Review on the impact of pregnancy and obesity on influenza virus infection

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A myriad of risk factors have been linked to an increase in the severity of the pandemic H1N1 2009 influenza A virus [A(H1N1)pdm09] including pregnancy and obesity where death rates can be elevated as compared to the general population. The goal of this review is to provide an overview of the influence of pregnancy and obesity on the reported cases of A(H1N1)pdm09 virus infection and of how the concurrent presence of these factors may have an exacerbating effect on infection outcome. Also, the hypothesized immunologic mechanisms that contribute to A(H1N1)pdm09 virus severity during pregnant or obese states are outlined. Identifying the mechanisms underlying the increased disease severity in these populations may result in improved therapeutic approaches and future pandemic preparedness.

Keywords antiviral, influenza, obesity, pregnancy, vaccine.

Introduction

The first cases of the novel pandemic (H1N1) 2009 influenza A virus were reported in March 2009, when nasopharyngeal swabs were collected from two epidemiologically unrelated children in California who had respiratory infections.1 Pandemic H1N1 2009 influenza virus [A(H1N1)pdm09 virus] is mostly self-limiting, and the infection mimics that of commonly circulating seasonal influenza viruses; however, A(H1N1)pdm09 virus continues to be a public health concern for several population groups because of increased risk of severe infection.

Pregnancy and obesity were identified as risk factors for developing severe A(H1N1)pdm09 virus-related illness.3–9 These populations are more likely to develop respiratory complications including pulmonary distress10,11 and have higher hospitalization and mortality rates than non-pregnant and non-obese populations.2,9 The reasons for the increased disease severity remain poorly understood. Some evidence suggests that the immune response may be involved because pregnant and obese patients are immunocompromised.12–18 However, numerous questions need to be answered to understand the mechanisms for enhanced disease in pregnant and obese patients including What are the immunologic mechanisms that promote increased severity of A(H1N1)pdm09 virus infection in these populations? Should current antiviral and vaccine options be revised for pregnant–obese individuals? Finally, does obesity during pregnancy worsen the outcome of infection during pregnancy? The goal of this review is to summarize the published literature on the clinical manifestations of influenza pandemics in pregnant and obese populations, the immunologic signatures associated with severe infection, and finally the prophylactic and therapeutic options targeted to pregnant or obese persons are also discussed (Table 1). We end with a brief discussion on the effect of obesity during pregnancy on A(H1N1)pdm09 virus-related disease.

Pregnancy as a risk factor

Clinical outcome of pandemic H1N1 2009 influenza virus (A(H1N1)pdm09 virus) infection in pregnant women

Serious influenza virus-induced complications in pregnant women are not a new phenomenon. Infection from seasonal or previous pandemic influenza outbreaks can cause otherwise healthy pregnant women to have disproportionately higher rates of hospital admissions and mortality than the general population.19–22 Within the first 4 months of
| Epidemiological Category | Factors that Influence Infection Outcome | Obesity | Pregnancy | Obesity + Pregnancy | References |
|--------------------------|-----------------------------------------|---------|-----------|---------------------|------------|
| Hospitalization          | Admittance into ICU                     | "Higher" | "Higher"  | Unknown             | 5,7,14,22,24,25,93 |
|                          | Mean duration of stay                   | Higher   | "Higher"  | Unknown             | 5,7,31,137  |
|                          | Viral Pneumonia                         | Higher   | Higher    | Unknown             | 5–7,12,22,25,31,93,115 |
|                          | Mortality                               | Higher   | Higher    | Unknown             | 7,12,22,25,31,137 |
|                          | Wound repair                            | Impaired | "Higher"  | Unknown             | 141 |
| Lung damage              | Inflammation                            | Higher   | "Higher"  | Unknown             | 52,53,56–58,62,157–160 |
|                          | Th1/Th2 polarization                     | Th1      | "Lower"   | Unknown             | 52,53,56–58,62,137,158–160 |
|                          | T cell number and function               | Lower    | "Lower"   | Unknown             | 12,13,16,59,61,64,68,144,145,148,151 |
|                          | B cell number and function               | Unknown in humans | "Reduced IgG2" | Unknown | 14,86,137,138 |
| Comorbidities            | **Diabetes                              | Higher (T2DM) | Higher (Gestational) | Higher (Gestational) | 5,7,27,130,132,133,138,177,178 |
|                          | **Asthma                                | Higher    | Normal    | Higher              | 5,7,27,121–124,177,178 |
|                          | **Hypertension                          | Higher    | Higher    | Higher              | 5,7,27 |
| Antiviral therapy        | Oseltamivir, Amantadine                  | Effective | "Effective" | Unknown             | 4,5,7,24,25,27,28,31,44–46,140,141 |
| Vaccines                 | Pandemic H1N1 2009                       | Preliminary – impaired long term | Preliminary – impaired long term | **High seroconversion | 36–41,139 |
|                          | Trivalent inactivated influenza (TIV); live attenuated | Preliminary – impaired long term | Preliminary – impaired long term | **High seroconversion | 33–35,139 |

