Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER 2

Immunological Changes in Pregnancy and Its Relation to COVID-19 Infection

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Humans are in constant exposition to microorganisms. Based on their effects on the body, microorganisms are classified into pathogenic and nonpathogenic organisms. This in turn regulates the body response: (1) interaction or (2) defense. The response is carried by an interactive network, which is called the immune system.

With the onset of pregnancy, the immune system has to resume its protective role despite hosting an antigen. In this phase, the aim is to protect the host and the growing antigen, the fetus. Several mechanisms take place to maintain an optimal immunological function without harming the growing intrauterine fetus. An interaction between local uterine components of the innate and adaptive immune response sets a balance to tolerate the "semiallogenic" fetus while securing the host against exogenous infection (Thellin et al., 2000).

OVERVIEW ON THE IMMUNE SYSTEM

Innate Immunity

Leukocytes

In comparison with the nonpregnant state and due to the increased inflammatory response, there is a significant increase in the total white blood cells (Melgert et al., 2012; Efrati et al., 1964). Eosinophil and basophil levels do not increase throughout the whole pregnancy. Yet, an increase in the degranulation of eosinophils has been recorded throughout the whole pregnancy, which decreases with the onset of delivery and drops furthermore until 1 month after labor. Significant higher-end products of eosinophil degranulation were detected after a caesarian section (Matsumoto et al., 2003). The increase was mainly due to the significant rise in neutrophil counts (Belo et al., 2005; Abbassi-Ghanavati et al., 2009). This could be explained by the higher gestational cortisol (Buss et al., 2012) or granulocyte macrophage colony-stimulating factor (GM-CSF) levels (Belo et al., 2005).

Despite the rise in the number of leukocytes due to an increase in neutrophils, a decrease in the phagocytic capacity occurs during pregnancy, as shown in Fig. 2.1 (Lampé et al., 2015).

Monocytes

One major change of the innate immune system is an increase number of monocytes (Luppi et al., 2002; Siegel and Gleicher, 1981). In normal pregnancies, there is a significant rise of the total monocyte count from 0.3 (0.1−0.8) $\times 10^9$ cells/L to 0.6 (0.4−0.9) $\times 10^9$ cells/L (Melgert et al., 2012).

On the contrary, a significant decrease in the phagocytic function of monocytes occurs in healthy pregnancies when compared with nonpregnant women, as shown in Fig. 2.1. This decrease is part of a maternal immunosuppression, which protects the semiallogenic fetus (Lampé et al., 2015). Parallel to the increase of placental mass associated with the increase in gestational age, a significant upregulation of the activation markers (CD11a, CD54, and CD64 surface antigen) takes place. The upregulation peaks with the onset of labor. In addition, monocytes increasingly produce interleukin-12 during pregnancy (Luppi et al., 2002). Other functional changes include the increased production of oxygen free radicals and different cytokine production. The latter is inconsistently reported in literature. Different studies also are contradictive with regard to the relative change of monocyte subsets (Faas and de Vos, 2017).

Complement system

A balanced activation of the complement system occurs and is protective against complicated pregnancies, e.g., preeclampsia and preterm birth.

While the complement factors C3a, C4a, and C5a are elevated in the second half of the pregnancy and C3, C4d, and C9 and serum complement membrane attack complex throughout the whole pregnancy, it is counterbalanced by an elevation in factor H, decay-accelerating factor (DAF), pregnancy-associated plasma protein A (PAPPA), CD46/CD55 like activities, C1 inhibitor (C1-INH), membrane cofactor protein (MCP), C4-binding protein (C4BP), complement receptor 1 (CR1), mannose-associated serine protease (MASP), and mannose-binding lectin (MBL) (Regal et al., 2015).

A failure to keep this balanced activation can lead into a pathological pregnancy. Many examples exist. A defect in the glycosylphosphatidylinositol (GPI) anchoring of complement regulators CD55 and CD59 in blood cells may result into complement-mediated hemolysis, thrombocytopenia, and thrombosis (Ray et al., 2000). In cases of pregnancy-associated atypical hemolytic−uremic syndrome, the levels of C3, C5, and properdin are low to undetectable, while an upregulation of cell-surface C3b deposition is detected (Zhang et al., 2020). There is also growing evidence of the complement factor dysregulation involvement, e.g., C5a-mediated trophoblasts dysfunction, in the pathogenesis of preeclampsia (Ma et al., 2018). Therefore, keeping a balanced upregulation of the complement system is important in the development of a physiological pregnancy (Regal et al., 2015).

