


SPECIAL ISSUE ARTICLE

Obesity as a contributor to immunopathology in pregnant and non-pregnant adults with COVID-19

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Abstract

The ongoing coronavirus disease 2019 (COVID-19) pandemic has led to a global public health emergency with the need to identify vulnerable populations who may benefit from increased screening and healthcare resources. Initial data suggest that overall, pregnancy is not a significant risk factor for severe coronavirus disease 2019 (COVID-19). However, case series have suggested that maternal obesity is one of the most important comorbidities associated with more severe disease. In obese individuals, suppressors of cytokine signaling are upregulated and type I and III interferon responses are delayed and blunted leading to ineffective viral clearance. Obesity is also associated with changes in systemic immunity involving a wide range of immune cells and mechanisms that lead to low-grade chronic inflammation, which can compromise antiviral immunity. Macrophage activation in adipose tissue can produce low levels of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6). Further, adipocyte secretion of leptin is pro-inflammatory and high circulating levels of leptin have been associated with mortality in patients with acute respiratory distress syndrome. The synergistic effects of obesity-associated delays in immune control of COVID-19 with mechanical stress of increased adipose tissue may contribute to a greater risk of pulmonary compromise in obese pregnant women. In this review, we bring together data regarding obesity as a key co-morbidity for COVID-19 in pregnancy with known changes in the antiviral immune response associated with obesity. We also describe how the global burden of obesity among reproductive age women has serious public health implications for COVID-19.

KEYWORDS

COVID-19, maternal health, obesity, pneumonia, pregnancy

1 | INTRODUCTION

The emerging coronavirus disease 2019 (COVID-19) pandemic caused by infection with the novel betacoronavirus SARS-CoV-2 continues to challenge public health systems globally. Although

the majority of patients with COVID-19 have self-limited disease consisting predominantly of mild respiratory symptoms, approximately 20%-30% develop acute respiratory distress syndrome (ARDS).¹⁻⁴ The Centers for Disease Control have recently refined their risk categories for COVID-19 to state that obesity

was a major risk factor.⁵ In pregnant women, severe COVID-19 disease is also associated with obesity.^{6,7} Over the last decade, non-communicable metabolic diseases such as hypertension, diabetes, and obesity have increased in prevalence globally.⁸ In the United States, more than one-third of reproductive age women are considered to be obese (body mass index [BMI] ≥ 30 kg/m²).⁹ At the same time, the immunology and pathophysiology associated with COVID-19 in pregnancy and especially in the setting of other comorbidities such as obesity are poorly understood. This review is directed toward summarizing how obesity affects the severity of COVID-19 clinical disease and negatively impacts the antiviral immune response.

2 | OBESITY AS A RISK FACTOR FOR SEVERE COVID-19

In non-pregnant populations, obesity has been associated with severe COVID-19 disease. A retrospective review of 770 patients with COVID-19 from the two medical centers in New York found that obese patients were more likely to present with symptoms; obese patients also had a significantly increased risk of ICU admission or death (RR 1.58) even after adjusting for race, age, and troponin levels.¹⁰ Another retrospective study from a third medical center in New York including 200 patients with COVID-19 found that a BMI ≥ 35 kg/m² was independently associated with higher in hospital mortality compared to a BMI of 25-34 kg/m² (adjusted odds ratio 3.78; 95% CI: 1.45-9.83). Similarly, BMI ≥ 35 kg/m² was a significant predictor for increasing oxygenation requirements and intubation.¹¹ An Italian retrospective study demonstrated similar findings with overweight or obese patients more often requiring ventilation and a higher level of care despite younger age than older patients with normal BMI.¹²

Obese pregnant women are at increased risk for complications of viral infection from influenza, cytomegalovirus, and SARS-CoV-1 and related complications such as ARDS.¹³⁻¹⁷ The increased risk of severe respiratory viral disease due to obesity and pregnancy was most striking with the H1N1 Pandemic in 2009.¹⁷ In a study of hospitalized patients with a confirmed H1N1 influenza A viral infection in the United States, class III obesity was associated with hospitalization regardless of whether the patient had chronic medical conditions.¹⁸ Immune changes in obesity have also been associated with increased susceptibility of viral infection including increased peak viral loads and delayed clearance in influenza.¹⁹