*Above the rate of individuals belonging to non-at-risk groups.
†Is decreased in pregnant women if antivirals are administered within 3 days of symptom onset; some reports indicate rate dependent largely on late gestational period of pregnancy.
‡Inflammatory responses are decreased in non-infected pregnant women to prevent fetal allograft rejection.
§Canonical Th2 cytokines are elevated during pregnancy: Interleukin-4 (IL-4), IL-6, IL-10, cytokine shift often occurs systemically.
*Decreased T-cell responses at the maternal–fetal interface.
**IgG2 deficiency effects overall outcome of A(H1N1)pdm09 virus in pregnant humans; reduced overall antibody responses to A(H1N1)pdm09 virus detected in pregnant mice.
††Region specific.
†‡Oseltamivir recommended (CDC) most effective in reducing viral replication if administered within 48 hours of symptom onset.
†§Vaccine coverage generally low.
**Generally well-tolerated; Vaccine uptake (VU) generally high.
the 2009 pandemic, several retrospective studies were conducted primarily within the United States (US), which reported an increase in severity of A(H1N1)pdm09 virus infection in pregnant women. In California alone, 10% of patients who were hospitalized or succumbed to A(H1N1)pdm09 virus infection were pregnant.22 This is striking because pregnant women make up a mere 1% of the entire US population. In a study by Siston et al.,3 this group accounted for approximately 5% of A(H1N1)pdm09 virus-related deaths. Approximately, 95% of pregnant women in the US hospitalized for A(H1N1)pdm09 virus infection were in their second or third trimester of pregnancy,5,7,23,24 indicating that the severity may be dependent at least in part to the gestational period. Despite the declaration of the end of the pandemic in August 2010 by the World Health Organization (WHO) and a general decline in A(H1N1)pdm09 virus activity worldwide, several regions continue to report severe cases of A(H1N1)pdm09 virus infection in pregnant populations. Latin America, Europe, Australia, and North America have reported an increase in severe infection and mortality rates in pregnant women.7,22,25–28

The most commonly reported A(H1N1)pdm09 virus-related symptoms in pregnant persons are not unlike those associated with seasonal influenza infections. Clinical features of A(H1N1)pdm09 virus in pregnant women include myalgia, vomiting, and acute febrile respiratory illness, which in many cases require mechanical ventilation.5,7 A study conducted from April to August 2009 in the US showed that the rate of hospitalization (57%) in infected women who received late treatment (4 days) was higher than that of hospitalized women who were treated early (5%) (1–2 days), demonstrating the importance of early intervention.5 The rates of commonly reported A(H1N1)pdm09 virus-related symptoms (e.g., muscle aches, sore throat, cough) in pregnant women are similar to those of non-pregnant women.7 An outcome unique to A(H1N1)pdm09 virus-related morbidity in pregnant women is adverse effects to the fetus.24 A recent retrospective study suggests that among women who delivered while hospitalized for influenza virus infection, 63–66% delivered preterm or very preterm and 43–80% delivered low-birth weight infants23 compared with U.S. averages of 12–3% for preterm birth and 8–2% for low birth weight.29

