COVID-19 AND PREGNANCY: EPIDEMIOLOGY, CLINICAL FEATURES, MATERNAL AND PERINATAL OUTCOMES. A SYSTEMATIC REVIEW

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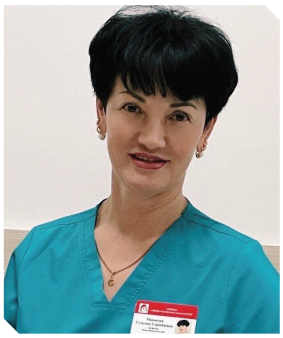

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INTRODUCTION

Based on the genome sequencing of the virus, reported in December 2019, the National Health Commission of China found that severe acute respiratory distress syndrome (ARDS) is caused by a new type of b coronavirus [1,2]. In January 2020, the WHO named the virus coronavirus (2019-nCoV), and in February 2020, the infectious disease was named COVID-19. The International Committee on Taxonomy of Viruses (ICTV), after a comprehensive genomic characterization, officially named the virus SARS-CoV-2 [3]. The rapid spread of the disease worldwide in March 2020 led to the declaration of a pandemic [4–6]. The presence of concomitant pathology, such as diabetes, hypertension, chronic respiratory diseases, kidney disease and oncologic pathology, were recognized as risk factors for worse COVID-19 disease prognosis and death [7].

Past experience of complicated pregnancy and maternal losses caused by SARS-type coronavirus infection during the influenza virus A H1N1 pandemic in 2009–2010 led the scientific community to hypothesize that a pregnant woman is considered potentially vulnerable to SARS-CoV-2-associated ARDS [8, 9]. In the context of the COVID-19 pandemic, in order to reduce the risks of infection of pregnant women and medical workers, many countries, along with quarantine measures and restriction of non-emergency medical care, have recommended limiting routine prenatal care and, if possible, replacing face-to-face communication with electronic consultations [9–12].

Physiological changes in the cardiovascular, respiratory, immune and hemostatic systems during pregnancy may have some influence on the severity of COVID-19 disease, which in turn may affect the course of pregnancy. Currently, active research is ongoing on the impact of COVID-19 on reproductive function, particularly, pregnancy, childbirth, and perinatal outcomes. In addition to the direct impact of the disease, maternal health can be adversely affected by limited access to medical care, psycho-emotional stress and socio-economic maladjustment brought about by the pandemic. Moreover, the infection can be asymptomatic, which creates certain difficulties in the prevention and treatment of the disease as well as raises the question of the need for screening studies for SARS-CoV-2 [9].

The introduction of telemedicine so as to avoid face to face contact in physical consultations was aimed primarily at reducing the prevalence of COVID-19. Nevertheless, the impact of such tactic on maternal and infant morbidity and mortality requires serious study.

The objective of this systematic review was to analyze published literature data on the epidemiology, risk factors, and clinical features of COVID-19 in pregnancy, maternal and perinatal outcomes.

MATERIALS AND METHODS

Search strategy

A comprehensive search was conducted based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) methodology [13]. A search was carried out on the electronic databases of PubMed, Scopus, Medline, Google Scholar, Web of Science and Central BMJ using MeSH terms or combinations of the keywords of "COVID-19", "SARS-CoV-2", "pregnancy", "epidemiology", "comorbid disease", "pregnancy and childbirth outcome", "preeclampsia" and "fetus" for the period from December 1, 2019 to February 28, 2022. The inclusion criteria for the study were a confirmed PCR diagnosis of COVID-19 in pregnant women, available information about the clinical features of the disease, as well as the course of pregnancy, maternal and perinatal outcomes.

Selection criteria

At the first stage, potentially relevant works were identified by titles and abstracts of articles. After review of the full-text content, if the selected criteria were met, the article was short-listed for full processing. The quality of studies was assessed, taking into account, the size and structure of the sample, the representativeness of the data presented the quality of statistical analysis, and the study of causal relationships. For the selection and methodological evaluation of studies, a questionnaire was compiled in accordance with the requirements for non-randomized studies – the Newcastle-Ottawa scale [5] (Table 1).