Several case series and cohort studies have reported an increased severity of COVID-19 in pregnancies complicated by elevated BMI and obesity (Table 1). An early report of two pregnant women with severe COVID-19 necessitating ICU admission in the postpartum period was notable for a BMI of 38 and 47 kg/m² in these cases.²⁰ In a cohort study of 46 pregnant women with COVID-19 in Washington State, obesity emerged as a key co-morbidity in women with severe COVID-19⁶; of five pregnant women with severe disease in which information to calculate the body

mass index was available, four were overweight or obese prior to pregnancy.⁶ In a study of pregnant women in Italy, it was reported that of 14 women with severe disease, the median BMI was 30 kg/m², which was significantly elevated compared to women with mild disease ($P = .02$).²¹ Another cohort study from 12 medical centers in the United States included 64 pregnant women hospitalized due to COVID-19; of 64 women with severe or critical COVID-19 disease, the average BMI was 33.5 kg/m².²² This study also demonstrated that critically ill pregnant women with COVID-19 had a lower BMI than severely ill women, suggesting that while obesity may be a risk factor for severe disease, obese women may have lower mortality than lean women. Interestingly, the idea that obese women may have a greater disease severity, but lower mortality than lean women mirrors other studies from the critical care literature, which have coined this finding as the "obesity paradox".²³ Maternal deaths have been linked with obesity, however. A case series from Iran including nine pregnant women with severe COVID-19 disease of which seven died, three women had a BMI >30 kg/m².²⁴ A case series of 124 maternal deaths from Brazil found that obesity (undefined) was significantly associated with mortality.²⁵ Further, several case reports or series from the United States and the United Kingdom have reported maternal deaths or severe maternal morbidity in women with obesity.²⁶⁻³² Finally, the largest series of pregnant women with COVID-19 to date including 427 cases in the United Kingdom demonstrated that 34% of cases were obese compared to 23% of controls.⁷

3 | IMMUNOPATHOLOGY OF COVID-19

Understanding the immunopathology of infection with this novel virus is rapidly evolving. SARS-CoV-2 shares 80% RNA sequence homology with SARS-CoV-1, allowing extrapolation of likely shared pathophysiology and immune response.³³⁻³⁵ Both viruses enter the cell via angiotensin-converting enzyme-related carboxypeptidase 2 (ACE2) receptor, though the SARS-CoV-2 spike protein binds ACE2 with significantly higher affinity than SARS-CoV-1.³⁶ Healthy individuals have higher concentrations of ACE2 in lung tissues, specifically bronchial smooth muscle cells, alveolar epithelium, type II pneumocytes, and alveolar macrophages.^{37,38} Extrapulmonary expression of ACE2 occurs in myocardial cells³⁸; enterocytes in the ileum and jejunum³⁹; and proximal tubular cells in the kidney,³⁸ oral mucosa,⁴⁰ and arterial and venous endothelium.⁴¹ In contrast, the strongest evidence suggests negligible placental expression of ACE2 and TMPRSS2, a serine protease that acts as a canonical mediator of cell entry for SARS-CoV-2 in conjunction with ACE2.⁴² Multiple cells, predominantly within the lung, but also within other target organs (eg, heart, kidney) express the canonical receptor for SARS-CoV-2 entry.

During the initial stage of most viral infections, the type I and type III interferon (IFN) response is the primary mechanism leading to viral clearance (Figure 1, right panel). Immune cells detect viral nucleic acids through pattern recognition receptors (PRRs), primarily