Given that pregnant women have increased susceptibility to a variety of infectious agents, the presence of comorbidities worsens the outcome of A(H1N1)pdm09 virus infection in this group. Little is known about the effect of A(H1N1)pdm09 virus infection in severely immunocompromised pregnant women. Influenza A virus-related death is more likely in non-pregnant patients undergoing chemotherapy,30 suggesting that cancer treatment and possibly immunocompromising infections may significantly heighten A(H1N1)pdm09 virus-related morbidity. Several other conditions can also result in a marked increase in severity of A(H1N1)pdm09 virus in pregnant women. In one study, a large percentage (49–3%) of pregnant women with A(H1N1)pdm09 virus infection in the US from April to August 2009 had underlying conditions such as asthma (22%), diabetes (67%), and hypertension (3%).5,31 High mortality rates in these patients were most correlated with asthma.5 Therefore, modifications in vaccine or therapeutic management require review in light of these newly identified comorbidities in pregnant populations.

**Prophylaxis and therapeutic options for the control of A(H1N1)pdm09 virus in pregnant women**

The severity of A(H1N1)pdm09 virus in pregnant women reinforces the public health message that they should be a high-priority group for vaccination. The standard trivalent inactivated influenza vaccine (TIV) is recommended for all pregnant women in the Northern Hemisphere and some regions of the European Union.32 TIV is safe and immunogenic in pregnant women33,34 and stimulates passive transfer of maternal antibodies.35 However, little is known about the efficacy of A(H1N1)pdm09 virus vaccines in pregnant women.36 A study conducted in France reported an overall VC of 12% for pregnant women.37 Similarly, in Western Australia, VC for pregnant women was 10–3% during a 13-month period.38 In contrast, a higher VC was reported in the US (up to 38%).39 However, the global VC for A(H1N1)pdm09 virus is currently unknown. The discrepancy of VC among regions worldwide reflects a major limitation in decreasing the severity of A(H1N1)pdm09 virus in pregnant women. Barriers such as negative perceptions to and low availability of vaccine must be overcome to ensure optimal vaccine uptake. Several studies suggest that seroconversion to the virus occurs in babies born to mothers vaccinated against A(H1N1)pdm09 virus,35,43 implying that vaccination of mothers may be a suitable approach to minimize morbidity in offspring.

The efficacy of A(H1N1)pdm09 virus vaccination in pregnant women remains uncertain. Despite implementation of mass A(H1N1)pdm09 virus vaccine campaigns in several regions, the effectiveness of vaccination has been reported to be low in some cases. Whether such phenomenon is the exception or is more common remains to be determined. Future studies are needed to determine the
degree to which A(H1N1)pdm09 virus vaccinations confer immunity in pregnant women.

The anti-influenza drugs neuraminidase inhibitors, oseltamivir, and zanamivir are standard therapeutic options to control influenza virus replication in the clinical setting. The WHO recommends oseltamivir or zanamivir for A(H1N1)pdm09 virus-based therapy in women who are pregnant or breastfeeding. In a study by Nakai et al., Japanese pregnant women who received treatment more than 48 hour after onset of symptoms developed more severe pneumonitis than those who received drugs within 48 hour of onset of symptoms. These results are similar to those of studies conducted in the US and Canada, indicating that early intervention in pregnant women is key and that early antiviral treatment in pregnant women was associated with fewer ICU admissions and deaths. Early treatment may also be favorable because of possible harmful effects of the virus to the fetus, such as miscarriage and congenital malformation. The M2 inhibitors or adamantanes are generally inducers of resistance in several influenza strains, including A(H1N1)pdm09 virus. There exists limited study on the efficacy of adamantanes to treat A(H1N1)pdm09 virus in pregnant women. Therapeutic regimens must be carefully chosen to decrease the risk of toxicity to the fetus or even to infants via breastfeeding.

Pregnancy: an immunocompromised state?