Table 1. Newcastle-Ottawa scale for selected studies

Author	Selection				Comparability		Assessment of outcomes of pregnancy	Adequate reporting
	Representation of pregnant patients	Selection of pregnant women with COVID-19	Presentation of the COVID-19 in pregnant women	Demonstration of coexisting disorders	Reporting of pregnant patient * = non-pregnant *	Reporting of pregnant patient * = fetus *		
Allotey J. [27]	*	*	*	*	**	**	*	*
Bellos I. [28]	*	*	*	*	INA	**	*	*
Brandt J.S. [24]	*	*	*	*	**	**	*	*
Carrasco I. [33]	*	*	*	*	INA	**	*	*
Chen L. [26]	*	*	*	INA	INA	**	*	*
Di Mascio D. [25]	*	*	*	INA	**	**	*	*
Diriba K. [32]	*	*	*	*	INA	**	*	*
Dixit A. [14]	*	*	INA	*	**	INA	INA	*
Epelboin S. [40]	*	*	INA	*	**	**	*	*
Figueiro-Filho E.A. [42]	*	*	*	*	INA	**	*	*
Juan J. [31]	*	*	*	INA	INA	**	*	*
Khan D.S.A [41]	*	*	INA	*	INA	**	*	*
Kim S.H. [16]	*	*	*	*	**	**	*	*
Knight M. [15]	*	*	INA	*	INA	**	*	*
Metz Torri D. [34]	*	*	*	*	INA	**	*	*
Mullins E. [56]	*	*	*	INA	**	**	*	*
Stock S.J. [35]	*	*	INA	*	INA	**	*	*
Villar J. [30]	*	*	*	*	INA	**	*	*
Vousden N. [48]	*	*	*	*	INA	**	*	*
Yee J. [59]	*	*	*	*	**	**	*	*
Zha L. [18]	*	*	INA	INA	**	INA	INA	*

Note: authors – only the first author is listed; * information is available; ** information is available on both points; INA – information not available.

Data collection and analysis

More than 600 published articles were analyzed by source names. After checking the compliance of the full-text content of the selected works with the inclusion criteria, 21 articles were short-listed for final evaluation. The number of pregnant or recently delivered women diagnosed with COVID-19 reported in the highlighted papers total 238,798. Nine systematic reviews, eight cohort studies, one case-control study, one retrospective study, one multicenter observational study and one cross-sectional study were included in the analysis comprising 103,736, 134,789, 61, 29, 105 and 78 study participants respectively. The articles selected for analysis included studies conducted in various countries namely, Australia, Brazil, Canada, China, France, Honduras, Italy, Iran, Japan, Korea, Netherlands, Peru, Scottish, Spain, Sweden, Turkey, UK and the USA. Table 2 shows the types of scientific studies, the number of patients, the frequency of the most common clinical manifestations of SARS-CoV-2 and risk factors for severe disease.

Table 3 presents data on pregnancy complications in women with SARS-CoV-2 ARDS, as Caesarean section rate, women and newborn intensive care unit (ICU) admissions, maternal and neonatal mortality.

RESULTS

The average age of pregnant women as represented in seven studies was 31.9 ± 1.47 years, with the proportion of women over 35 years of age as represented in 8 studies being 30.53 ± 12.31%. Hyperthermia was noted in more than half of pregnant women with COVID-19 (50.18 ± 16.89%), cough in 48.05 ± 10.97%; myalgia in 21.35 ± 12.04% and shortness of breath in 22.49 ± 8.55% during hospitalization. Multi-segmental pneumonia, pneumonitis, ground "glass pattern" and other changes in chest CT were detected in 66.34 ± 24.02% of pregnant women. The presence of obesity in 44.85 ± 21.79% of pregnant women was evidenced by the data of seven studies. Nine studies indicated the presence of previous diabetes (11.45%) and gestational diabetes – in 12.14 ± 6.19% of women with a confirmed COVID-19 diagnosis. In addition, 26.39 ± 13.18% of women as represented in 15 studies have a history of comorbid diseases (chronic arterial hypertension, diseases of the lungs, kidneys, cardiovascular system).

Table 2. Types of scientific studies, the number of women covered, the frequency of the most common clinical manifestations of SARS, ac-SARS-CoV-2 and risk factors for COVID-19

