 10%). Chen et al[54] described a series of nine newborns from infected mothers during the third trimester. Two (2 of 9, 22%) had a low birthweight and four (4 of 9, 44%) were premature (for fetal distress in two cases), none experienced a severe adverse outcome. Yu et al also reported a series of seven newborns from infected mothers during the third trimester, without adverse outcomes. One

of these neonates had a positive SARS-CoV-2 PCR 36 hours after birth, leading to the suspicion of a perinatal transmission. Liu et al[53] described briefly the outcomes of 13 newborns from infected mothers. Induced prematurity was noted in 54% (7 of 13) but none had neonatal complications. In the New-York series,[41] which presented the outcomes of 18 infants from infected mothers, all but one had negative neonatal testing for SARS-CoV-2. One infant had an "indeterminate" test result, which was clinically managed as a "presumptive negative" diagnosis, as this result may reflect low level detection. In this series, three (3 of 18, 17%) instances of fetal distresses were noticed, one infant (1 of 18, 6%) was premature and one (1 of 18, 6%) presented with RDS with a concern for sepsis. Zeng et al[55] reported the largest series to date, with 33 newborns included. A perinatal infection was suspected in three of them (3 of 33, 9%), with a positive PCR at days 2 and 4 of life. Infected newborns presented with higher rates of FGR, prematurity, and complications at birth (fever, pneumonia, RDS, and shortness of breath) than noninfected newborns: 33% vs 7%, 33% vs 10%, and 100% vs 10%, respectively. Wang[60] reported one case with a positive PCR in both the mother and her newborn (whereas placental and umbilical blood samples were negative). This newborn had lymphocytopenia, abnormal liver function, and elevated creatine kinase, although was clinically stable. Congenital or perinatal transmission was also suspected in three other cases.[66,67] SARS-CoV-2 IgM antibodies were elevated in these three newborns, although their nasopharyngeal PCRs were negative. In an editorial related to these cases, Kimberlin[68] pointed out that false-positive results due to cross-reactivity of IgM could occur and perinatal testing remains a challenge.

Interestingly, Zamaniyan et al[69] described a case of positive SARS-CoV-2 amniotic sample from a newborn, raising concern about potential vertical transmission in mothers with serious illness. Indeed, possible vertical transmission has been questioned by other authors[66,67] and remains unclear.

A case of second trimester miscarriage was reported by Baud et al[70] in a patient at 19 WG positive for SARS-CoV-2. Virological findings confirmed the presence of the virus in the placenta, but not in fetal tissue or maternal samples, suggesting a potential impact of SARS-CoV-2 early in the pregnancy.

In other CoV infections during the second or third trimester of pregnancy, it is interesting to note that placental changes seem to precede FGR. Severe maternal respiratory illness related to CoV infection may lead to a circulatory insufficiency in both the placenta and the fetus. Thus, a maternal COVID infection could affect the oxygen supply, leading to placental insufficiency, intrauterine growth restriction (IUGR), fetal distress, and/or fetal demise. A direct impact of the virus itself, by increasing fibrin deposits or thrombo-embolic events in the placenta, cannot be excluded and warrants further investigation.

Similarly, maternal SARS related to CoV-2 infection during the first trimester of pregnancy could disrupt the uterine placental flow, leading to miscarriage. Although the risk of miscarriage has been described with SARS-CoV-1 infection, no cases have yet been reported with SARS-CoV-2 infection.

5 | MANAGEMENT OF PREGNANT WOMEN WITH A SEVERE ACUTE RESPIRATORY DISEASE

Currently, no curative agent has been found for COVID-19. Studies conducted so far (including randomized controlled trials, RCTs) have been plagued by poor methods and reporting, such as exclusion of patients with worse outcome from the treated group, different endpoints between protocols and published reports, premature stopping of RCT (leading to lack of statistical power), use of endpoints of no clinical value (such as viral load), and degrees of severity of enrolled patients (so that the benefit of a treatment or lack thereof in a cohort of patients may not generalizable to patients with different degrees of severity, lack of optimization of treatment dose, or duration of treatment, to name but a few).