Although pregnancy is associated with significant changes to the respiratory physiology that are required to meet the increased metabolic demands of the mother and fetus, including increased edema and mucopolysaccharide content, alterations to the chest wall and diaphragm, and a reduction in functional residual capacity (FRC; reviewed in ), we will focus our review on changes to the immune response. Pregnancy is associated with immunologic suppression and increased susceptibility to various pathogens. The general paradigm is that during normal pregnancy, the immune system of women acquires a suppressed state that promotes fetal implantation. The presence of ‘foreign’ fetal antigens or fetal ‘allograft’ induces immunologic tolerance, wherein a cascade of ‘tolerogenic’ signals alters the maternal immune system. This phenomenon was first described by Medawar et al., who found that pregnant women are capable of immune recognition of self- versus non-self-antigens. Many studies have been performed on how the immune system of pregnant women ‘tolerates’ the fetal allograft. Alterations in cellular immune responsiveness are thought to be the primary mechanism of maternal tolerance.

A unique feature of cellular responses during pregnancy is a shift toward a predominately T-helper type 2 (Th2) phenotype. A proinflammatory or Th1 response promotes abortions or pregnancy-related complications. Along with skewing of the Th1/Th2 balance, pregnancy results in alteration of cytokine production. Pregnancy affects the activation and function of lymphocytes. Secretion of proinflammatory Th1 cytokines TNF-α, IFN-γ, and IL-2 is especially deleterious and promote fetal loss. Some evidence suggests that these signals may be site specific, which may be an important factor for anti-influenza responses throughout the body. The systemic systemic and decidua exhibit diverse immune responses. The site of the decidua has a high proportion of natural killer (NK) cells and macrophages. Numbers of T lymphocytes are high in the decidua, but may be low in the peripheral bloodstream. It is likely that a Th-2-biased environment plays a role in the susceptibility to lipopolysaccharide antigens and the response to pathogen infections during pregnancy.

The immunologic changes that occur during normal pregnancy may explain the increased susceptibility of pregnant women to A(H1N1)pdm09 virus. Typically, dysregulation of early immune responses is a hallmark of severe influenza infection in humans and mice. The secretion of cytokines and chemokines is critical in limiting influenza replication. In contrast, exacerbated proinflammatory cytokine responses increase severity of avian H5N1 influenza disease, demonstrating that the extent of inflammation may differ depending upon influenza subtype. A recent study found an impairment of innate Th1 cytokines TNF-α and IFN-γ responses in the bloodstream of A(H1N1)pdm09 virus-infected non-pregnant patients. Conversely, another study showed that elevation of Th1 cytokines is associated with severe A(H1N1)pdm09 virus infection. In a recently described mouse model, levels of proinflammatory cytokines were associated with increased susceptibility of pregnant mice to A(H1N1)pdm09 virus. These results are surprising given that pregnant women acquire mostly anti-inflammatory (Th2) responses. Future studies are essential to determine what role, if any, does cytokines and other arms of the immune system (adaptive) play in the severity of A(H1N1)pdm09 virus in pregnant populations. Interestingly, obesity, which has also been identified as a risk factor for severe A(H1N1)pdm09 virus infection, is associated with increased levels of Th1 cytokines, thus demonstrating that the immune pathways leading to A(H1N1)pdm09 virus-related morbidity and mortality may differ among certain at-risk groups.

Adaptive immune responses are also important for controlling influenza. In a recent report, severely infected pregnant women displayed decreased levels of serum immunoglobulin G2 (IgG2), suggesting a role for the IgG subclasses in the outcome of A(H1N1)pdm09 virus infection. In summary, Th2 skewing is likely to be a major contributing factor in increased A(H1N1)pdm09 virus morbidity during pregnancy.
Obesity as a risk factor

The main underlying causes of obesity are increased caloric intake (versus expenditure), a myriad of genetic factors, and exposure to an increasingly obesogenic environment (e.g., sedentary lifestyle). The rates of obesity have risen to epidemic proportion worldwide. According to the WHO, in 2008, at least 1.5 billion adults were overweight [body mass index (BMI) ≥25 kg/m²], with 400 million of these individuals being obese (BMI ≥30 kg/m²). In the US alone, two of every three persons (~68% of the population) are estimated to be overweight or obese.