TABLE 1 Studies on COVID-19 in pregnancy with reports on obesity

Study	Country	N	N with obesity	Maternal outcomes	Neonatal outcomes
Andrikopoulou et al ¹⁰⁹	USA (NY)	158	80 (50.6%)	Similar rates of obesity for mild (52%) and severe (47%) COVID-19	Two PTB for maternal decompensation
Hantoushzadeh et al ²⁴	Iran	9	3 (33%)	1/7 (14%) maternal deaths in obese women	Three IUFD, two NND
Knight et al ⁷	UK	427	140 (34%)	3 maternal deaths	50/243 iatrogenic PTB, 29 (46%) due to COVID-19, three IUFD, two NND
Lokken et al ⁶	USA (WA)	46	15 (35.7%)	6 (15%) severe COVID-19, 5/6 (80%) of severe cases in obese women	One PTB in an obese patient for respiratory compromise, one IUFD
Mendoza et al ¹¹⁰	Spain	42	Mean BMI 26.1 in non-severe COVID-19 cases, 27.9 in severe COVID-19 cases	8/42 (19%) severe COVID-19	Three PTB due to respiratory compromise
Pierce-Williams et al ²²	USA (PA, NY, NJ, OH)	64	Mean BMI 33.5 in severe COVID-19 cases, BMI 29.7 in critical COVID-19 cases	44 (69%) severe, 20 (31%) critical COVID-19	88% of women with critical disease had PTB
Savasi et al ²¹	Italy	77	Mean BMI 22.8 in total study, Mean BMI 30 in cases with severe COVID-19	14 (18%) severe COVID-19	4/11 (36%) of severe COVID-19 cases had PTB

Abbreviations: BMI, body mass index; IUFD, intrauterine fetal demise; NJ, New Jersey; NND, neonatal demise; NY, New York; OH, Ohio; PA, Pennsylvania; PTB, preterm birth; UK, United Kingdom; USA, United States of America; WA, Washington State.

endosomal receptors Toll-like receptor (TLR)3/7/9 and cytosolic receptors melanoma differentiation-associated protein-5 (MDA-5), and retinoic acid-inducible gene-I (RIG-I), which leads to the activation of both type I IFN and inflammatory cytokine production.^{43,44} Type I IFN upregulates hundreds of interferon-stimulated genes, which activate antiviral signaling and provide positive feedback and amplification of inflammation.⁴⁵ SARS-CoV-1 has been demonstrated to use multiple mechanisms to evade this initial IFN response including ubiquitin degradation of MDA-5 and RIG-I, inhibition of downstream signaling molecules mitochondrial antiviral signaling protein (MAVS) and TNF-receptor associated factor (TRAF)3/6, and blockage of phosphorylation of signal transduction and activation of transcription (STAT) family transcription factors.⁴⁶⁻⁴⁸ In addition, ACE2 is itself an IFN-induced gene. Activation of the normal antiviral response therefore leads to upregulation of the receptor for viral entry.⁴¹ Early data from SARS-CoV-2 suggest that this virus is also able to modulate the IFN response.⁴⁹

As the infection progresses, there is increasing viral-induced cell death with release of additional viral particles as well as cellular components. In addition to infecting respiratory epithelial cells,³⁸ SARS-CoV-1 can also infect immune cells such as T cells and antigen-presenting cells such as monocytes and dendritic cells.⁵⁰ These signals activate tissue macrophages that further amplify the inflammatory response by producing pro-inflammatory cytokines (TNF- α , IL-1, IL-6), which, in turn, lead to additional lung injury and immune cell recruitment.^{51,52} Cytokines and chemokines result in the activation of adaptive immune T and B cells as well as recruitment of neutrophils and monocytes. Viral-specific CD8 T cells are cytotoxic primarily to infected cells and serve to limit the release of additional viral particles, while neutrophils non-specifically release reactive oxygen species and leukotrienes, which are directly toxic to pneumocytes and endothelial cells. Additionally, high levels of IFN and pro-inflammatory cytokines also lead to cell death directly with and without viral infection through induction of apoptosis. Patients with severe COVID-19 typically have high levels of systemic pro-inflammatory cytokines, lymphopenia, and inflammatory lung infiltrates, which is consistent with a maladaptive patterns of cytokine production and inflammatory misfiring.⁵³⁻⁵⁶ Elevated cytokines are also associated with multiple pathologic effects in the lung including endothelial apoptosis and vascular leaking, an ineffective antiviral response, diffuse alveolar damage, inflammatory cellular infiltrates, and intravascular thrombosis.⁵⁷⁻⁵⁹