5.1 | Pharmacological options for SARS-CoV-2 in pregnancy

Several drugs are currently being evaluated as potential treatment for SARS-CoV-2 including hydroxychloroquine, lopinavir-ritonavir combination, remdesivir, oseltamivir, Interferon alpha (INFα), darunavir, baricitinib, tocilizumab (TCZ), and immunoglobulin therapy.

Hydroxychloroquine use in pregnant women has raised concerns in the past especially for an increased risk of cardiac malformation[71] and its retinal and ototoxicity,[72,73] related to the use of chloroquine and not hydroxychloroquine, findings which were not confirmed in more recent case series.[74,75,76,77] In the most recent systematic review and meta-analysis conducted in 2016, Kaplan and Koren[78] found no increase "in the rates of major congenital craniofacial and cardiovascular, nervous system and genitourinary malformations in the infants." However, there was a significant increase in the spontaneous abortion rate, which could be associated with the underlying disease activity rather than the treatment. That being said, (hydroxy)chloroquine is one of the antimalarial drugs considered compatible with pregnancy in all trimesters for prophylaxis and treatment of malaria.[79,80] A recent article gathered evidence on its use during lactation and found that it was compatible with breastfeeding,[81] concluding that hydroxychloroquine could be used for the treatment of COVID-19 infection, in usual rheumatological doses (200-400 mg/d) if proven to be effective.

The lopinavir-ritonavir combination is used as part of the HAART regimen to treat HIV infected women during pregnancy.[82] In a systematic review that included 4864 LPV/r-exposed pregnancies, the authors reported the rate of congenital abnormalities to be similar to that of the general population. However, the stillbirth rate was higher than in the general population in the UK (9.2 per 1000 infants against 4.7 per 1000 infants in 2013).[83] There has been general concern regarding protease inhibitor exposure in utero and its association with an increased risk of preterm birth[84]; however, to our knowledge, this risk has not been evaluated specifically for lopinavir and ritonavir alone and could be associated with the underlying disease activity rather than the treatment. Finally, moderate adverse events such as

TABLE 1 Fetal and neonatal outcomes after coronavirus infection during pregnancy

	MERS-CoV[31,34]	SARS-CoV-1			SARS-CoV 2												
	Alfaraj et al (2019)[36]	Wong et al (2004)[29]	Zhang et al (2003)[24]	Total	Zhu et al (2020)[50]	Li et al (2020)[51]	Breslin et al (2020)[41]	Yu et al (2020)[52]	Liu et al (2020)[53]	Chen et al (2020)[54]	Zeng et al (2020)[55]	Liu et al (2020)[56]	Zhang et al (2020)[57]	Yin (2020)[58]	Yang et al (2020)[59]	Case reports[60-65]	Total
First trimester infection	n = 1	n = 7	n = 0	n = 7	n = 0	n = 0	n = 0	n = 0	n = 0	n = 0	n = 0	n = 0	n = 0	n = 4	n = 0	n = 0	n = 4
TOP		2 (29%)		2 (29%)										3 (75%)			3 (75%)
Miscarriages	0 (0%)	4 (57%)		4 (57%)										0 (0%)			0 (0%)
Second and third trimester infection	n = 10	n = 5	n = 5	n = 10	n = 10	n = 17	n = 18	n = 7	n = 13	n = 9	n = 33	n = 10	n = 16	n = 17	n = 13	n = 11	n = 174
FGR	[a]	2 (40%)	[a]	2/5[a] (40%)	2 (20%)	3 (18%)	[a]	0 (0%)	[a]	2 (22%)	3 (9%)	[a]	[a]	1 (6%)	[a]	1 (9%)	12/102[a] (12%)
Fetal distress	[a]	1 (20%)	[a]	1/5[a] (20%)	6 (60%)	2 (12%)	3 (17%)	[a]	[a]	2 (22%)	[a]	3 (3%)	1 (6%)	1 (6%)	[a]	3 (27%)	21/141[a] (15%)
Fetal demise	2 (20%)	0 (0%)	1 (20%)	1/10 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)	1 (9%)	1/174 (1%)
Preterm birth < 37 wk	5 (50%)	2 (40%)	[a]	2/5[a] (40%)	6 (60%)	4 (24%)	1 (6%)	0 (0%)	7 (54%)	4 (44%)	4 (12%)	6 (60%)	3 (19%)	5 (29%)	2 (15%)	7 (64%)	49/174 (28%)
Neonatal demise	1 (10%)	0 (0%)	[a]	0/5[a] (0%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (9%)	2/173 (1%)
RDS at birth	[a]	2 (40%)	[a]	2/5[a] (40%)	6 (60%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)	4 (12%)	0 (0%)	1 (6%)	0 (0%)	3 (23%)	2 (18%)	14/173 (8%)
Other complications	[a]	2 (40%)	[a]	2/5[a] (40%)	6 (60%)	1 (6%)	0 (0%)	0 (0%)	[a]	0 (0%)	4 (12%)	0 (0%)	1 (6%)	0 (0%)	[a]	4 (36%)	16/147[a] (11%)
Suspected perinatal infection	[a]	0 (0%)	[a]	0/5[a] (0%)	0/9[a] (0%)	0 (0%)	1 (6%)	1/3[a] (33%)	[a]	0/6[a] (0%)	3 (9%)	0 (0%)	0/10[a] (0%)	0 (0%)	0 (0%)	2/10[a] (20%)	7/146[a] (5%)