Clinical outcome of A(H1N1)pdm09 virus 2009 in obese individuals

Epidemiologic data have identified obesity as a risk factor for severe morbidity and increased mortality from infection with A(H1N1)pdm09 virus influenza. Obesity was one of the most commonly reported comorbidities in patients admitted to intensive care units worldwide.

Previously, neither obesity nor morbid obesity was described as a risk factor for severe infection with seasonal influenza in humans, suggesting that obesity-related severity may be associated with certain influenza strains or that levels of obesity have reached a point of ‘critical mass’ and can significantly affect the extent of influenza illness.

Within the first 4 months of the A(H1N1)pdm09 virus pandemic, morbid obesity in adults was reported to be significantly associated with increased risk of hospitalization from A(H1N1)pdm09 virus infection (odds ratio [OR] = 4.9, 95% CI: 2.4–9.9) even while excluding chronic medical conditions commonly associated with obesity (OR = 4.7, 95% CI: 1.3–17.2). In California alone, 62% of A(H1N1)pdm09 virus patients had a BMI ≥30 kg/m², 30% of whom had a BMI ≥40 kg/m². Obesity was also reported to increase the severity of infection and intensive care requirement. In Michigan, nine of 10 severely ill patients requiring intensive care had a BMI ≥30 kg/m², seven of whom had a BMI ≥40 kg/m². Data from other states show that 74% of patients in Utah and 48% of patients at the Mayo Clinic in Minnesota had a BMI ≥30 kg/m². In New York City, 58-1% of patients who died from A(H1N1)pdm09 virus between April and July 2009 were obese or extremely obese.

The association between increased BMI and severity of A(H1N1)pdm09 virus has also been reported in other parts of the world. A significant number of patients admitted to the intensive care unit (ICU) in Mexico had a BMI ≥30 kg/m². In the Southern Hemisphere, 28.5%–44% of patients admitted to ICUs were obese; obesity was identified in patient populations in Chile, New Zealand, Australia, and South Africa.

The mortality rates in A(H1N1)pdm09 virus-infected, obese individuals vary by geographical region, but diabetes and a BMI ≥30 kg/m² were the most frequent underlying conditions in patients older than 20 years who died from A(H1N1)pdm09 virus infection. A study in California suggested that obese persons were more likely to die when hospitalized with A(H1N1)pdm09 virus and extreme obesity (BMI ≥40 kg/m²). In the Southern Hemisphere, 14.5%–21.9% of persons who died from influenza-like illness were obese, and this number rose to 57.2% in morbidly obese patients. Fatalities from influenza infection in obese persons have been reported in France, Turkey, United Kingdom, and China. However, not all studies have found associations between obesity and A(H1N1)pdm09 virus-related mortality. In Mexico and Canada, mortality rates for obese and non-obese patients were similar. Overall, these results indicate that obesity is a significant risk factor for increased mortality from A(H1N1)pdm09 virus infection.

Although obesity does appear to be a major risk factor for morbidity and mortality from A(H1N1)pdm09 virus, there are several reasons why data may vary geographically. Temporally, many of these studies do not encompass the entire infection period, which could affect the numbers of individuals admitted to the hospital or reported cases. Geographically, although obesity is a global problem, rates of obesity vary among countries, leading to changes in size of the at-risk population and differences in infection prevalence. Also, these numbers reflect only those individuals who sought medical attention for severe illness; the real number of infections in healthy and overweight or obese individuals is unknown, as many individuals with mild illness may not have opted to see a physician. Finally, these studies look at A(H1N1)pdm09 virus infection in adult populations only. Although there may be a possible association between A(H1N1)pdm09 virus-related illness and obesity in pediatric patients, there is not yet enough data available to make a significant correlation. Also, as no standard definition of childhood obesity is used worldwide, it is unclear whether the same definition applies universally.