4 | OBESITY-INDUCED CHANGES TO IMMUNITY AND PHYSIOLOGY

Adipose tissue is an active endocrine and immune organ consisting primarily of adipocytes, but also multiple immune cell types, which represent the second most frequent type of cells in this tissue.^{60,61} Macrophages are the most common immune cell type in adipose tissue and, in lean individuals, produce type 2 cytokines (IL-4, IL-10) and anti-inflammatory molecules.^{62,63} However, in obese individuals,

activated macrophages in adipose tissue produce pro-inflammatory cytokines TNF- α , IL-1 β and IL-6, which results in recruitment and activation of additional monocytes, as well as NKT cells and mast cells (Figure 1, left panel). Adaptive immune cells also play a role in obesity-associated inflammation. Adipose tissue from lean individuals is composed primarily of CD4+ Th2 cells and regulatory T cells (Treg), which promote an anti-inflammatory environment, while obese adipose tissue is enriched for CD4+ Th1 and Th17 cells as well as cytotoxic CD8+ T cells.⁶⁴⁻⁶⁶ Changes in T-cell polarization may be due to altered metabolite availability in obesity, which contributes to T-cell differentiation and response to pulmonary infection.^{67,68} In addition to changes in T-helper cell phenotype, obesity is also associated with T-cell dysfunction (Figure 1, left panel). Obesity results in increased production of memory T cells, and in a mouse

model of viral infection, the memory T-cell response to viral infection in obese animals resulted in increased pathogenesis rather than a protective response.⁶⁹ The chronic inflammation in obesity has also been associated with T-cell exhaustion, which may be responsive to treatment with biologic therapies.^{70,71}

Adipose tissue and cytokine-like hormone released from adipocytes, called adipokines, may directly and indirectly impair the pulmonary immune response (Figure 1, left panel). The adipocyte overflow hypothesis suggests that when an adipocyte can no longer hypertrophy to accommodate storage of new lipids, an "overflow" of fatty acids occurs into the body^{72,73}; lipids may then be recognized by innate immune pathogen recognition receptors at ectopic sites to stimulate a low-grade inflammatory response.⁷⁴ Adipose tissues also release adipokines that can act as powerful regulators