Abbreviations: FGR, fetal growth restriction; RDS, respiratory distress syndrome.

[a]Missing data in the description of fetal/neonatal outcomes.

gastro-intestinal symptoms[85] and an increased risk for alteration in fasting glycemia[86] were reported. Lopinavir and ritonavir are drugs considered compatible with pregnancy in all trimesters for HIV treatment and has been associated with very low excretion into breastmilk.[79,80]

Regarding remdesivir, no adverse effect was reported in pregnant participants in a RCT on Ebola virus.[87] Safety data on remdesivir in pregnancy are still scarce.

Oseltamivir was used during the 2009 influenza A/H1N1 pandemic and notably in pregnant mothers. In the most recent population-based study[88] conducted on 946 176 pregnancies in Denmark from 2002 to 2013 of which 1898 were exposed to oseltamivir during pregnancy, Ehrenstein et al found no increased risk of any major congenital malformation, fetal death, preterm birth, SGA, or low 5-minutes APGAR score. This confirmed previous observations from the European registry study[89] and the Roche Global Safety Database.[90] Oseltamivir could be considered compatible with pregnancy in all trimesters if proven effective in COVID-19 treatment and has been associated with very low excretion into breastmilk.[79,80]

The Interferon alpha drug is used to treat essential thrombocythemia, chronic myelocytic leukemia, or hepatitis B and C in pregnant women. In a recent review including 43 exposed women, Sakai et al found that no adverse event had required discontinuation of the treatment but alerted physicians to "pay attention to (...) rare adverse events, such as impaired liver function, interstitial pneumonia, and attempts at suicide."[91] Safety data on INFα in pregnancy are scarce, but its similarity to beta interferon, of which safety data during pregnancy are substantial and reassuring, makes it compatible in pregnancy if proven effective for COVID-19 infection.

Regarding darunavir, no embryotoxicity or teratogenicity of this molecule was found in animal studies.[92] In a brief review of darunavir use in pregnant women, the authors concluded that it is a well-tolerated molecule that has few minor adverse effects.[93] Darunavir is considered compatible with pregnancy in all trimesters for HIV treatment despite its lack of safety data in pregnancy as its maternal benefit outweighs the potential unknown risks.[79,80]

Animal studies have demonstrated embryotoxicity of baricitinib,[94] and no safety data are available in human.

Analysis of the Roche Global Safety Database does not suggest a substantially increased risk of malformations with the use of TCZ. However, an increased rate of preterm birth and low birth weight children was possibly associated with TCZ exposure and could be associated with the underlying disease activity rather than the treatment.[95] Safety data in pregnancy are limited and due to treatment-induced immunosuppression, an increased risk of maternal-fetal infections is theoretically possible in pregnant women treated with TCZ.