Obesity is also associated with decreases in lung function as well as the development of chronic respiratory conditions both of which can be risk factors for developing severe influenza infection. Recent epidemiologic studies have suggested a relationship between asthma and obesity. Although the exact nature of this association has not been fully elucidated, epidemiologic data suggest that the prevalence and severity of asthma may be increased in obese people and that the effectiveness of drugs normally used in treatment might be less effective. These changes
may occur because of the systemic, chronic, low-grade inflammation, and oxidative stress associated with the obesogenic state.\textsuperscript{125–129}

Diabetes is also significantly associated with severe A(H1N1)pdm09 virus influenza infection. A study showed that diabetes tripled the risk of hospitalization from A(H1N1)pdm09 virus and quadrupled the risk of ICU admission once hospitalized.\textsuperscript{130,131} The global prevalence of diabetes in 2010 was 6\%4, a significant increase from 4\% in 1995. This prevalence is projected to increase to approximately 7.7\% of the world population by 2030. The close association between obesity and diabetes, famously coined ‘diabesity,’ has been known for a number of years.\textsuperscript{132,133} Indeed, individuals with a BMI $\geq 30$ kg/m\textsuperscript{2} have a 60- to 80-fold increased risk of developing T2D.\textsuperscript{53} The association of obesity with the development of asthma and diabetes could contribute to the increased risk of severe A(H1N1)pdm09 virus influenza infection. In summary, further studies are needed to understand whether obesity and/or one of its commonly associated comorbidities are responsible for the increased severity of influenza virus infection, and whether modifications in vaccine or therapeutic management are required in light of these newly identified comorbidities in obese populations.

**Propylaxis and treatment of A(H1N1)pdm09 virus infection in obese patients**

Obesity and increased BMI are associated with decreased antibody titer or non-response to vaccination for both hepatitis B and tetanus vaccines in children and adults.\textsuperscript{134–137} More recently, this decreased antibody response to hepatitis B has also been shown in genetically obese rodents.\textsuperscript{138} The reduction in vaccine response in obese individuals may help explain the significant increase in obese patients admitted with severe A(H1N1)pdm09 virus infection. Although further studies are needed to understand the efficacy of influenza vaccination in an increasingly obese population, a recent study demonstrated that a higher BMI was associated with a greater decline in influenza antibody titers and decreased CD8\textsuperscript{+} T-cell activation as compared with healthy weight individuals.\textsuperscript{139} These results suggest obesity may impair the ability to mount a protective immune response to influenza virus.

In terms of antiviral therapy, there have not been many studies on the efficacy of these antivirals in an obese population. Ariano \textit{et al.}\textsuperscript{140} recently showed that there are no significant differences in oseltamivir pharmacokinetics in obese and non-obese patients. Studies by our group have also shown that oseltamivir treatment protects against severe A(H1N1)pdm09 virus in obese mice.\textsuperscript{141} Overall, these results suggest that antiviral treatment could be a good option for treating A(H1N1)pdm09 virus infection in an obese population if started within the first few days of infection.

**Mechanisms for increased disease severity in obese patients**

Like pregnancy, obesity is associated with significant changes in respiratory physiology and lung function including mechanical changes, reduced lung volumes, and increased respiratory rates (reviewed in.\textsuperscript{124,142} However, we will focus our review on changes to the immune response. Obesity can be considered an immunocompromised state, and the consequences of the obesogenic state on the response to infectious diseases have been reviewed elsewhere.\textsuperscript{137} Although the exact mechanism for altered immune cell functionality in obese individuals has not yet been elucidated, several studies have shown altered immune responses in obesity models. In terms of the innate immune system, diet-induced obese (DIO) mice have reduced antiviral cytokine expression, and both genetic and DIO rodent models have decreased natural killer (NK) cell activation and cytotoxicity, reduced macrophage functionality, and decreased numbers of dendritic cells (DCs) with impaired antigen presentation.\textsuperscript{16,18,143–147} In terms of the adaptive immune response, obesity has been shown to alter numbers of circulating T-cell subsets and decrease T-cell functionality, especially CD8\textsuperscript{+} T-cell subsets, in both human and animal models.\textsuperscript{15,148–151}

