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CHAPTER

3

Immunobiological aspects of vaccines in pregnancy: Maternal perspective

Helen Y. Chu[a], *Arnaud Marchant*[b]

[a]Departments of Medicine and Epidemiology, University of Washington, Seattle, WA, United States, [b]Institute for Medical Immunology, Université libre de Bruxelles, Brussels, Belgium

Introduction

Pregnancy is associated with important changes in the maternal immune system that have profound consequences for the fetus and the newborn infant. Tolerance of the fetus and successful pregnancy require a highly regulated immunological environment at the materno-fetal interface [1]. Maternal immune components are transferred across the placenta and in breastmilk that provide protection against pathogens in early life and contribute to immune development. Although pregnancy cannot be considered a state of immunodeficiency, infections with some pathogens cause more severe diseases in pregnant as compared to non-pregnant women. Vaccination during pregnancy has the potential to provide protection against pathogens affecting the mother and the newborn infant [2,3]. However, the efficacy of this approach can be limited by diseases affecting maternal immune responses and transfer of maternal immune components to the offspring. Recognizing that the health of the mother during pregnancy is essential to the health of the newborn infant, maternal vaccination has a great potential to reduce morbidity and mortality in mothers and children.

Maternal Immunization
https://doi.org/10.1016/B978-0-12-814582-1.00003-6

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Susceptibility to infectious diseases in pregnancy

Infections with some pathogens, including influenza virus, varicella zoster, hepatitis E, listeria, and malaria, cause more severe diseases in pregnant as compared to non-pregnant women. The mechanisms underlying this increased susceptibility have not been fully defined. Pregnancy-induced changes in the maternal immune system may play a role. On the other hand, pregnant women also have hormonal and physiologic changes including increasing levels of estradiol and progesterone and decreased pulmonary reserve and increased cardiac output that may contribute to reduced pathogen control and more severe clinical symptoms. As discussed below, emerging evidence suggest a central role for pathogen-specific mechanisms rather than processes common to multiple pathogens (Fig. 1). Understanding these mechansims is critical for the development of interventions protecting pregnant women and their offspring.

Influenza and other respiratory viruses

Pregnant women have higher morbidity and, in some studies, mortality due to influenza infection as compared to non-pregnant adults [4]. In the 1918 pandemic, 27% mortality was observed in pregnant women [5,6].

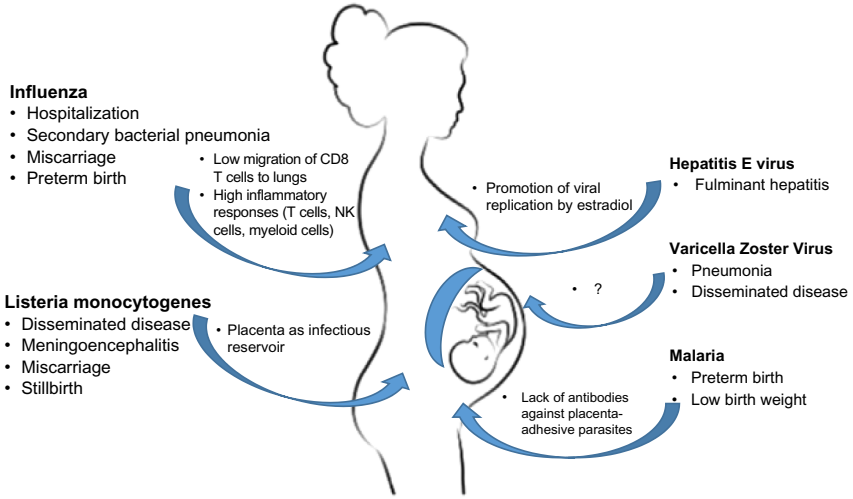

FIG. 1 Pathogens causing severe infections in pregnant women. Several pathogens cause more severe diseases in pregnant as compared to non-pregnant women. The pathogenesis underlying this increased susceptibility remains incompletely understood. Studies indicate that they involve pathogen-specific mechanisms rather than a global state of immunodeficiency *(arrows)*. Severe symptoms can compromise the survival of the mother and of the unborn fetus.