Author	Type of study	No. of pregnant women (COVID-19 +)	Fever, %	CT lung changes, %	Cough, %	Obesity (mean/%) / DM, % / GDM, %	Mean maternal age / age > 35, %	Pre-existing comorbidities, %	Dyspnoea, %	Myalgia, %
Allotey J. [27]	Systematic review	11 432	40%	33%	39%	INA	0 / 43.4%	31%	4.40%	59.4%
Bellos I. [28]	Systematic review	158	69.40%	98.60%	35%	0 / 0 / 2.5%	30 (29–34%)	INA	10.80%	3.80%
Brandt J.S. [24]	Case-control study	61	24.10%	INA	25.9% *; 100%**	0 / 45.9% / 28.6% / 0	0 / 27.9%	42.90%	3.7%*; 85.7%**	9.3%*; 14.3%**
Carrasco I. [33]	Multicentric observational study	105	36.20%	61.5%	35.20%	INA	34.1	34.3%	19.00%	13.30%
Chen L. [26]	Cohort study	118	75%	79%	73%	INA	31 / 0	INA	7%*; 33%**	INA
Di Mascio D. [25]	Systematic review	79	84.2%	94.7%	57.1%	INA	34.6 / 0	INA	27.3%	INA
Diriba K. [32]	Systematic review	1316	66.1%	57.90%	52.7%	9.6% – GD	INA	32.90%	31.7%	20.8%
Dixit A. [14]	Systematic review	67 271	INA	INA	INA	0 / 5.02% / 4.95%	0 / 5.29%	3.92%	INA	INA
Epelboin S. [40]	Retrospective analysis	874	INA	INA	INA	0 / 8.4% / 0,8% / 15.9%	30.5 (±5,4)	INA	INA	INA
Figueiro-Filho E.A. [42]	Systematic review	10 966	39.9%	87.80%	51.80%	0 / 73.5% / 0 / 10.6%	22.80%	50.80%	25.39%	43.50%
Juan J. [31]	Systematic review	324	46.8	5.10%	34.20%	INA	INA	INA	13.20%	9.20%
Khan D.S.A [41]	Systematic review	3158	INA	INA	INA	OR: 1.37; 95% CI: 1.15–1.62 (mean body mass index (BMI) – 0.60 (-6.39 to 5.19)	1.62 (0.05–51.11)	respiratory disorder (OR: 1.64; 95% CI: 1.25–2.16)	INA	INA
Kim S.H. [16]	Cross-sectional study	78	INA	INA	INA	17.8% – GDM	20–44 / 0	11.00%	INA	INA
Knight M. [15]	Prospective national cohort study	427	66%	INA	56.20%	69% / 0 / 0	41%	34%	37.50%	INA
Metz Torri D. [34]	Observational cohort study	1219	INA	INA	34%	BMI: 28.3–32.3	INA	yes	19%	19%
Mullins E. [56]	Large cohort studies	4005	48.4%	INA	56.5	27.8 ± 6.4 / 0	32.0 ± 5.4 / 0	INA	28.2%	16.70%
Stock S.J. [35]	Dynamic cohort study	123 004	INA	INA	INA	BMI > 25 = 39.2%	16.90%	34.40%	INA	INA
Villar J. [30]	Multinational cohort study	706	28.2%	INA	34.1%	48.6%	30.0 ± 6.1 / 0	yes	12.6%	INA
Vousden N. [48]	Prospective cohort study	4436	INA	79.70%	INA	0 / 63.5% / 0 / 24.4%	53.1– 58.9%	29.90%	INA	INA
Yee J. [59]	Systematic review	9032	28%	INA	51%	0 / 0 / 4.2%	INA	4.70%	21%	16%
Zha L. [18]	Retrospective study	29	INA	INA	INA	INA	> 30–39 – 41.4%	6.90%	INA	INA

Notes: authors – only the first author is listed; * mild, ** severe disease; INA – information not available.

Table 3. Clinical outcomes of pregnancy and childbirth for mother and fetus, frequency of caesarean section, hospitalizations in the ICU in women with SARS-CoV-2 associated SARS

Author	No of pregnant women (COVID-19 +)	Preterm birth < 37 weeks	Preeclampsia	Miscarriage (abortion, ectopic pregnancy)	Small-for-gestational age (SGA)	Cesarean section	Admitted to ICU	Maternal death	Fetal distress	Newborns admitted to ICU	Neonatal death	Still birth
Allotey J. [27]	11 432	18.6%	25%	INA	INA	38.60%	1.80%	0.30%	14.30%	28.10%	0.40%	0.90%
Bellos I. [28]	158	29.7 %	5.40%		7.9 %	83.50%	11%	1.30%	6.10%		1.30%	
Brandt J.S. [24]	61	57.10%	7.40%	INA		16.70%	14.30%	no death	5.6% (mild); 42.9% (severe)	85.2% (mild); 100% (severe)	1.9	INA
Carrasco I. [33]	105	20.6%	INA		5.6%	36.2% (28.9% – by COVID)	4,80%	no death		16.8%	2.86%	INA
Chen L. [26]	118; 92% – mild, 8% – severe	21% / 57% – iatrogenic	INA	INA	INA	93% (63% – by COVID)	8%	no death	INA	INA	INA	INA
Di Mascio D. [25]	79	41.1%	16.2%	64.7%	11.7%	93%	31.4%	11.4%	34.1%	25%	8.3%	INA
Diriba K. [32]	1316	14.3%	5.9%	14.5%	2.8%	56.9%	31.3%	2.7%	26.5%	11.3%	2.2%	INA
Dixit A. [14]	67 271		4.21%									
Epelboin S. [40]		16.70%	4.80%	INA	INA	32.90%	5.9%	0.20%	33,00%	INA	0.23%	INA
Figueiro-Filho E.A. [42]	10 966	21%	3.01%	17.00%	11%	68%			4.86%	18.45%	0.80%	1,70%
Juan J. [31]	324	24.40%	7.90%	1.23%	7.8% (< 2500)	78% (55.0% – by COVID)	4,70%	2 cases – 0.61%	INA	28.30%	0.50%	INA
Khan D.S.A [41]	3158	< 37 weeks (OR: 2.10; 95% CI: 1.04–4.23); < 34 – 4.34 (0.52–36.14)	1.84 (1.01–3.38)		3.80 (0.47–30.52)	OR: 1.40; 95% CI: 1.17–1.67	OR: 13.25; 95% CI: 5.60–31.34	11.87 (0.67–21.22)	INA	OR: 1.96; 95% CI: 1.59–2.43	0.82%	1.05 (0.37–2.97)
Kim S.H. [16]	78	5.50%	1.4%; 5.5% – gestation hypertensive	INA	INA	78.1% vs. 54.7%	6.4% – oxygen	0%	4.10%	INA	INA	0%
Knight M. [15]	427	27%	INA	2%		16% – COVID; 44% – other	10%	1%	INA	INA	1%	1%
Metz Torri D. [34]	1219	41.8% – critical; 15.2% – severe; 11.9% – moderate	23.40%	0.820%	8.0% – moderate; 12.2% – critical; 9.9% – severe	36.9%; 29% – by COVID	35.30%	4%	INA	50.4% (critical)	5 cases	
Mullins E. [56]	4005	12–16.1%	INA	2%	8.20%	44.80%	INA	0.50% – 0.46% – 0.17%	INA	INA	0.2%, 0.3%, 0.3%	0.5%, 0.6%, 0.4%
Stock S.J. [35]	123 004	4.10%	INA	17%; termination – 27.6%	5.8% < 2500	INA	INA	INA	INA	INA	0.20%	0.50%
Villar J. [30]	706	22.50%	8.40%		13.7%	49.00%	8.4%;	1.60%	12.30%	perinatal morbidity and mortality index (RR 2.14; 95% CI 1.66–2.75		
Vousden N. [48]	4436	mild 9.9%; severe 52.5%	4.20%	3.30%		Prelabor: 29.4 – 76.1%; in labor – 14.6 – 7.5%	85.90%	INA	INA	14.7–66.7%	0.2– 0.6%	1.2–3.3%
Yee J. [59]	9032	30%	3.70%		17.4%	18.2–100%			2%		0.4%	
Zha L. [18]	29	INA	INA	INA	INA	INA	4.6% – oxygen	0	INA	INA	INA	INA