One possible mechanism by which obesity could result in both an inflammatory and immunocompromised state is via the overexpression of adipokines. Obesity results from the overaccumulation of white adipose tissue (WAT) within the body. Research in the past two decades has shown that WAT is not only a storage depot for fats within the body but can also act as an endocrine organ, secreting numerous factors that affect several metabolic pathways. These adipokines participate in a wide variety of physiologic and/or physiopathologic pathways such as food intake, insulin sensitivity, and inflammation. In addition, many adipokines play an intricate role in various aspects of the innate and adaptive immune response.\textsuperscript{152–156} The secretion of adipokines is directly correlated with adipose tissue mass, and the overaccumulation of WAT in obese individuals has been hypothesized to result in a low-grade, chronic inflammatory state. Obese individuals have increased expression of interleukin (IL)-6, tumor necrosis factor-\textit{z}, and C-reactive protein (CRP).\textsuperscript{157–160}

Leptin is an adipokine linked to obesity that has been implicated in immune functionality. Leptin, a 16-kDa peptide derived mainly from adipocytes, functions primarily in the hypothalamus as an anorexigenic signal to decrease food intake and increase energy expenditure.\textsuperscript{161} Leptin mediates its effects through receptors that signal through the Jak-STAT pathway, and leptin receptors are present in
human circulating CD4+ and CD8+ T lymphocytes as well as many other cells of the immune system. In terms of influenza infection, leptin induces an acute-phase shift toward a Th1 cytokine-production profile, which is necessary for recovery from influenza infection. The few reported human patients with leptin deficiency have reduced numbers of circulating CD4 T cells and impaired T-cell proliferation and cytokine release, all of which can be reversed by recombinant human leptin administration. It is unclear whether obesity-associated ‘leptin resistance,’ which is more common than genetic leptin deficiency in adult obesity, is also associated with the same extent of changes in immune cells and cytokines. Although these studies are still in their infancy, it is apparent that the changes in circulating factors in the obese state could affect the ability to respond to influenza infection.

The obesity–pregnancy complexity

According to the US National Health and Nutrition Examination Survey (NHANES), obesity in US women increased from 25-4% in the 1988–1994 survey to 35-5% in the 2007–2008 survey. Globally, BMI for females has increased by 0.5 kg/m² per decade from 1980 and 2008; worldwide, age-standardized prevalence of obesity in women rose from 7-9% to 13-8% in the same time period. This means that an estimated 297 million women over the age of 20 years were obese in 2008. More than 30% of women in North America were obese in 2008. Similar prevalence is seen in many other parts of the world.

These trends also seem to be reflected in the prevalence of obesity before and during pregnancy. In the US, 59-5% of women of reproductive age are overweight or obese; however, there are limited data on the incidence of obesity in pregnant women. Several cohort studies have shown that increases in BMI in pregnant women are increasing. According to data from the Pregnancy Risk Assessment Monitoring System (PRAMS), pre-pregnancy obesity rates in the US increased by 70% between 1993 and 2003. Data from the PRAMS from 29 participating states show that an average of 24-1% of women had a pre-pregnancy BMI classified as obese in 2008 (http://www.cdc.gov/prams/). There appears to be very little data on temporal changes in weight gain during pregnancy; however, a study conducted by Frischknecht et al. over an 18-year period in Switzerland found that not only did pre-pregnancy obesity rates double between 1986 and 2004, but the percentage of mothers who gained 20 kg or more during pregnancy increased from 46% to 14-2%. In a Canadian study, Crane et al. found that 52-3% of women gained more weight than recommended, based on their pre-pregnancy BMI. In a study by the Institute of Medicine and National Research Council, 38% of normal-weight, 63% of overweight, and 46% of obese women gained more than the recommended amount of weight during pregnancy.