In the 2009 influenza A/H1N1 pandemic, pregnant women with influenza particularly towards the end of pregnancy in the third trimester had increased disease severity, higher rates of secondary bacterial pneumonia, and increased risk of both hospitalization and admission to the intensive care unit as compared to non-pregnant adults [7]. Higher rates of stillbirth, miscarriage, and preterm birth were additionally observed with A/H1N1 pandemic influenza infection during pregnancy [8]. Epidemiologic data do not clearly support an increased risk of acquisition of infection; rather the risk is in progression to severe disease once infected [9]. However, a recent systematic review emphasized the relatively low quality of available information on the incidence rate of severe influenza in pregnant women [10]. The mechanisms underlying severe influenza in pregnancy remain unclear and could involve both anatomic and physiologic changes increasing the risk of respiratory failure, reduced immune control and increased inflammatory responses [9]. Enhanced natural killer (NK) cell and T cell responses to influenza infection were observed in pregnant as compared to non-pregnant women, suggesting that suppression of cell-mediated immune responses is unlikely to be a major contributor to disease severity [11]. Mouse studies suggest a role for impaired migration of anti-viral CD8 T lymphocytes to the lungs [12]. Increased proinflammatory responses of monocytes and dendritic cells to *in vitro* influenza infection were observed in pregnant as compared to non-pregnant women, suggesting a role for immunopathologic responses [13]. Influenza vaccine is safe, immunogenic and efficacious in pregnancy, as has been demonstrated in several randomized clinical trials [14–17].

Few studies have evaluated the role of respiratory viruses other than influenza during pregnancy [18]. However, recently, two maternal influenza immunization trials have conducted secondary analyses of respiratory illness data during pregnancy to describe the incidence of maternal respiratory disease due to respiratory syncytial virus (RSV) during pregnancy [14,16]. In Nepal, where women with a fever and respiratory symptoms had a nasal swab collected, RSV prevalence was low at 0.2%, with an incidence of 3.9/1000 person-years overall [19]. In South Africa, RSV prevalence based on the presence of respiratory symptoms was much higher at 2%, or an incidence of 14.4–48.0 cases per 1000 person-years overall [20]. Rhinovirus, coronavirus, parainfluenza viruses 1–4, and human metapneumovirus have also recently been detected in cases of respiratory viral infections in pregnant women [21,22]. Rhinovirus is described as a cause of influenza-like illness in several studies in pregnant women, and Middle Eastern Respiratory Syndrome and Severe Acute Respiratory Syndrome coronaviruses have been shown in case reports to be associated with severe disease in pregnant women [23,24]. Other respiratory viruses were commonly detected in Nepal in women with fever and respiratory symptoms, with the most common being rhinovirus [22]. Health care-seeking

was also common, ranging from 0% to 33% depending on the viral etiology. In a region of the world with limited access to medical care, this was a notable finding. Additionally, rhinovirus and human metapneumovirus infections with fever and respiratory symptoms during pregnancy both were found to be associated with increased risk of fetal growth restriction, manifested as low birth weight or small-for-gestational-age births [21]. Overall, these studies demonstrate that respiratory viral infections during pregnancy may adversely affect maternal and fetal outcomes.

Varicella zoster virus

Pregnant women may be at increased risk of progression of varicella to pneumonitis, particularly in the third trimester, with a mortality rate of 44% [25]. However, much of these data are based on case reports [26]. To our knowledge, no prospective studies have been conducted comparing the risk of varicella pneumonitis in pregnant versus non-pregnant women. Varicella infection during pregnancy is associated with disseminated disease and with adverse outcomes in the fetus, including congenital varicella, characterized by limb hypoplasia, optic nerve atrophy, microcephaly, seizures, cutaneous lesions [27]. Varicella zoster vaccination is now routine as part of the childhood immunization series in some countries; prior to vaccination, the majority of individuals were exposed during childhood with acquisition of immunity prior to pregnancy. Treatment for varicella infection in pregnancy is with acyclovir; use of live vaccines are contraindicated during pregnancy due to potential risk of fetal transmission.