Notes: authors – only the first author is listed; INA – information not available.

According to 18 studies, one from five pregnant women had a premature birth with more than half of the cases being iatrogenic preterm births. In addition, eight studies noted that 13.57% of women had pregnancy losses up to 12 weeks. The incidence of pregnancy complications with preeclampsia as shown by 15 studies was 9.03% ranging from 3.01% to 25%.

10% of newborns, had had a birth weight that was "low for gestational age", and according to the data of eight studies one from three newborn needed observation in the neonatology department or in the ICU. Fetal distress was diagnosed in 16.15 ± 10.65% of antenatal cases (including during labor) and neonatal deaths averaged 1.47%, ranging from 0.2 to 8.3%. Five studies provided information on stillbirths, giving a rate of 1%. The proportion of Caesarean sections averaged 54.04% ranging from 10.2% to 82%. The number of pregnant women in need of intensive care unit stays and resuscitation was 16.58% ranging from 4.6% to 85.9%, while maternal death rate was 1.97%, with a range of 0.2 to 11.4%.

DISCUSSION

The onset of the SARS-CoV-2 pandemic dictated the need to ensure the safety of both patients and healthcare workers, creating a challenge for healthcare systems globally. Indicators of maternal as well as neonatal morbidity and mortality serve to ensure the delivery of antenatal and perinatal care of sufficiently high standard.

The incidence of COVID-19 among pregnant women, according to different authors, ranges from 4.9% to 10.0% [14, 15]. According to the Centers for Disease Control and Prevention (CDC, USA) by mid-June 2020, the number of cases and deaths due to COVID-19 in the USA were 2,104,346 and 116,140 respectively, whereas the number of women aged between 15 to 44 years with positive test results for SARS-CoV-2 was 326,335; 9.0% (8,207) of these women were pregnant. A 5.4 times greater risk of hospitalization was noted in pregnant women compared with non-pregnant women (31.5% vs. 5.8%) [17].

According to Kim S.H. et al. (2022), pregnant women are not at increased risk of COVID-19 infection and the incidence among them is lower than in non-pregnant women aged 20–44 years (0.02% vs. 0.14%, $p < 0.0001$) [16]. The authors emphasize that asymptomatic forms of the disease are not uncommon, especially in the absence of screening examinations, which does not allow identifying the true extent of the spread of the disease. Despite a low incidence compared to non-pregnant women of reproductive age, pregnant women require hospitalization more often, have a significantly higher risk of severe form of COVID-19 with the need for observation in the ICU (Kim S.H. et al. [16]: 6.4% vs. 1, 6%, $p < 0.05$, Ellington S. et al. [17]: adjusted risk ratio (aRR) = 1.5, 95% confidence interval (CI) = 1.2–1.8 [16, 17]. According to Zha L. et al. (2022), in pregnant women compared with non-pregnant women COVID-19 is characterized by a milder course, and Parums D.V. et al. (2021) also report a slight increase in the risk of severe maternal morbidity and mortality [18, 19].