Increased BMI and excessive weight gain during pregnancy are associated with short- and long-term morbidity and mortality for both the mother and the offspring. The amount of maternal fat stores in early pregnancy usually increases to meet the feto-placental and maternal demands of gestation and lactation. An increased amount of maternal fat either before or during pregnancy can lead to a number of complications. Obesity during pregnancy can result in increased maternal mortality, increased miscarriage and fetal/neonatal death, hypertension, gestational diabetes, respiratory complications (asthma and sleep apnea), pre-eclampsia, thromboembo(lism, increased birth weight (macrosomia), and congenital abnormalities and malformations.

Negative effect of increased weight gain during pregnancy on response to influenza infection

Pregnancy and obesity are risk factors for increased severity of A(H1N1)pdm09 virus influenza infection; however, the interaction between the two comorbidities is unknown. The individual contributions to increased severity and their possible combined effects are summarized in Table 1. Pregnant or obese individuals have increased risk of community-acquired respiratory infection, increased severity of influenza infection, altered immune functionality, decreased lung functionality, and increased risk of developing other risk factors for influenza severity. Independently, obesity or pregnancy can lead to an immunocompromised state, and their combination could possibly exacerbate this state; however, the mechanism for this suppression remains unknown. The two factors polarize Th1 and Th2 responses by completely different mechanisms. Obesity leads to an inflammatory Th1 state, while pregnancy triggers a Th2 response. It is possible that the warring combination between both states could potentially dysregulate the immune system, resulting in increased immune suppression and increased severity of influenza infection.

In addition, protection against influenza infection could be altered in the obese, pregnant state. The effectiveness of a vaccine to elicit a protective response against illness or serious complications from influenza depends not only on the similarity of the virus strains in the vaccine to currently circulating in the population but also on the immunocompetence of the individual. Although influenza vaccination is protective in pregnant populations (Prophylaxis and therapeutic options for the control of A(H1N1)pdm09 virus in pregnant women), the obese state appears to reduce the ability of the body to generate protective antibodies. In addition to a possible decrease in vaccine
responses, the compounding effects of both obesity and pregnancy result in increases in potential risk factors for increased influenza severity. Obesity during pregnancy increases the possibility of developing diabetes, asthma, and hypertension, all of which could increase the risk of influenza in the obese, pregnant population. Therefore, it is likely that obesity increases the risk of influenza infection in pregnant women, resulting in an increase in the number or possibly severity of infection.

**The obese, pregnant influenza patient: long-term implications, unanswered questions, and future directions**

There are several unanswered questions regarding the interplay of obesity and pregnancy in the context of influenza infection. First, evidence suggests that obese, pregnant women may be more susceptible than their ‘normal’-weight counterparts to influenza infection and influenza-related complications. In future seasonal and pandemic influenza outbreaks, the interplay between both morbidities during influenza needs to be studied; however, this may be difficult because true evaluation requires a fully integrated epidemiologic, virologic, and hospital surveillance program to monitor the scope of influenza infection in obese, pregnant women. Second, although antiviral treatment may be efficacious in both pregnant and obese individuals, no studies have assessed the protective capacity of influenza vaccination in obese humans. Because vaccination is suggested for all pregnant women, the protective capacity of the vaccine to prevent influenza infection in obese, pregnant women should be compared with that of obese and healthy weight individuals. Finally, because a significant number of women are gaining more than the recommended weight during pregnancy, both pre-pregnancy obesity and increased weight gain during pregnancy should be considered a risk factor for influenza infection and should be addressed at different gestational periods.

**Conclusions – The obese, pregnant individual in the context of influenza and public health**

Along with the epidemic of obesity, the prevalence of obesity both before and during pregnancy is increasing at an alarming rate. Both obesity and pregnancy are associated with increased severity of influenza infection; however, the severity of influenza infection in the obese, pregnant patient is unknown. Future studies need to focus on this potentially susceptible population to understand how obesity during pregnancy can affect immune response to primary infection as well as preventative and therapeutic strategies for reducing the severity of both seasonal and pandemic influenza.

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