Innate lymphoid cells

Newly, innate lymphoid cells (ILCs) have been identified. These are undifferentiated lymphocytes not expressing

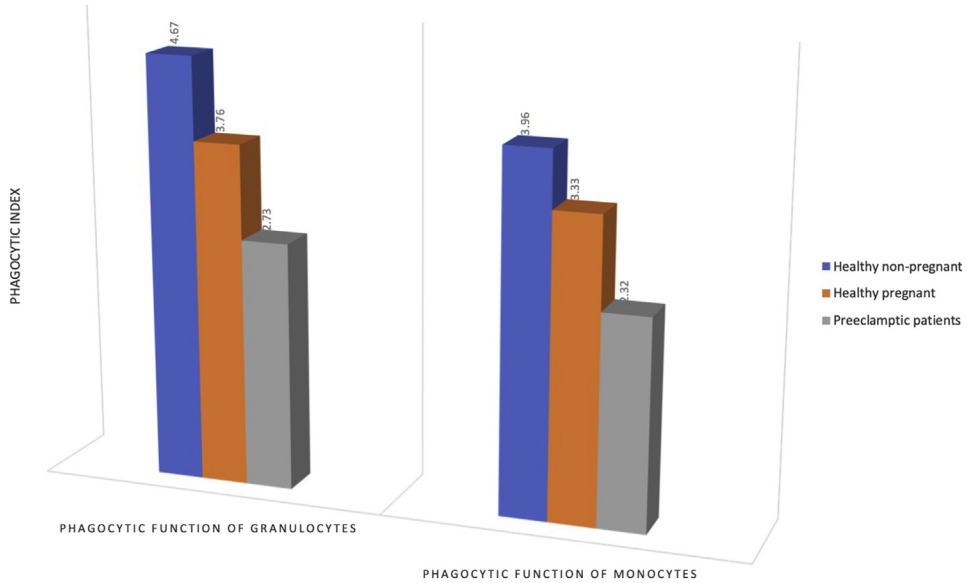

FIG. 2.1 Comparison of the phagocytic index of granulocytes and monocytes in healthy nonpregnant, healthy pregnant, and preeclamptic individuals (Lampé et al., 2015).

the antigen receptors, which are found on T and B cells (Vivier et al., 2018). They are subdivided into three types.

Together with the NK cells, ILC type 1 contributes to the placentation including spiral arteries remodeling and trophoblastic uterine invasion. The necessary tissue remodeling is facilitated by the production of interleukin-8, vascular endothelial growth factor (VEGF), stromal cell−derived factor 1 (SDF-1), and interferon gamma-induced protein 10 (IP-10). NK cells are furthermore subclassified into peripheral (pNK) and decidual NK (dNK) cells, with the decidual subtype being unable to attack trophoblasts (Abu-Raya et al., 2020).

The invasion of the anchoring trophoblasts is promoted by the NK cells and ILC3. Yet, dNK cells have contradicting roles. On one hand, it induces the myometrial invasion by secreting chemokines, e.g., IL-8, IP-10, and XCL1 and GM-CSF. On the other hand, this invasion is inhibited by secreting TGF-β. dNK also promotes spiral artery remodeling by producing angiogenic factors, e.g., VEGF, angiopoietin (Ang) 1 and 2, placental-derived growth factor, and hepatocyte growth factor. To prevent attacking the growing fetus, the gestational hormones (estradiol [E2], progesterone [PRG], and human chorionic gonadotropins [hCGs]), decidual stromal cells (DSCs), and the trophoblasts neutralize the pNKs to induce a functional competence and self-tolerance. E2 and PRG prevent NK degranulation. hCG and E2 promote furthermore dNK proliferation, which does not attack trophoblasts. DSC suppresses additionally the expression of CD16, rendering the pNK less cytotoxic (Chang et al., 2020; Mendes et al., 2020). Ongoing investigations are directed to whether the cytotoxic pNKs become less in number or function or are increasingly converted to pNKs.

Adaptive Immunity

T lymphocytes

An early comparison of total T cells, T-helper cells (CD4+), and T suppressor cells (CD8+) percentages in the peripheral blood showed no difference on all T cell subsets in the peripheral blood (Coulam et al., 1983). A different behavior of CD3+, CD4+, and CD8+ was also observed in a different population (Mahmoud et al., 2001). More recent observations showed a decrease in the absolute numbers of lymphocytes during pregnancy, which return to the nonpregnant state in puerperium. A decrease in the CD4+ T cells during pregnancy followed by a postpartum increase in CD3+TCRα/β1- and CD3+TCRγ/-1+ may explain the increased susceptibility to viral infection during pregnancy (Watanabe et al., 1997). Additionally a significant increase was observed in HLA-DR+ and CD56+ in the first trimester followed a steady decrease with ongoing pregnancy (Kühnert et al., 1998). Yet, the T-helper cell function remained adequate throughout gestation (Bailey et al., 1985) with a decreased Th1

(IL-2 and interferon ɣ secretion) and increased Th2 response (IL4 and 10 secretion) throughout the whole pregnancy and postpartum period (Matthiesen et al., 1998).