The relatively low incidence of COVID-19 amongst pregnant women can probably be explained by the following. The physiology of pregnancy usually allows a degree of immunological tolerance such that the woman's body is able to allow the development of a semi-allogeneic fetus. This is mostly mediated by the production of immunosuppressive Th2 cytokines [20–23]. The immunosuppressive Th2 cytokines may confer some protection to pregnant women in cancelling out the effect of the cytokines produced by SARS-CoV-2 infection.

COVID-19 and pregnancy: clinical features

The most typical clinical manifestations of COVID-19 in pregnant women are hyperthermia with studies quoting values ranging from 24.1% to 84.2% [24, 25], cough ranging from 25.9% to 73% [24, 26], shortness of breath ranging from 3.7 % to 85.7% depending on the severity of the disease and myalgia ranging from 3.8% to 59.4% [24, 27–29]. According to Villar J. et al. (2021), dyspnoea and pyrexia, regardless of duration of symptoms, are associated with a high risk of severe maternal (RR 2.56; 95% CI 1.92–3.40) and neonatal complications (RR 4.97; 95% CI 2, 11–11.69) [30].

The frequency of changes in the chest, according to computed tomography (CT), varied from 5.1 to 98.6%, and the proportion of cases of severe pneumonia, according to Juan J. et al. (2020) – from 0% to 14% with all these patients needing ICU care [28, 31]. The most common CT findings in pregnant women infected with coronavirus were "ground glass" (65.8%) and bilateral pneumonia (57.9%) [32]. A number of studies [26, 33–35] have shown that women are most vulnerable in the third trimester of pregnancy, which can be explained by physiological changes [26, 36, 37].

Such physiological changes include increase in body weight, change in the shape of the chest, relaxation of the ligamentous apparatus of the ribs as well as decreased tone of the chest and abdominal wall musculature. These changes are coupled with a restriction of respiratory excursion, as a result of decreased amplitude of body wall movements and also due to splinting of the diaphragm that occurs as the pregnancy advances into the third trimester. All these changes contribute to a decrease in the lungs' vital capacity together with an additional progressive decrease in expiratory reserve volume and a decrease in residual lung volume by approximately 20% to the end of pregnancy. Thus, it is possible to explain the high frequency of lung lesions in pregnant women in the third trimester [38, 39].

Comorbid status of pregnant women with COVID-19

One in four pregnant women diagnosed with COVID-19 suffered from other comorbid medical conditions. According to Allotey J. et al. (2021), chronic arterial hypertension and previous diabetes mellitus (DM) increase the risk of hospitalization (odds ratio (OR) 4.21; 95% CI 1.06–16.72; I2 = 0%;) in ICU and invasive ventilation (OR 4.48; 95% CI 1.40–14.37; $I^2 = 0\%$) more than 4 times [27]. The importance of chronic hypertension as a risk factor for severe coronavirus infection was also pointed out by Khan D.S.A. et al. (OR: 2.07; 95% CI: 1.38–3.10), Villar J. et al. (OR 2.0, 95% CI 1.14 to 3.48; $I^2 = 0\%$) and Epelboin S. et al. (in pregnant women – 0.9% vs. 0.3% in non-pregnant women) [30, 40, 41].

Another significant risk factor for the severe course of COVID-19 is obesity, which, according to our analysis, was

present in almost half of women (44.85 ± 21.79%; Dixit A. et al. (2021), min – 5.02%; Figueiro-Filho E.A. et al. (2020), max – 73.5%). Overweight as an independent factor aggravating the course and prognosis of COVID-19 in pregnant women was reported by many authors (Allotey J. et al. (2021): OR 2.38, 95% CI 1.67–3.39; I^2 = 0%, Khan D.S.A. et al. (2021): OR: 1.37, 95% CI 1.15–1.62, Villar J. et al. (2021): 48.6%, Vousden N. et al. (2022): OR 2.52, 95% CI 1.97–3.23) [14, 27, 30, 41–43].

Several possible mechanisms are known to explain the almost three-fold increase in the severity of COVID-19 in the presence of overweight. Firstly, there is a general increase in subcutaneous adipose tissue as well as the volume of ectopic fat in the visceral, perivascular, epicardial and other areas of the body. Secondly, obesity is characterized by a sluggish systemic inflammatory response with corresponding activation of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumour necrosis factor α (TNF-α) and chemokines. Thirdly, a decrease in adiponectin production predisposes to a pro-inflammatory state and oxidative stress, the development of insulin resistance, metabolic disorders and generalized endothelial dysfunction [44, 45]. In addition, the social requirements of lockdown exacerbate the behavioral characteristics of the population associated with a sharp limitation of physical activity, overeating and other factors [46].