Hepatitis E

Hepatitis E is acquired via fecal-oral transmission, and is a pathogen often associated with limited access to running water and basic sanitation. In a field study of viral hepatitis in pregnant versus non-pregnant adults in the 1980s, incidence of non-A non-B hepatitis was increased in pregnant women (17.3% vs. 2.1%, respectively). In this study, fulminant hepatitis developed in 22% of pregnant women as compared to no cases of fulminant hepatitis in non-pregnant women [28]. The incidence is increased in the second and third trimester as compared to the first trimester. Mortality has been estimated at 25–30% in pregnant women [29]. The mechanisms underlying the increased susceptibility of pregnant women to hepatitis E infection and not to other hepatitis viruses is not clear. A role for estradiol promoting hepatis E virus replication has been suggested [30]. Thus far, no treatment is available other than supportive care and no vaccine is available.

Listeria monocytogenes

Listeria is a bacterial infection that is associated with consumption of raw meats or vegetables, or drinking unpasteurized milk. Risk is higher in Hispanic populations, the elderly, those with malignancy, as well as pregnant women. Pregnant women are considered a high-risk group for development of disseminated disease, commonly manifested as bacteremia or meningoencephalitis [31]. Listeria has a predilection for invasion of the placenta, and is associated with adverse pregnancy outcomes, including miscarriage and stillbirth [32,33]. In a study in Britain between 1967 and 1985, 34% cases of listeria were during pregnancy, with an association with intrauterine fetal death and neonatal infection [32]. Although the pathogenesis of severe listeriosis during pregnancy is not well understood, it may involve establishment of an infectious reservoir at the level of placenta and uncontrolled dissemination to maternal organs [34].

Malaria (*Plasmodium falciparum*)

In malaria-endemic regions, pregnant women are estimated to have three-times increased risk of severe malaria as compared to non-pregnant adults [35]. *Plasmodium falciparum* has a tropism for the placenta and increases the risk of low birth weight and preterm birth. Women who are in their first pregnancy, as well as those who are younger, are at higher risk than multigravida women. This reflects acquisition of antibodies against placenta-adhesive parasites during consecutive pregnancies [36]. Chemoprevention against malaria is recommended during the second and third trimesters in endemic areas [37]. Therapy with artemesin was thought to be toxic to fetal development. However, the use of artemisin derivatives has now been demonstrated to be safe and effective in treatment of pregnant women early in pregnancy [38]. Maternal immunity transferred across the placenta provides protection against severe malaria in infants [39].

Other pathogens transmitted from the mother to the fetus and newborn infant

Several pathogens that are often asymptomatic in pregnant women cause a serious threat to the fetus and the newborn infant. These pathogens are therefore considered as targets for immunization of children, teenagers or women of childbearing age. This approach has been successfully applied to the prevention of congenital rubella syndrome in high income countries and, increasingly, in low and middle income countries [40].

Herpes simplex virus

Primary genital herpes infection during pregnancy may be associated with fulminant hepatitis and disseminated disease, as compared to

primary herpes simplex virus (HSV) infections in non-pregnant adults, though the data for this is not conclusive [41]. The risk of neonatal herpes is substantially higher in women with primary disease with both HSV1 and HSV2 during pregnancy, rather than those who have disease reactivation during pregnancy [41]. Because many women with genital herpes are asymptomatic or have mild symptoms, diagnosis and treatment may be challenging, requiring the use of serology for evidence of preexisting antibody to HSV1 and HSV2. The target population for vaccination against herpes is likely prior to onset of sexual activity; however, currently no licensed vaccine exists. Multiple vaccine candidates have not shown efficacy in prevention of primary infection; however, multiple new vaccines are under development [42,43]. Mouse studies recently demonstrated the maternal HSV immunization confers protection against neonatal mortality and behavioral morbidity [44]. Neonatal herpes is associated with a 60% mortality rate if untreated. The route of acquisition is most commonly through exposure in the genital tract during vaginal delivery; therefore caesarean section is indicated in women with known active genital herpes at the time of delivery.