The Th1 cell response was referred to being destructive toward pregnancy, and vice versa regarding the Th2 cell response (Szekeres-Bartho and Wegmann, 1996). Mostly animal studies highlighted the effect of an immunomodulatory protein known as progesterone-induced blocking factor, which alters the Th1/Th2 balance. In summary, a different cytokine secretion pattern was suspected to decrease the cell-mediated responses during pregnancy (Abu-Raya et al., 2020).

Yet, different conclusions were reported in different studies (Abu-Raya et al., 2020) ranging from a shift toward Th2 cell response only in early gestation (Raghupathy et al., 2000), Th2 cell response domination throughout the whole pregnancy (Wegmann et al., 1993; Wegmann, 1984; Szekeres-Bartho and Wegmann, 1996), a shift toward Th2 response throughout on antigen presentation the whole pregnancy (Marzi et al., 1996), lower Th1 and no Th2 change at the end of third trimester (Saito et al., 1999), rise of the Th1 response after delivery (Aghaeepour et al., 2017), and no change at all (Lissauer et al., 2014).

With regard to T cell subsets, different response among ethnicities is suggested, making populations more prone to infections during pregnancies than others (Mahmoud et al., 2001). Yet, it has to be mentioned that the study populations in all the aforementioned trials is too low to make a conclusion on a whole population.

B lymphocytes and immunoglobulins

B lymphocytes decrease in number in physiological pregnancies. According to a study, this decrease was not statistically significant (Kühnert et al., 1998). In several other studies, the absolute and relative numbers of conventional CD19+ B cells were shown to decrease significantly during pregnancy with a postpartum return to the nonpregnant state (Bhat et al., 1995; Watanabe et al., 1997; Lima et al., 2016; Mahmoud et al., 2001; Zimmer et al., 1998). In contrast, pregnancies ending in preterm labor were associated with an increase in the CD19+ B cells (Busse et al., 2020; Sendag et al., 2002). With increased CD19+ B cells, B-regulatory cells decrease (Busse et al., 2020). This suggests a role of the downregulation of B lymphocytes to maintain a normal pregnancy. In turn, this leads to a decreased production of the IgG, IgA, and IgM. Some studies suggest an initial increase in IgM and IgA at the beginning of the pregnancy followed by a decreased production later in pregnancy (Amino et al., 1978; Miller and Abel, 1984; Yasuhara et al., 1992).

In summary, the immunological response has been controversially described in literature. It is yet to be mentioned that all studies are involving a relatively low number of patients, present often an oversimplified idea of the pregnancy as one unit, carry bias, and do not consider other biological and mechanical changes during pregnancy (Mor and Cardenas, 2010). In addition, populations of different ethnicities seem to respond different to gestation (Mahmoud et al., 2001). This may explain some discrepancies between the aforementioned studies, which needs to be better understood.

Respiratory Adaptations to Pregnancy

In addition to the aforementioned immunological adaptations, which may lead to increased susceptibilities to some viral infection, additional pulmonary adaptations may favor a more severe course in viral respiratory infections (Goodnight and Soper, 2005). With the onset of pregnancy, there is a 30%–40% increase in tidal volume. As the respiratory rate does not change, the minute ventilation is increased by 50%, leading to an increase in minute oxygen uptake. This increase meets the increased maternofetal gestational needs and results in a respiratory alkalosis. The latter is met by an increased renal bicarbonate excretion; thus, the arterial pH remains physiological. No changes in the lung compliance, forced vital capacity, or diffusing capacity was described. As a result of all the aforementioned change, the residual capacity, expiratory reserve volume, and functional residual capacity decrease by 15%–20% at term. Gestational hormones also decrease the total pulmonary resistance. To further improve the oxygenation to encompass the fetal and increased maternal needs, the hemoglobin amount increases. Due to an increase in plasma volume, a physiological anemia develops. The growing uterus elevates the diaphragm. To adapt to that, the transverse chest diameter increases (LoMauro and Aliverti, 2015). All the aforementioned changes result in a decreased ability of the host to contain respiratory infections (Goodnight and Soper, 2005). The details are presented in the lines to come.