Previous diabetes mellitus, on the one hand, aggravates the course of COVID-19, and on the other hand, severe coronavirus infection can have a specific negative impact on the course of diabetes, both by the direct effect of the virus on the pancreas and by the use of steroids in the COVID-19 therapy program, which contributes to hyperglycemia [43, 47]. According to Allotey J. et al. (2021) (OR: 2.51; 95% CI 1.31 4.80; I^2 = 12%) and Villar J. et al. (2021) (OR: 2.12; 95% CI 1.62 2.78; I^2 = 0%), previous diabetes increases the risk of severe COVID-19 in pregnant women by more than two and a half times. In addition, diabetes, both pre-existing and gestational is more frequently reported among pregnant women than among non-pregnant women [17, 27].

The data obtained from the performed analysis indicate the presence of pre-existing DM (11.45%) or gestational diabetes (GD) (12.14 ± 6.19%) in one from five pregnant women with a confirmed COVID-19 diagnosis. The severe course of COVID infection in diabetic mothers can be attributed to the diabetogenic state of pregnancy imparted by the production of hormones such as oestriol, human placental lactogen, prolactin and cortisol by the placenta.

The literature has shown that women of older reproductive age have a more severe course of ARVI, as-SARS-CoV-2. The risk of severe COVID-19 has been shown to almost double with age (Villar J. et al.: OR: 1.82; 95% CI 1.27 2.63; I^2 = 30.1%; 7 studies; 3561 women) [27, 30, 40, 48]. According to our analysis, one in three women with a COVID-19 diagnosis was over the age of 35, which confirms the importance of the age factor in the course of coronavirus infection.

COVID-19 and pregnancy: maternal and perinatal outcomes

Preeclampsia is a common pregnancy complication in women with COVID-19. According to the analyzed literature, pre-eclampsia was diagnosed in one in ten women, and it was found that there is a twofold to fourfold increased risk of developing pre-eclampsia among pregnant women with COVID-19 infection (Di Mascio D. et al. (2020): OR 2.19; 95% CI 4.2–34.1; Metz Torri D. et al. (2021): 40.4% vs 18.8% control, aRR 1.61, 95% CI 1.18–2.20, Villar J. et al. (2021): OR: 4.21, 95% CI 1.26–14.0, I^2 = 0%). A possible explanation for the increased incidence of pre-eclampsia may be the direct affinity of the SARS-CoV-2 virus to the angiotensin-converting enzyme 2 (ACE2) receptors [49, 50]. Besides, the potential role of the renin-angiotensin system in the genesis of pre-eclampsia [51], immunological factors, endothelial dysfunction, and systemic inflammation [52] could also have an important part to play.

The incidence of spontaneous preterm birth with COVID-19 ranges from 6% (Allotey J. et al., 2021) to 52.5% (Vousden N. et al., 2021); and up to 57% (Chen L. et al., 2021) of them may be iatrogenic due to the severe course of coronavirus infection [26, 27, 48]. According to Khan D.S.A. et al. (2021), pregnant women with COVID-19 are two times more likely to have preterm births and early pregnancy losses than healthy pregnant women (OR: 2.10; 95% CI: 1.04 4.23) [41]. According to Wilkinson M. et al. (2022), more often preterm birth is observed in women with symptomatic COVID-19 disease (14/62, 22.6%) compared to asymptomatic pregnant women (9/109, 8.3%, p = 0.008) and control group of healthy pregnant women (5/62, 8.1%, p = 0.025) [53]. Banerjee J. et al. (2021) reported a 22% preterm birth rate, and Carrasco I. et al. (2021) a rate of 20.6% [33, 54]. Two studies reported an association between prematurity and maternal pneumonia (OR: 6.970, 95% CI: 2.340–22.750) [33, 54]. According to our analysis, preterm births, including the iatrogenic ones and spontaneous abortions associated with COVID-19 were observed in one in five women.

As already noted, pregnant women with SARS-CoV-2, acute respiratory viral infection (ARVI) often need hospitalization in the ICU (OR: 13.25; 95% CI: from 5.60 to 31.34) and included those on mechanical ventilators (OR: 15.56; 95% CI: 2.96 to 81.70). Interestingly enough, their newborns were also found to have a higher likelihood of being admitted to the ICU (OR: 2.66; 95% CI, 1. 69–4.18) [30, 41, 55]. According to Allotey J. et al. (2021), a quarter of all newborns from COVID-19 infected mothers are hospitalized in the neonatal unit or ICU (OR: 3.13, 95% CI 2.05 4.78) [27]. A possible explanation for the greater need for hospitalization in pregnant women with COVID-19 may be the higher incidence of infection towards the end of pregnancy. The physiological changes, particularly, in the cardiovascular and respiratory systems, towards the third trimester may contribute to the development of more severe ARDS.