Cytomegalovirus

Women with cytomegalovirus (CMV) infection during pregnancy generally exhibit a range of disease severity similar to non-pregnant adults, ranging from asymptomatic infection to a mononucleosis-like syndrome with fevers, rash, and lymphadenophathy. Risk factors for primary CMV infection during pregnancy include exposure to infected young children excreting the virus for prolonged periods of time. Clinical manifestations of CMV infection in the fetus include sensorineural hearing loss, chorioretinitis, intrauterine growth restriction, preterm birth, hepatosplenomegaly, microcephaly, and fulminant disease [45]. Primary infection early in pregnancy is associated with a higher risk of transmission to the fetus, with estimates of 32% with primary infection as compared to 1% following recurrent infection. Recurrent infections include both reactivation of latent virus and acquisition of a new strain of CMV [46]. Similar to herpes simplex, the target of CMV vaccination would be young children or adolescents prior to pregnancy. A number of CMV vaccine candidates are currently in development [47,48], though none are licensed.

Zika virus

Zika virus is a re-emergent pathogen that has particular implications for pregnant women. Symptoms of Zika virus infection during pregnancy include maculopapular rash, arthralgia, conjunctivitis and low grade fever [49]. Like CMV and rubella, infection with zika earlier in pregnancy is associated with increased risk of congenital birth defects, including microcephaly and intrauterine growth retardation. Pregnant women are likely

to have prolonged viremia due to zika virus, as compared to non-pregnant adults, and infection during pregnancy is associated with increased risk of congenital birth defects [50]. The United States Centers for Disease Control guidelines recommend that laboratory studies for zika virus by molecular testing or serology are indicated in women with clinical suspicion of zika virus infection, with history of exposure via travel or residence in a region where mosquito-borne transmission of zika is documented, or unprotected sexual contact with a partner who has traveled to these areas [51]. Viral infection during pregnancy is thought to lead to placental infection, and transmission to fetal neuronal cells, leading to cell injury and death. The risks of congenital infection appear to be high in women with documented zika virus infection during pregnancy; in a prospective study in Brazil, 42% of infants born to women with diagnosed infection during pregnancy had abnormal clinical or brain imaging findings [52]. These occurred in 55%, 52% and 29% of pregnancies where infection occurred in the first, second or third trimester of pregnancy, respectively. No specific treatment or vaccine is currently available, with current recommendations including avoidance of travel to endemic areas, use of barrier contraception to protect against sexual transmission, and use of standard precautions to prevent mosquito bites.

Innate and adaptive immune responses in pregnancy

The fetus expresses paternal antigens and is therefore a semi-allogeneic graft for the pregnant women. Multiple redundant mechanisms have been selected to promote immunological tolerance of the fetus and to allow successful pregnancy. At the materno-fetal interface, the placenta is a highly immunoregulated environment containing large numbers of innate and adaptive immune cells, including NK cells, T lymphocytes and myeloid cells, actively suppressing fetal tissue rejection [1].

Pregnancy is also associated with significant changes in the number and function of immune cells at the systemic level. Recent analyses of immune cell responsiveness to activation signals indicate dynamic and coordinated changes from the first to the third trimester of pregnancy, suggesting an "immune clock" regulating immune functions in pregnant women [53]. Relevant to antibody responses to vaccination are B cells, follicular helper T cells and antigen-presenting cells. Studies have examined the influence of pregnancy on B cells and antigen-presenting cells but its impact on follicular helper T cells remains to be assessed. Most studies showed that pregnancy is associated with decreased B cell numbers in peripheral blood [54–59]. Studies in mice indicated that estrogens produced during pregnancy reduce B cell lymphopoiesis [60]. Studies of the influence of hormones on B cell functions indicate that pregnancy may impact the production of