Infections and Pregnancy

With onset of pregnancy, the aforementioned changes result in an immunomodulation rather than an immunosuppression, like earlier believed. Different immunological changes throughout the whole pregnancy result in a differential reaction toward an antigen depending on the host parameters, gestational age, and antigen

TABLE 2.1
Different Susceptibility and Clinical Course Based on the Type of Different Infections During Pregnancy in Comparison With Nonpregnant Women (Kourtis et al., 2014).

Infection	Increased Susceptibility	Increased Severity
Influenza	No	Yes
Hepatitis E infection	No	Yes
Herpes simplex infection	No	Yes
Malaria	Yes	Yes
Listeriosis	Yes	No
Measles	No	Yes
Smallpox	No	Yes
HIV type 1	Yes	No
Varicella	No	Yes

characteristics (Mor and Cardenas, 2010). In the coming paragraphs, viral infections during will receive a special focus.

When discussing a viral infection during pregnancy, special aspects become important: the susceptibility during pregnancy, the effect of the pregnancy on the course of the disease, and the maternofetal complications of the disease.

As presented in Table 2.1, there is a variable susceptibility and disease severity depending on the type of infection and other parameters (Kourtis et al., 2014). A possible explanation for the variable body response is summarized in the different and contradictive immunological changes, which is still not completely understood, during pregnancy.

After the emergence of the first cases of human infection with COVID-2 infection, a heavy international debate took place regarding its importance, severity, and implication on daily life. On the night of January 10, 2021, 15 months after the emergence of the first reports in October 2019, we made a PubMed search on the phrase "COVID-19." PubMed reported over 90,000 papers to that date. The gush of papers, with different qualities and contradictive outcomes, fostered the confusion. We need to recall the conflicting studies about immunological changes, especially with regard to a possible ethnical different response, to understand different study outcomes. One of the biggest debates revolves around calling COVID-19, a kind of flu, and its impact similarity with the influenza virus. In the coming lines, we will therefore discuss influenza and COVID-19.

Influenza

Influenza is a highly infectious viral disease responsible for the demise of 0.1−223.5 per 100,000 infected individuals yearly depending on the age, underlying chronic disease and region of residence (Iuliano et al., 2018). Pregnancy may be a moderate but not significant risk factor for the development of severe maternal morbidity (González-Candelas et al., 2012).

In the pregnant population, an influenza infection comes with a higher risk for hospitalization. Yet, no increased mortality has been recorded in a systematic metaanalysis involving 152 studies (OR 1.04; 95% CI 0.81−1.33) (Mertz et al., 2017). A possible explanation is the immunological alternation that occurs during pregnancy and gestational immunomodulatory downregulation of the B cell response (Swieboda et al., 2020). Yet, it remains a subject of debate, whether pregnancy is per se a risk factor or other known or unknown underlying conditions for the development of severe maternal morbidity and mortality. Further research is awaited.

There is no conclusive evidence whether exposure to influenza increases the rate of spontaneous abortion and still births, despite the seasonal variations of spontaneous abortions (Rasmussen et al., 2018). Whether exposure to influenza increases the risk for congenital anomalies is a subject of debate (Luteijn et al., 2014, 2015; Xia et al., 2019).

In a recent study, H1N1 influenza illness was not proven to be a major contributor to preterm delivery in the overall obstetrical population (no pH1N1 diagnosis: adjusted HR [aHR] = 1.0; 95% CI = 0.98, 1.1;

pH1N1 diagnosis: aHR = 1.0; 95% CI = 0.88, 1.2). However, patients with preexisting medical conditions possess a higher risk for preterm delivery after influenza infection (Fell et al., 2018). Furthermore, little and conflicting evidence supports an association between SGA births (pooled odds ratio 1.24; 95% CI 0.96−1.59) and influenza infection. In mild to moderate and severe influenza, the relative risk for fetal demise was 1.9 and 4.2, respectively (Fell et al., 2017).

Based on the aforementioned evidence and interventional studies, several guidelines and studies recommended influenza vaccination during pregnancy to avoid potential adverse maternofetal outcomes (CDC, 2019; Berger et al., 2018) and has been proven to be safe, even if given in the first trimester (Speake et al., 2020).

Comparison With COVID-19

In a French study, the characteristics, morbidity, and mortality of seasonal influenza and COVID-19 infection were compared retrospectively. The study included 89,530 patients with COVID-19 and 45,819 patients with seasonal influenza infections. Almost twice patients were admitted due to COVID-19 in comparison with seasonal influenza. The mortality of hospitalized patients was three times higher, especially in older-age categories. Yet, despite being lower, the mortality rates of children hospitalized due to COVID-19 were four times higher than the mortality rate of adults. With regard to influenza and COVID-19, the mortality rate increased with the presence of comorbidities. The authors suspect that the increased admission, morbidity, and mortality in COVID-19 cases are due to the absence of a vaccine, as is the case in influenza virus (Piroth et al., 2020).