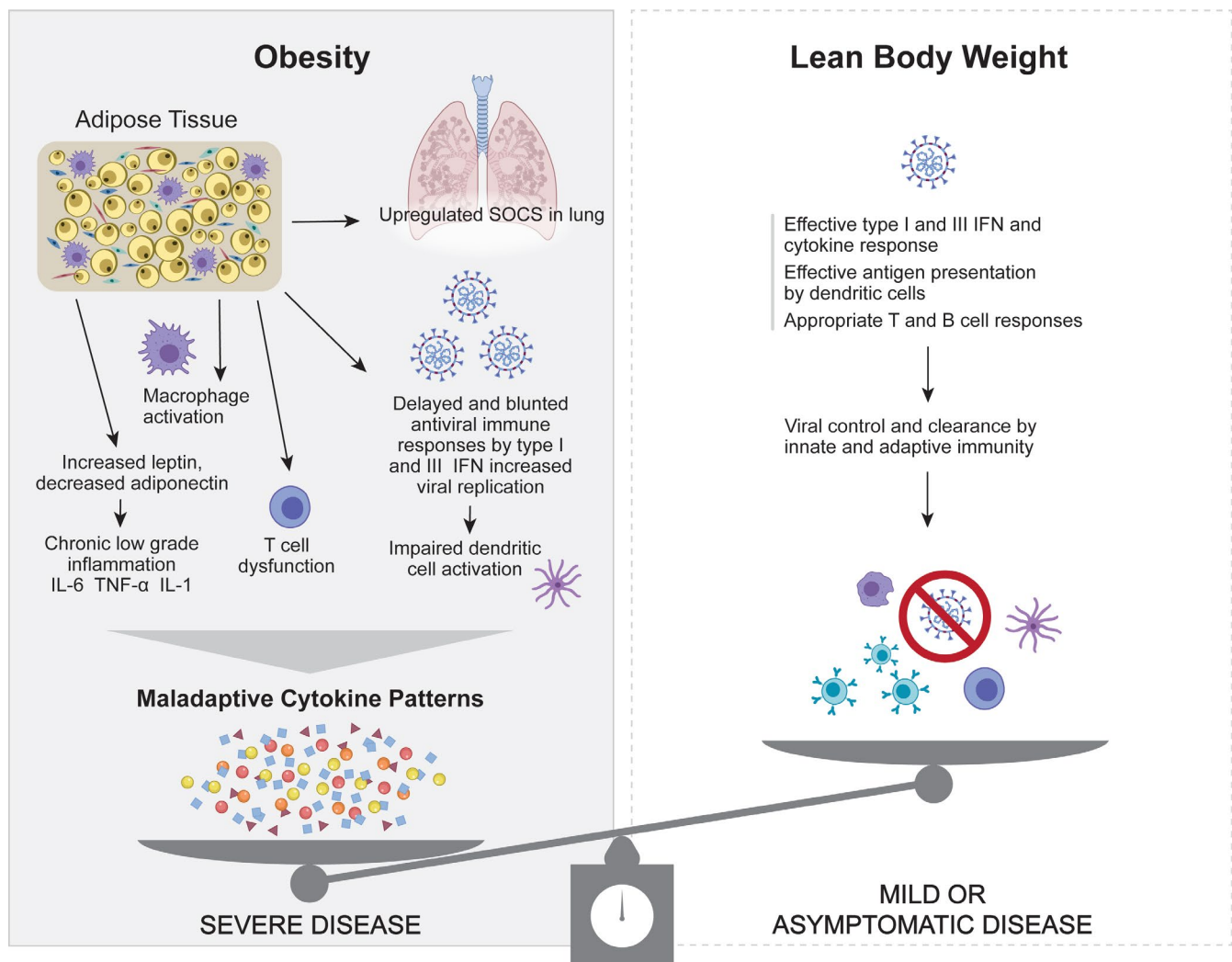


FIGURE 1 Potential mechanisms for increased COVID-19 severity in pregnancy associated with obesity. In pregnant women with lean body weight (right panel), there is typically an effective type I and III IFN responses to viruses through antigen presentation by dendritic cells and coordinated innate and adaptive immune responses. In obese pregnant women (left panel), there is an inhibition of viral clearance through blunting of type I and III IFN responses, as well as inadequate antigen presentation by dendritic cells and T-cell dysfunction. Obesity is also associated with chronic inflammation, M1 macrophage activation, altered adipokine production (eg, leptin, adiponectin) and upregulation of suppressors of cytokine gene signaling (SOCS), which can lead to excessive lung injury. The combination of defective viral clearance, increased inflammatory lung injury and altered lung mechanics in obese pregnant patients can synergize to increase the risk of severe or critical COVID-19 disease

of the immune response. Leptin is a key adipokine and can regulate both innate and adaptive immunity to mediate a pro-inflammatory immune response.⁷⁵ An inflammatory microenvironment can also downregulate production of adiponectin by adipocytes, which impairs the anti-inflammatory response. Interestingly, high levels of leptin that is typical in obese individuals increase the risk of the severity of respiratory infections in both humans and mouse models.⁷⁶ High circulating leptin levels were associated with mortality in non-pregnant adults hospitalized for acute respiratory distress syndrome due to pneumonia, even after adjusting for BMI.⁷⁶ The placental trophoblast and amnion also secrete leptin, which may further impair the pulmonary immune response in pregnant women.⁷⁷ Finally, adipose tissue is present in subcutaneous, visceral, and omental locations; the cellular and metabolic properties of each type of tissue are unique. Alterations in visceral adiposity have been associated more closely with adverse metabolic and health outcomes and immunologic dysfunction.^{78,79}

In addition to inducing immunologic dysfunction, excess adipose tissue also changes the mechanics and physiology of respiration. The increased metabolic requirements in obesity result in higher oxygen consumption and increased work of breathing.⁸⁰ Obesity also results in greater production of carbon dioxide, which leads to decreased respiratory drive. Mechanically, increased fat deposits within the abdominal cavity reduce the compliance of the respiratory system.⁸¹ Increased abdominal adipose tissue mass leads to elevated abdominal pressure and lower lung volume by reducing expiratory reserve and functional residual capacity.⁸² Obesity is also associated with airway narrowing which can lead to gas trapping.⁸³ The combination of decreased lung volumes, increased abdominal pressure, and narrowing of the airway leads to increased work of breathing with early fatigue of respiratory muscles.