Finally, serum from convalescent COVID-19 patients and hyperimmune globulins specific to the novel coronavirus are currently being evaluated as therapeutic options.[96]

Specific hyperimmune globulins have been used in several indications during pregnancy, including prevention of mother to child transmission of infectious diseases such as Hepatitis B virus (HBV)[97] and Cytomegalovirus,[98] as well as convalescent serum recently in the Ebola virus disease (EBV).[99]

In a systematic review assessing the benefits and safety of hyperimmune globulins to prevent HBV mother to child transmission in 2440 pregnant women, only one study mentioned adverse events consisting in swelling in two women.[97] More recently, convalescent serum to treat the EBV was evaluated in a nonrandomized comparative study of 99 patients that included eight pregnant women. No serious adverse reaction was associated with the transfusion.[99]

Two cases of pregnant women report the use of convalescent serum to treat SARS-CoV-2 infection.[45,100] In the first case of a 31-yo pregnant woman, no serious adverse event related to the use of convalescent plasma was reported but its relative contribution to survival could not be determined due to other concomitant treatments. The authors concluded that its clinical benefit remained unknown.[45] In the second case of a 35-yo pregnant woman with severe comorbidities who received both convalescent serum and remdesivir, no conclusion regarding safety or benefit of convalescent plasma could be drawn by the authors.[100]

Data on the use of specific hyperimmunoglobulins to prevent infections in pregnant women seem reassuring as well as those on the use of convalescent serum although they are more scarce. If they proved to be effective in COVID-19 treatment, convalescent serum and specific hyperimmunoglobulins directed against SARS-CoV-2 could be considered compatible with pregnancy in all trimesters.

5.2 | Prenatal monitoring

Regarding potential asymptomatic infected pregnant women, the WHO recommends careful monitoring of patients with epidemiological history of contact with infected individuals, whereas ACOG suggests routine antenatal care in this situation (Table 2). An algorithm for assessment and management of symptomatic parturients has been proposed by ACOG, classifying them in three categories of risk: low, moderate, and elevated. For mild presentations, women without comorbidities (low risk) should self-isolate at home, whereas those with health problems, obstetrical issues, or the inability to care for themselves (moderate risk) should be seen in an ambulatory setting. According to RCOG, pregnant women with moderate symptoms should self-isolate, unless they attend a maternity unit where patients in the second or third trimester meeting public health england (PHE)

criteria (≥1 of: (a) clinical/radiological evidence of pneumonia, (b) ARDS, (c) fever ≥37.8 and at least one of acute persistent cough, hoarseness, nasal discharge/congestion, shortness of breath, sore throat, wheezing, or sneezing) should be tested for COVID-19 and treated as infected until results are available. When pregnant women present with severe symptoms (high risk), they should immediately go to an emergency department according to ACOG algorithm. All guidelines agree that administration of corticosteroids for fetal lung maturity is still recommended per protocol in the setting of a high risk of preterm birth when the mother's condition is stable.

Regarding fetal growth surveillance, RCOG recommends an antenatal ultrasound 14 days after acute illness resolution for hospitalized patients, whereas ACOG suggests a third trimester ultrasound for COVID-19 pregnant women infected in second and third trimester. A detailed anatomy ultrasound could be considered for first trimester infections (ACOG).

5.3 | Risk of thromboemboloic disease

Data suggest that COVID-19 may be associated with an increased thromboembolic risk with a rate of venous thromboembolism (VTE) of 39% in ICU patients.[14] Therefore, routine VTE prophylaxis for hospitalized COVID-19 patients is recommended by the American Society of Hematology, the Society of Critical Care Medicine, and the International Society of Thrombosis and Haemostasis,[101-103] in absence of contraindications. The decision between low-molecular-weight heparin (LMWH) and unfractionated heparin should be discussed with consideration for the risks and benefits. RCOG advises measures such as hydration and mobility for pregnant women isolated at home who are not taking thromboprophylaxis. If a woman has risk factors for VTE, a clinical review should be attempted and VTE risk assessed to consider the introduction of prophylactic treatment with LMWH at home. Routine thromboprophylaxis for hospitalized parturients with LMWH is suggested unless birth is expected within 12 hours. In the postpartum period, VTE risk should be assessed and the first dose of LMWH should be administrated as soon as possible after birth. At the time of discharge from hospital, all women (antepartum or postpartum) should be prescribed at least 10 days of LMWH, according to RCOG recommendations. For management of critical illness, the WHO recommends the use of LMWH to reduce the incidence of VTE.