The situation for COVID-19 is quite similar to its impact during World War I, where unknown huge numbers of the international population died in its first waves. Due to the novelty of the virus, hence neither herd immunity nor vaccines are present, the impact of COVID-19 is currently worse than influenza.

COVID-19 AND PREGNANCY ISSUES

Introduction

SARS-COVID-19 (also referred to as SARS-CoV-2/human/Wuhan/X1/2019_XYZ12345) is an enveloped positive-strand RNA virus, which is transmitted via respiratory droplets, i.e., from coughing and sneezing (Wölfel et al., 2020). After being inhaled, it starts replicating in the nasopharynx. The virus is first present in the nasal cavity and induces a limited innate response. At this stage, the virus can be detected using nasopharyngeal swabs (Corman et al., 2020). Consequently, it propagates to the lower respiratory systems, where it induces a more pronounced innate immune response. It is as this stage, where the viral infections express the known clinical pictures in the host body (Zhu et al., 2020a, 2020b; Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020).

Most of the knowledge about the immune response against SARS-COVID-19, especially with regard to long-term effects, is derived from the previous experience with other type of Coronaviridae, e.g., severe acute respiratory disease syndrome (SARS) of 2003 (Zhao et al., 2010) and Middle East respiratory syndrome (MERS) of 2012 (Alshukairi et al., 2018; Ko et al., 2017).

Initial studies on the immunological response to SARD-COVID-19 showed a leuco- and lymphopenia in 25% and 63% of the patients, respectively. Additionally, prothrombin time and D-dimer levels were higher in patients requiring an intensive care unit (ICU) management. Aspartate aminotransferase and troponin-I were also described to be increased in ICU patients (Huang et al., 2020).

Another study showed significantly lower lymphocyte subsets ($CD3^+$ T cell, $CD4^+$ T cell, $CD8^+$ T cell and B cell ($CD19^+$), and NK cell ($CD16^+56^+$)) in patients with severe clinical courses. While T lymphocytes continued to decrease in severe and demised cases, it showed a gradual increase in nonsevere cases with a favorable outcome (Premkumar et al., 2020). The reduction in the T lymphocyte subsets results in a decreased function of antigen-presenting cells, B lymphocytes, other T lymphocytes, secretion of cytokines, and direct killing of target cells (Budd and Fortner, 2013).

A significant increase in the C3 complement activation occurred in severe cases (Premkumar et al., 2020), thus inducing a proinflammatory response responsible for the acute lung injury (Merle et al., 2015). No obvious decrease was detected regarding B and NK cells with when considering the severity of cases (Premkumar et al., 2020).

With regard to the humoral immunity, an initial study showed a seroconversion of total antibodies, IgM, and IgG of 93.1%, 82.7%, and 64.7%, respectively. Within 7 days of the onset of symptoms, <40% of the antibodies are positive. The seroconversion of total antibodies, IgM, and IgG rises quickly after day 15 of the onset of symptoms to 100%, 94.3%, and 79%, respectively (Huang et al., 2020). A metaanalysis of 38 publications from Asia, Europe, and the United States fostered the results of initial trials. Thus, the sensitivity

TABLE 2.2
The Sensitivity and Confidence Interval of the Antibody (Total Antibodies, IgM and IgG) Testing in a Metaanalysis of 38 Studies (Deeks et al., 2020).

Time Interval Between Onset and Testing (Days)	Sensitivity (%)	Confidence Interval
1–7	30.1	21.4–40.7
8–14	72.2	63.5–79.5
15–21	91.4	87.0–94.4
21–35	96	90.6–98.3

for the diagnostic accuracy increased with the increasing interval between the time of onset of the disease and time the antibody testing is done as shown in Table 2.2 (Deeks et al., 2020). Initial studies suggest the presence of a long-term immunity, yet these data need to be verified (Mudd and Remy, 2021).

A current limitation is the lack of studies showing the long-term sensitivity of antibodies after 35 days of the onset of infection and in asymptomatic but infected patients. Due to the short interval between the beginning of the international pandemic and follow-up, these studies are still awaited, especially with regard to the effectiveness of immunized patients. This may give rise to the current scepsis, despite the increasing economic and social need, toward a destined vaccine (Cyranoski, 2020). On the other hand, some evidence suggests that a protracted vaccination program, i.e., not able to vaccinate at least 40% of the population, might not lead normalization of daily life (Moghadas et al., 2020).