5 | IMMUNOLOGY IN PREGNANCY AND IMPACT OF OBESITY

Pregnancy provides both a physiologic challenge and a immunologic challenge for the maternal host during which it must balance providing access to nutrition, protection from infection, and tolerance of a genetically foreign fetus. To accommodate these functions, there is dynamic regulation of the maternal immune system, both systemically and at the maternal-fetal interface during pregnancy. Pregnancy requires both pro-inflammatory and tolerogenic immune responses at specific times during gestation.⁸⁴⁻⁸⁶ During the early first trimester, a localized inflammatory response is necessary for embryonic implantation into the uterine decidua.^{87,88} At the time of human parturition, a functional progesterone withdrawal in humans coupled with an inflammatory response direct the cascade of biological events that culminate in birth.⁸⁹⁻⁹² However, during the second and third trimesters, immune cells and cytokines promote a tolerogenic environment to accommodate the fetus and promote uterine quiescence.^{93,94} Pathologic inflammation and inflammatory cytokine production (IL-6, IL-8, TNF- α , IL-1 β) is associated with adverse pregnancy outcomes including abortion, fetal growth restriction, preterm birth, and preeclampsia.⁹⁵

Multiple immune adaptations during pregnancy result in alterations to antiviral immunity. First, syncytiotrophoblast cells that line the placental chorionic villous tree actively secrete type III IFN, which act as an immunologic and physical barrier to viral infection.⁹³ Systemic immune cellular and cytokine changes during pregnancy can favor either a pro-inflammatory (IL-1, IL-6, IL-12, IFN- γ , TNF- α) or tolerogenic (IL-4, IL-10, IL-13) response depending on the time in gestation.⁹⁶⁻⁹⁸ SARS-CoV-1 and influenza infections in pregnancy have been associated with an increased pro-inflammatory response

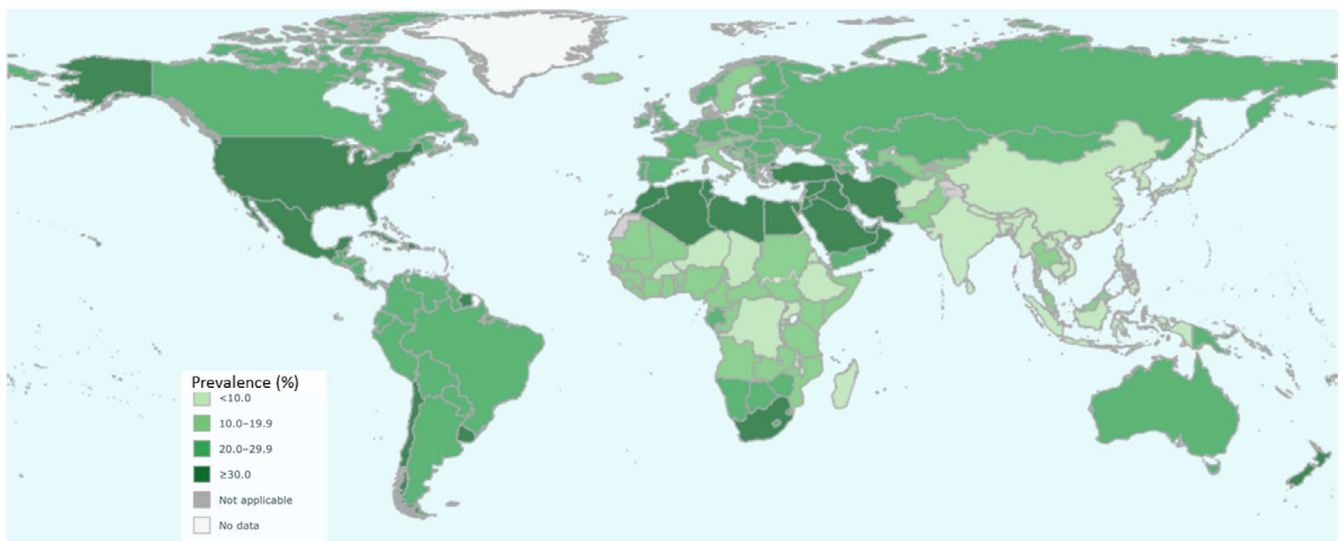


FIGURE 2 Global distribution of obesity among adult women. This global map demonstrates the geographic distribution of obesity (BMI >30) in adult women (>18 y old). The highest prevalence of obesity (>30%) is concentrated within the United States, Mexico, North Africa, South Africa, the Middle East and a few additional countries. Reprinted with permission: World Health Organization 2017 | Source: Global Health Observatory (<http://www.who.int/gho/en/>)

within the lungs, which resulted in decreased viral clearance and increase immune-mediated lung injury.^{99,100} Currently, data are insufficient to determine whether the systemic changes in pregnancy immunity play a role in enhancing COVID-19 disease pathogenesis.