Use of prophylactic aspirin for the prevention of preeclampsia and other indications, such as antiphospholipid syndrome or prevention of FGR, is controversial in the context of COVID-19 infected women.[104] Use of nonsteroid antiinflammatory drugs can worse pulmonary disease and symptomatic COVID-19 nonpregnant patients treated with ibuprofen have experienced disease progression.[105,106] However, ongoing RCTs are evaluating the early use of aspirin in COVID-19 patients, which has the effects of inhibiting virus replication, antiplatelet aggregation, antiinflammatory, and antilung injury.[107] For pregnant women, ACOG suggests decision on low-dose aspirin treatment should be taken individually. According to Kwiatkowski et al,[108] benefits of placental complications prevention outweigh the potential risks of adverse outcomes of SARS-CoV-2 infection related to low-dose aspirin prophylaxis.

6 | SUMMARY

For the first time in a century, we are facing a SARS-coronavirus global pandemic, and we have to deal with numerous new challenges in terms of public health service. The global impact on pregnant women can only be hypothesized from recent observations gathered during the past few months from different parts of the world.

Other coronavirus epidemics, such as SARS-CoV-1, had a higher impact on pregnant women encompassing 40% of ICU admissions and 12% of mortalities. The MERS-CoV epidemic was even more lethal with a 40% mortality without significant difference of severity between pregnant and nonpregnant women. In this review, we gathered more than 150 cases of SARS-CoV-2 in pregnancy and identified a maternal mortality of 2.7% (nine cases) among those described in the literature. ICU admissions were between 6.9% and 8%. The proportion of severe complications seems to be equal to the nonpregnant population; however, these must still be anticipated in pregnant women. These rates will have to be reviewed when the true denominator (number of infected pregnant women) is known, as a significant proportion of patients remain asymptomatic.

Past coronavirus epidemics were associated with adverse outcomes for the fetus and/or newborns including miscarriages (57%), preterm birth, fetal distress, and FGR with SARS-CoV-1 infection during the second and third trimesters. Also, MERS-CoV infection resulted in fetal and neonatal demise in 27% of cases. In this review, we found that of 142 cases of SARS-CoV-2 infections in pregnancy, 28% experienced preterm birth and 14% had adverse fetal/neonatal outcomes (FGR, fetal/neonatal demise, severe symptoms at birth). Potential mechanisms include placental changes, as observed with SARS-CoV-1, and severe respiratory maternal illness, which could lead to placental insufficiency, IUGR, and fetal distress/demise. The role of SARS-CoV-2 in early adverse pregnancy outcomes needs further investigation.

With regards to pharmacological management, most agents currently tried are safe in pregnancy. As of 22 April 2020, prenatal management should be adapted to the patient's condition as indicated by ACOG and other algorithms.[109] There is currently no agreement on specific prenatal ultrasound surveillance, but due to the potential risk of IUGR, it would seem reasonable to assess fetal growth surveillance during the third trimester of pregnancy. Administration of corticosteroids in pregnant women at risk of preterm birth should be administered per protocol, with consideration for the patient's condition. We recommend considering parental preferences, the severity of illness, and obstetrical indications when addressing the mode of delivery.

Guidelines for pregnancy management will continue to be updated and professionals should stay informed about new guidelines.

7 | CONCLUSIONS AND FUTURE WORK

The acquisition of robust data on the impact of emergent pathogens on pregnant women is often lacking or only available after a considerable delay,[4] leaving scientists and clinicians to develop knowledge from intuition, extrapolation, and case series as they emerge. Adaptive systems enabling prospective and structured collection of information on pregnant women during epidemics are needed. They allow for faster knowledge acquisition, through specific epidemiological studies

TABLE 2 Comparison of different recommendations for management of COVID-19 pregnant women