Some studies suggest that the maternal death rate is higher in a cohort of pregnant women with COVID-19 as opposed to controls (Epelboin S. et al. (2021): 0.2% vs. 0.005%, p < 0.001; Mullins E. et al. (2021): 0.5%; Metz Torri D. et al. (2021): 0.3%) [34, 40, 56]. Conversely, in other studies, there were no cases of maternal loss (Kim S.H. et al., 2022; Zha L. et al., 2022; Wilkinson M. et al., 2022) [16, 18, 53] or differences in groups between pregnant and non-pregnant women were not found to be significant (Ellington S. et al. (2020) [17]: aRR = 0.9, 95% CI = 0.5–1.5). Given the lack of consensus between studies on this issue, when planning

antenatal care, it is reasonable to assume pregnancy as being a risk factor for severe disease making these women more at risk of requiring ICU admission, mechanical ventilation, extracorporal membrane oxygenation, and having a greater mortality risk than non-pregnant women of reproductive age, should they develop COVID-19 infection [57, 58].

Most studies observed a higher proportion of deliveries by caesarean section (CS) in pregnant women with COVID-19 and this was directly related to the severity of the course of the disease. Rates reported in the literature varied widely, with Knight M. et al. (2021) reporting a CS rate of 16% as opposed to a CS rate of 55% reported by Juan J. et al. (2020) [15, 31]. The likelihood of CS tended to be higher in women with a confirmed COVID-19 PCR diagnosis compared to asymptomatic pregnant women with the disease (OR: 1.40, 95% CI: 1.17 to 1.67) [15, 31]. The presence of concomitant risk factors was found to more than double the likelihood of severe symptoms of the disease and delivery by CS [30, 41]. According to Di Mascio D. et al. (2020), in the case of a severe form of COVID-19 disease, CS was done in 84% of cases, and Yee J. et al. (2020) reported a 100% CS rate [25, 59]. On average, according to the review, half of pregnant women with COVID-19 were delivered by CS. However, this indicator included both obstetric indications and COVID-19.

Interestingly, the literature reported, a higher incidence of venous thromboembolism (VTE) among pregnant women with severe disease (6%) compared with mild and moderate disease (0.2%; 95% CI 2–11%) [34]. The relationship between venous thromboembolism and COVID-19 infection can be most likely attributed to the latter's pathophysiology. The cytokine activation inherent to COVID-19 disease, along with impaired platelet function and the underlying inflammation of the endothelium could all be factors that are directly responsible for the increased incidence of VTE in pregnant women with COVID-19 [60, 61]. According to Epelboin S. et al. (2021), the frequency of VTE among pregnant women is insignificant for statistical analysis [40]. It is likely that the combination of physiological hypercoagulability during pregnancy and the risk of VTE associated with COVID-19 may be mutually aggravating conditions. However, this assumption requires further research.

There is evidence that SARS-CoV-2 infection during pregnancy is associated with adverse neonatal outcomes such as stillbirths, neonatal mortality, the birth of children with a small weight for gestational age, and fetal distress. Thus, Juan J. et al. (2020) reported that in up to one third of 219 women with COVID-19 newborns, which were hospitalized in the ICU, there was one case (0.5%) of neonatal asphyxia and death. In a series of nine cases of severe COVID-19, the same authors reported seven maternal deaths, four intrauterine fetal deaths, and two neonatal losses [31].

While, comparing groups of 706 pregnant women diagnosed with COVID-19 and 1424 healthy pregnant women, Villar J. et al. (2021) found the neonatal (OR: 2.66; 95% CI, 1.69–4.18) and perinatal (OR 2.14; 95% CI, 1.66–2.75) morbidity and mortality index were more than double in the COVID-19 group as opposed to the control group [30]. Khan D.S.A. et al. (2021) after analyzing the course and outcome of pregnancy in 3158 women (1900 symptomatic and 1258 asymptomatic pregnant women) reported that the mean birth weight of newborns from mothers with symptomatic COVID-19 was significantly lower. The probability of having children with small body weight was higher by up to one and a half times in these women (OR: 1.85; 95% CI: 1.06–3.24) [28]. Stillbirth was also reported as an adverse neonatal outcome associated with maternal COVID-19 in a number of studies [15, 27, 35, 42, 48, 56].

According to our analysis, the frequency of birth of newborns with a small weight for gestational age (SGA) was 9.27± 3.18%; the incidence of fetal distress was 16.15 ± 10.65%, the incidence of newborn hospitalizations in the ICU was 34.63 ± 17.7%, and the incidence of neonatal losses was 1.47 ± 1.25%.

Thus, the systematic review of literature data on epidemiology, clinical features, maternal and perinatal outcomes in pregnant women with COVID-19 allows us to draw some conclusions and identify possible promising areas for further research.

The relatively low incidence of COVID-19 amongst pregnant women can probably be explained by the production of immuno-suppressive Th2 cytokines characteristic of pregnancy to confer immune tolerance to the semi-allogeneic fetus [20–23]. These same cytokines may confer some protection to pregnant women in cancelling out the effect of the pro-inflammatory cytokines produced by SARS-CoV-2 infection. Ultimately, there is no increase in maternal loss rate that the medical community experienced during the 2010–2012 H1N1 influenza pandemic. This assumption requires further in-depth research.