In overweight and obese pregnant women, immunologic and metabolic dysfunction likely contributes to the increased severity of COVID-19 disease (Figure 1, left panel). The negative impact of obesity on the host response to respiratory viral pathogens may partially derive from an increased availability of glucose to the virus, changes to the adaptive immune system allowing propagation of viruses as well as a state of increased inflammation, inflammatory stresses, and poor wound healing.¹⁰¹ Chronic inflammation and elevated adipokine leptin levels result in inhibition of the type I IFN antiviral response through upregulation of suppressor of cytokine signaling (SOCS) genes.¹⁰² Obesity also results in higher baseline levels of inflammatory cytokines including IL-6, TNF- α , and IL-1 β ¹⁰³; notably, serum IL-6 levels are one of the strongest clinical correlates for severe COVID-19 disease.^{104,105} In addition, a change in CD4+ T-cell polarization from Th2 and Treg cytokines (IL-4, IL-10, IL-13) to a pro-inflammatory Th1 and Th17 response observed in obese individuals is associated with production of pro-inflammatory cytokines, such as TNF- α , IL-1, IL-6, and IL-17, which provides a potential mechanism for an earlier initiation of cytokine release and inflammatory misfiring in obese patients. The expression of ACE2 by adipocytes and immune cells also suggests the possibility that adipose tissue may represent a potential reservoir for viral infection and may lead to increased viral burden or persistence; however, no studies to date have demonstrated that adipocytes can be directly infected with SARS-CoV-2. These obesity-driven alterations in the immune response likely contribute to the severity of COVID-19 in obese pregnant women.

6 | CONCLUSION

Maternal obesity has emerged as a key risk factor increasing susceptibility of pregnant women to severe COVID-19 disease. This is likely the result of complex immunologic, metabolic, endocrine, and physiologic changes associated with obesity, which affect the immune response to viral infection. The increasing global burden of obesity may lead to more severe pregnancy morbidity and has the potential to regress decades of progress in global health and, by extension, to improvements in reproductive and pregnancy care worldwide (Figure 2). Analyses comparing obesity rates in over the last three decades show that obesity among pregnant women has increased drastically worldwide.¹⁰⁶ In 2017-2018, obesity among women 20 years and older was 41.9% in the United States.⁹ Currently, the United States also has the highest number of COVID-19 infections worldwide.¹⁰⁷ In light of the global COVID-19 pandemic, there has been a call for renewed prioritization of non-communicable diseases such as obesity that increase susceptibility of women with SARS-CoV-2 infection to severe disease or mortality.¹⁰⁸ Carefully designed epidemiologic studies are required to assess the linkage between COVID-19 disease severity, obesity,

and associated socioeconomic factors. There is also an urgent need to focus research on how risk factors, like obesity, alter the immune response to SARS-CoV-2 and influence disease pathogenesis of COVID-19 (Box 1). Finally, given global trends in the rise of obesity over the last 3 decades, urgent action is needed to address this critical health condition for global health.¹⁰⁶

1 | Box Research questions

1. What is the mechanism of increased risk for severe COVID-19 disease in obese non-pregnant and pregnant women?
2. Does the second and third trimester of pregnancy represent a time of increased risk for severe COVID-19? If yes, how does gestational age modify the effect of obesity on COVID-19 disease severity?
3. Is preterm birth more common in obese pregnant women with COVID-19 due to concern for respiratory compromise?
4. Are certain therapies more effective for treatment of severe COVID-19 in obese pregnant women compared to lean or non-pregnant women?
5. Does increased surveillance for COVID-19 in obese pregnant women improve health outcomes?
6. Can adipose tissue serve as a reservoir for SARS-CoV-2 viral infection through adipocyte ACE2 expression?
7. Are viral loads higher of SARS-CoV-2 in obese versus lean pregnant women? Are the kinetics of viral clearance different in obese versus lean pregnant women?
8. Can we design epidemiologic studies to further assess whether the risk of severe COVID-19 infection in obese pregnancy is directly related to obesity itself or to associated socioeconomic factors?

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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