	WHO[a]	ACOG[b]	RCOG[c]	RCPCH[d]
Pregnant women with history of SARS-CoV-2 exposure	Monitor carefully	If asymptomatic, routine prenatal care	…	…
Mild/moderate symptoms, suspected or confirmed COVID-19 pregnant women	Woman-centered, respectful skilled care, including obstetric, fetal medicine, and neonatal care, as well as mental health and psychosocial support, with readiness to care for maternal and neonatal complications	In presence of comorbidities, obstetric issues or inability to care for self, see patient in ambulatory setting. If not, self-isolation is recommended. Pregnant women should be prioritized for COVID-19 testing	Self-isolation at home. If attending a maternity unit and meet PHE criteria[e], pregnant women in second or third trimester should be tested. Should be treated as infected until results are available	…
Moderate/Severe symptoms, COVID-19 positive women		In case of severe symptoms (ACOG algorithm[f]), admission to emergency unit in isolation. Fetal management as any ill pregnant women	Hourly monitored (oxygen Sat >94%). Prophylactic LMWH (unless birth expected within 12 h). Chest CT if indicated. Assess if Cesarean birth or labor induction is indicated	…
Fetal monitoring for COVID-19 positive mothers	…	First trimester infection: Detailed anatomy ultrasound could be considered. Second to third trimester infection: fetal growth ultrasound in third trimester	Refer to antenatal ultrasound for fetal growth surveillance 14 d after resolution of acute illness for patients who have been hospitalized only	
Corticosteroid administration for fetal benefit (when risk of preterm birth)	For mildly symptomatic mothers when fetal benefits outweigh potential harm to the mother	Recommended between 24 0/7 weeks and 33 6/7 weeks of gestation. Not routinely recommended in late preterm period	Indicated as in NICE guidance[g]	Indicated as normal practice

Note: General guidance for healthcare staff: using appropriate PPE (WHO, ACOG, and RCOG).

Abbreviations: ACOG, The American College of Obstetricians and Gynecologists; RCOG, Royal College of Obstetricians and Gynaecologists; RCPCH, Royal College of Paediatrics and Child Health; WHO, World Health Organization.

[a]Clinical management of severe acute respiratory infection when COVID-19 disease is suspected: Interim guidance V 1.2. WHO. 13 March 2020. Last update 29 April.

[b]Novel coronavirus 2019 (COVID-19), practice advisory. The American College of Obstetricians and Gynecologists. 13 March 2020. Last update 23 April.

[c]Coronavirus (COVID-19) infection in pregnancy, information for healthcare professionals version 7. Royal College of Obstetricians & Gynaecologists. 17 April 2020.

[d]COVID-19—guidance for neonatal settings. Royal College of Paediatrics and Child Health. 14 April 2020.

[e]Current criteria PHE criteria (correct at the time of publishing this update) are: Women who are being/are admitted to hospital with one of the following:• Clinical/radiological evidence of pneumonia,• Acute Respiratory Distress Syndrome (ARDS),• Fever ≥37.8 and at least one of acute persistent cough, hoarseness, nasal discharge/congestion, shortness of breath, sore throat, wheezing or sneezing.

[f]ACOG algorithm available at: https://www.acog.org/clinical/clinical-guidance/practiceadvisory/articles/2020/03/novel-coronavirus-2019.

[g]Preterm labor and birth, NICE guideline (NG25), published 20 November 2015, updated 02 August 2019. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ng25/chapter/recommendations#maternal-corticosteroids.

based on robust data and tailoring of preventive and screening strategies to improve maternal, fetal, and neonatal outcomes in a timely manner. Recruitment of pregnant women with COVID-19 in cohort studies should be encouraged globally to allow for evidence-based management. Currently, several registries are open for recruitment. COVI-Preg is an international hospital-based registry enrolling pregnant women at any stage of pregnancy with a suspected SARS-CoV-2 infection.[110] Pregnancy Coronavirus Outcomes Registry is a US nationwide study of pregnant or postpartum women who are either under investigation for coronavirus infection (COVID-19) or have been confirmed to have COVID-19.[111] Coronavirus Health Outcomes in Pregnancy and Neonates is a hospital-based registry aiming to collect real-time data on pregnant women who are infected with SARS-CoV-2 in Australia, New Zealand, and the Pacific region.[112] International Registry of Coronavirus (COVID-19) Exposure in Pregnancy is a patient-based registry enrolling any women who are currently pregnant or have been pregnant within the last 6 months and who have been tested for SARS-CoV-2 (regardless of the result) or have been clinically diagnosed with COVID-19 by a health care professional.[113]

These initiatives should provide several datasets available for research aiming to improve pregnant patient care during the COVID-19 pandemic in the near future.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA ACCESSIBILITY

Research data are not shared.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

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