Following the Cochrane analysis—specific antibodies against a domain of SARS-CoV-2, the receptor-binding domain (RBD) of the spike protein was identified. The sensitivity of the antibodies was 94%, 77.5%, and 69% for IgG, IgA, and IgM, respectively, after 9 days of the onset of symptoms (Premkumar et al., 2020). In a larger study involving 309 acute and received SARS-COVID-2 cases, mostly with mild disease, IgG antibodies against the RBD alone were sufficient for the serological diagnosis in SARS-COV-2-RNA-positive cases, offering a new option for detection and therapy plans (Indenbaum et al., 2020). Some developers of the awaited vaccine therefore developed a modified mRNA vaccine that encodes the trimerized RBD of the spike glycoprotein of SARS-CoV-2 (Mulligan et al., 2020). The first safety reports revealed similar results to other viral vaccines (Walsh et al., 2020; Polack et al., 2020; Baden et al., 2020).

It is too early to have solid knowledge about the long-term antibody response to SARS-COVID-2 infections and reinfection due to the relatively short duration of the pandemic. Yet, it is known from SARS cases that the long-term antibody response fades away over time with an increased susceptibility to infection after 3 years of the first exposure (Wu et al., 2007). The positive samples (IgG and IgM) over times are shown in Fig. 2.2.

With regard to pregnancy and COVID-19 infection, several questions need to be considered:

1. Are pregnant women more susceptible to an infection?
2. Is the course of the infection in the aforementioned population more severe?
3. Vertical and peripartum infections?

Susceptibility to Infection during Pregnancy

An ideal tool to identify the susceptibility to infection is based on the proper knowledge of the prevalence of infection. Therefore, countries with studies based on active surveillance programs, i.e., screening asymptomatic and symptomatic individuals on a wide scale, are more suitable to reproduce the prevalence of the disease within a society. With regard to viral susceptibility among the pregnant population, the knowledge of the pregnancy status of the screened population is necessary.

In a German prospective trial, all pregnant women presenting between April and May 2020 were tested on SARS-CoV-2. The screening was performed by a nasopharyngeal swab as indicated by the Robert Koch Institute. A total of 234 pregnant women were tested. 96.2% of the patients were tested negative. In a trial to investigate, whether infection has occurred in the past, specific SARS-CoV-2 IgG in serum was tested in around 78% of the patients. In only 0.6% of the study population, antibodies (IgG) were found. In this

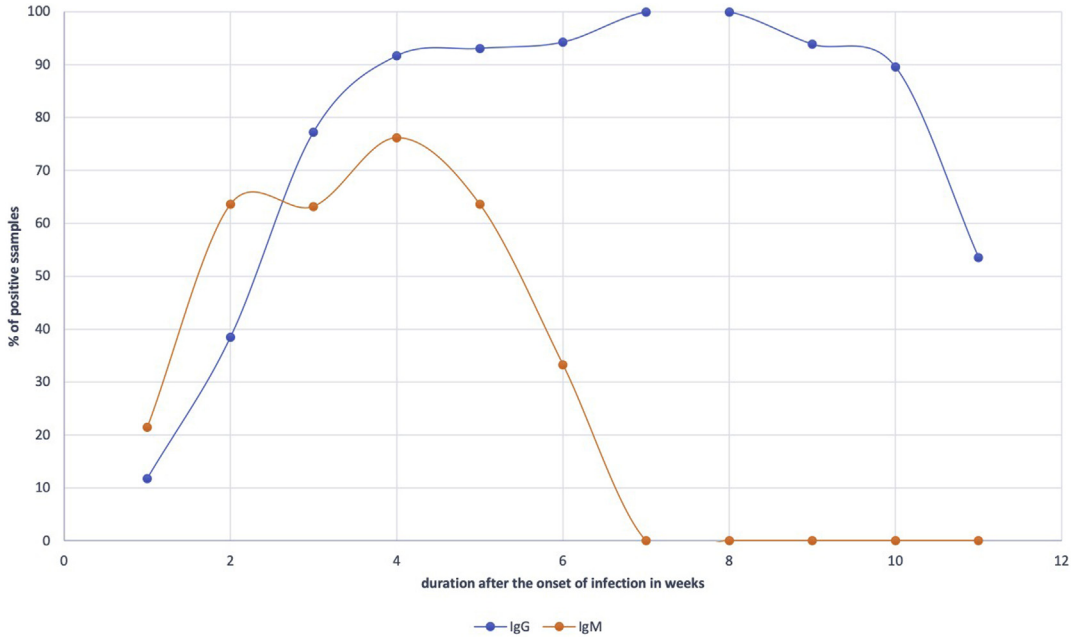

FIG. 2.2 Chart showing the primary rise of IgG and IgM followed by a decline over time after SARS infection (Wu et al., 2007). *SARS*, severe acute respiratory disease syndrome.