CONCLUSIONS

Despite the ongoing accumulation of information on the mutual relationship between pregnancy and COVID-19 infection, the data is sometimes contradictory and our understanding of the COVID-19 disease course in pregnancy, is still in its infancy. Further studies are needed, in particular, when it comes to the pathophysiology of COVID infection to better our knowledge of the increased incidence of severe COVID disease in the pregnant population cohort as well as the increased risk of pregnancy complications such as VTE in such individuals. Such understanding would further benefit the scientific community in helping us to develop innovative ways to prevent pregnancy complications in women with COVID-19 infection.

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Conflict of Interests

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COVID-19 AND PREGNANCY: EPIDEMIOLOGY, CLINICAL FEATURES, MATERNAL AND PERINATAL OUTCOMES. A SYSTEMATIC REVIEW

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Background and objectives: COVID-19 pandemic had quite a significant impact on a number of obstetric outcomes. This is often directly attributed to complications of COVID-19. This article is a systematically review literature on the epidemiology, clinical features, maternal and perinatal outcomes of COVID-19 in pregnancy.
Materials and methods. A PRISMA methodology search was conducted on the databases of PubMed, Scopus, Medline, Google Scholar, Web of Science and Central BMJ using MeSH keywords or combinations of the words "COVID-19", "SARS-CoV-2", "pregnancy", "epidemiology", "comorbid disease", "pregnancy and childbirth outcome", "preeclampsia", "fetus". Only articles published between December 1, 2019 to February 28, 2022 were considered. After preliminary analysis of more than 600 publications, 21 articles were short-listed for final processing. The studies were selected using a Newcastle-Ottawa scale style questionnaire. The clinical features, risk factors, co-morbid conditions, maternal and neonatal outcomes were presented in two separate tables respectively.
Results. COVID-19 incidence in pregnancy ranged from 4.9% to 10.0%. Such women were 5.4 times more likely to be hospitalized and 1.5 times more to need ICU care. Dyspnoea and hyperthermia were associated with a high risk of severe maternal (OR 2.56; 95% CI 1.92–3.40) and neonatal complications (OR 4.97; 95% CI 2.11–11.69). One in ten of neonates had a small weight for gestational age (9.27 ± 3.18%) and one in three required intensive care unit observation.
Conclusions. Despite the increasingly emerging evidence on the associations between pregnancy and COVID-19 infection, the data is sometimes contradictory necessitating further studies.

Keywords: pregnancy, COVID-19, clinical features, perinatal outcomes.

COVID-19 І ВАГІТНІСТЬ: ЕПІДЕМІОЛОГІЯ, КЛІНІЧНІ ОСОБЛИВОСТІ, МАТЕРИНСЬКІ ТА ПЕРИНАТАЛЬНІ РЕЗУЛЬТАТИ. СИСТЕМАТИЧНИЙ ОГЛЯД

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Обґрунтування та мета: Пандемія COVID-19 значно вплинула на низку акушерських результатів. Це часто безпосередньо пов'язують з ускладненнями COVID-19. Ця стаття є систематичним оглядом літератури з епідеміології, клінічних особливостей, материнських та перинатальних наслідків COVID-19 під час вагітності.
Матеріали та методи. Пошук за методологією PRISMA проводили в базах даних PubMed, Scopus, Medline, Google Scholar, Web of Science і Central BMJ за допомогою ключових слів (MeSH) або комбінацій слів «COVID-19», «SARS-CoV-2», «вагітність», «епідеміологія», «супутні захворювання», «перебіг вагітності та пологів», «прееклампсія», «плід». Розглядали лише статті, опубліковані з 1 грудня 2019 року до 28 лютого 2022 року.
Після попереднього аналізу понад 600 публікацій 21 стаття була відібрана для остаточного опрацювання. Дослідження відібрано за допомогою опитувальника за шкалою Ньюкасла – Оттави. Клінічні ознаки, чинники ризику, супутні захворювання, материнські та неонатальні результати були представлені у двох окремих таблицях відповідно.
Результати. Частота захворюваності на COVID-19 під час вагітності коливалася в межах від 4,9 до 10,0%. Такі жінки мали в 5,4 раза більше шансів бути госпіталізованими і в 1,5 раза частіше потребували лікування у відділенні інтенсивної терапії. Задишка та гіпертермія були пов'язані з високим ризиком тяжких ускладнень у матері (співвідношення шансів – 2,56; 95% ДІ 1,92–3,40) і неонатальних ускладнень (співвідношення шансів – 4,97; 95% ДІ 2,11–11,69). Кожен десятий новонароджений мав малу вагу для гестаційного віку (9,27 ± 3,18%) і кожен третій потребував спостереження у відділенні інтенсивної терапії.
Висновки. Незважаючи на те що дедалі частіше з'являються докази зв'язку між ускладненим перебігом вагітності та інфекцією COVID-19, дані іноді суперечливі, що диктує потребу проведення подальших досліджень.

Ключові слова: вагітність, COVID-19, клінічні прояви, перинатальні наслідки.