population, the prevalence and seroconversion among pregnant patients were below 5% and 1%, respectively. It should be added that the screening occurred during a lockdown, which has lowered the spread of cases (Zöllkau et al., 2020). Other prevalence studies among pregnant patients showed similar results within a lockdown after the first wave in the beginning of 2020 (Tanacan et al., 2020; Mattern et al., 2020; Trahan et al., 2021). In countries with a similar established and widespread screening programs, the seroprevalence of the SARS-CoV-2 was shown to range from 1.2% to 10.4% (Herrmann, 2020; Anand et al., 2020; Prabhu et al., 2020; Savirón-Cornudella et al., 2021). Bigger cohorts are awaited from the International COVID-19 and Pregnancy Registry. The project is currently still in the phase of recruitment (Panchaud et al., 2020).

Unlike expected and based on the aforementioned limited data, the infectivity of pregnant patients despite their immunological adaptations and respiratory proinfection gestational changes was shown to be lower than the nonpregnant adult population. Therefore, there is no conclusive evidence for the increased susceptibility based on German observations, which included many asymptomatic infections in comparison with other populations, where testing only occurred with the onset of COVID-19-like symptoms or direct exposure.

Course of the Disease

Initial data from China, the United States, and Italy did not show an increased risk for infection, increased morbidity, or mortality among pregnant patients in comparison with the general population (Chen et al., 2020b; Yan et al., 2020; Ferrazzi et al., 2020; Breslin et al., 2020).

In a Chinese study, 118 pregnant women with COVID-19 infection in Wuhan were identified (Chen et al., 2020b). 42 pregnant women were identified in the Italian collective, and 43 women were identified in an American collective (Breslin et al., 2020; Ferrazzi et al., 2020). In the Chinese collective, 92% had mild disease, and 9.8% had severe disease (hypoxemia), one of whom received noninvasive mechanical ventilation (Chen et al., 2020b). Similar findings were reported in the American and Italian collectives (Breslin et al., 2020; Ferrazzi et al., 2020). The authors of the three trials concluded that the course of illness is similar as in nonpregnant adults. The symptoms and signs are summarized in Fig. 2.3.

Data from a German national survey (CRONOS Registry) included 247 cases from 65 German hospitals. The survey included >20% of the hospitals involved in delivery in Germany. The mortality rate was 0.4% and 9.7% required a more intensive therapy, due to a severe course (Pecks et al., 2020).

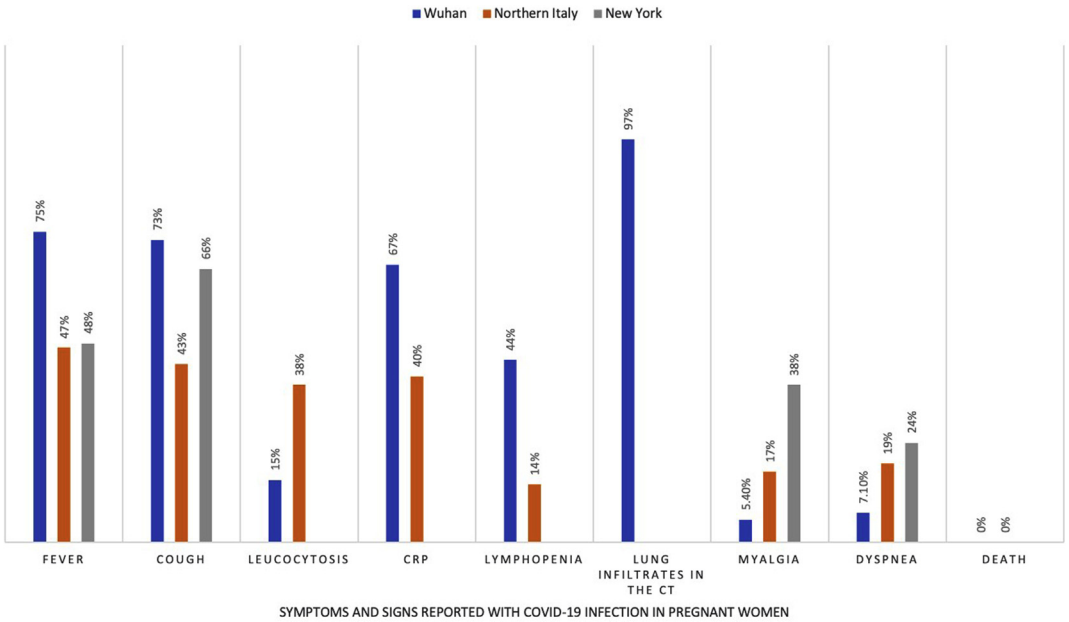

FIG. 2.3 Chart presenting the spectrum of symptoms and signs in the three initial collectives.

On the other hand, the Center for Disease Control in the United States directly compared the characteristics of symptomatic pregnant and nonpregnant women of reproductive age with laboratory-confirmed COVID-19 infection between January 22 and October 3, 2020. Around 400,000 female cases in the reproductive age between 15 and 44 years with known pregnancy status were included. 5.7% of these patients were symptomatic and pregnant. As presented in Table 2.3, pregnant women were at an increased risk for ICU admission, invasive ventilation, and extracorporeal membrane oxygenation. In addition, pregnant COVID-19 patients are at a 70% increased risk of death in comparison with nonpregnant female patients of the same age.

In summary, there is a higher likelihood of a complicated maternal course, including maternal death, if compared with nonpregnant women of the same age. Yet, it remains rare. The patients and caregivers have to be aware of preventive measures. Until vaccination processes prove to be effective and safe, pregnant patients have to be considered a risk group.

Fetal Outcome

A vertical transmission of COVID-19 may occur following a maternal viremia, which leads to placental infection. A high placental viral load might lead to a fetal/neonatal infection (Vivanti et al., 2020). Yet, it is still unknown, which patients and gestations are more prone to fetal infection and which are not.

TABLE 2.3
Comparison of the Rates of Complicated Courses Between Pregnant and Nonpregnant Women Between 15 and 44 Years of Age According to (Zambrano et al., 2020).

	RATE PER 1000 CASES			
	Pregnant	**Nonpregnant**	**aRR**	**95% CI**
Admission to ICU	10.5	3.9	3.0	2.6–3.4
Invasive ventilation	2.9	1.1	2.9	2.2–3.8
ECMO	0.7	0.3	2.4	1.5–4.0
Death	1.5	1.2	1.7	1.2–2.4

aRR, adjusted risk ration; *CI*, confidence interval; *ECMO*, extracorporeal membrane oxygenation; *ICU*, intensive care unit.

A characteristic pattern of placental pathology following placental COVID-19 infection is still being investigated (Algarroba et al., 2020; Baud et al., 2020; Hosier et al., 2020; Penfield et al., 2020; Shanes et al., 2020; Sisman et al., 2020; Vivanti et al., 2020). Histological examination may reveal histiocytic (CD68 positive) intervillositis and villitis associated with villous karyorrhexis and necrosis, focal basal chronic villitis, focal parabasal infarct, and features of meconium straining in the fetal membranes (Sisman et al., 2020). A possible explanation is a fetal under perfusion, secondary to fetal vascular thrombosis (Prabhu et al., 2020). Electron microscopy may reveal viral particles, which are 89−129 nm in diameter, within membrane-bound cisternal spaces in the syncytiotrophoblastic cells (Sisman et al., 2020).

Initially, vertical transmission was not detected in cohorts and case reports (Chen et al., 2020a; Zhu et al., 2020a; Penfield et al., 2020; Algarroba et al., 2020; Savirón-Cornudella et al., 2021; Rottenstreich et al., 2020). However, a metaanalysis, which analyzed 161 studies reporting 2059 cases of maternal infections with COVID-19, reported 61 neonatal cases with intrauterine COVID-19 infection (Rodrigues et al., 2020). Yet, only mild neonatal cases with a good outcome were reported until this date (Zeng et al., 2020).

A growing concern resides in the rising rate of preterm birth and still birth during the COVID-19 pandemic with subsequent lockdown. Two possible explanations exist. On one hand, the neonatal complications may be a direct consequence of maternal, placental, and/or neonatal infection, which may result into an iatrogenic preterm birth. On the other hand, patients tend to avoid or delay visiting hospitals with the onset of classical obstetrical complications, e.g., reduced fetal kicks, hypertensive diseases in pregnancy, and gestational diabetes; hence, many cases with possible adverse outcomes cannot be treated (Khalil et al., 2020). This may reduce the effectiveness of healthcare infrastructure in developed countries, rendering them less efficient with regard to neonatal outcome.

In summary, vertical transmission is rare but exists. It has a good outcome. The bigger concern remains the increased rate of preterm labor and still birth, which may be directly and indirectly related to COVID-19 infection. Yet, due to the low incidence of vertical infections and complicated maternal outcomes, it is still difficult to form a conclusive statement.

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