immunoglobulins. Estrogen increases the production of immunoglobulin G (IgG) by human B cells and prolactin decreases the threshold of B cell activation [61,62]. However, total serum IgG levels are lower in pregnant than in non-pregnant women in both low and high income country settings, a phenomenon that probably involves hemodilution [63,64]. On the other hand, populations living in low income countries, including pregnant women, commonly have elevated serum levels of IgG, probably as a result of high and chronic exposure to microbial antigens, such as malaria [63,65,66]. A recent study indicated that estrogen stimulates the production of natural antibodies against bacterial oligosaccharides [67]. These antibodies were transferred from the mother to the offspring and protected mice against entheropathogenic *Escherichia coli* infection. Together, these studies indicate that sex hormones and pregnancy modulate the number of B lymphocytes and their production of immunoglobulins.

Significant changes in the quality of IgG are also observed during pregnancy. IgG are glycoproteins carrying N-glycans at both the Fc and Fab segments [68,69]. The composition of the N-glycans influences the three-dimensional structure of the Fc segment of IgG and the interaction of IgG with Fcγ receptors and complement. In total, 36 glycovariants can be attached to the Fc segment of IgG. In combination with the four IgG subclasses, this diversity offers the potential to fine tune IgG effector functions [69]. Pregnancy is associated with increased galactosylation and sialylation and with decreased fucosylation of total IgG Fc [70]. These changes have the potential to modulate the capacity of IgG to activate NK cells and complement and to reduce their inflammatory properties [71,72]. The clinical relevance of these modifications is supported by the association of IgG galactosylation and remission of rheumatoid arthritis in pregnant women [73]. Mouse studies suggest that estrogen upregulates the expression of the activation-induced deaminase, the enzyme that initiates class switch recombination and somatic hypermutation of immunoglobulins [74]. The impact of estrogen and pregnancy on the subclass and the avidity of antigen-specific IgG remains poorly characterized.

Changes in antigen-presenting cells are also observed in pregnant women. The absolute number of myeloid dendritic cells (mDC) was shown to increase in the first trimester and decrease as pregnancy progressed to reach similar counts in the third trimester as in non-pregnant women [75,76]. In contrast, the numbers of plasmacytoid (p)DCs were shown to be reduced during the third trimester of pregnancy, resulting in a higher mDC: pDC ratio [75,77,78]. Pregnancy is also associated with changes in Toll-like receptor (TLR) expression by circulating DC subsets. Increased expression of TLR-1 by mDC and of TLR-7 and TLR-9 by pDC was detected [79]. The role of these changes in the modulation of immune responses during pregnancy have not yet been explored.

Potentially relevant to the modulation of immune responses during pregnancy are the changes in the composition of the maternal microbiome. The composition and the diversity of the microbiome is influenced by pregnancy at several body sites, including the oral cavity, the gut and the genital tract [80]. Mouse studies suggest that changes in the gut microbiome may promote inflammatory responses and participate in the physiological changes in metabolism associated with pregnancy [81].

Effect of pregnancy on vaccine responses

The impact of pregnancy and sex hormones on B cells, antigen-presenting cells and microbiome suggests a possible influence on the magnitude and quality of antibody responses to vaccines. This notion is supported by the observation that the magnitude of antibody responses to vaccines is often higher in women than in men [82]. Overall, vaccines are immunogenic in pregnant women [2,3]. However, relatively few controlled studies have compared vaccine responses in pregnant and non-pregnant women. Available data come from studies of influenza or pertussis immunization and are not consistent across studies. Four studies described similar antibody responses to seasonal influenza vaccines in pregnant and non-pregnant women [83–86]. On the other hand, other studies reported lower responses in pregnant women following immunization with seasonal and pandemic influenza vaccines [87–89]. Whether the gestational stage of pregnancy affects responses to vaccines is uncertain. Similar antibody responses to seasonal and pandemic influenza vaccination were observed throughout pregnancy in two studies whereas a recent study reported a decline in the antibody response to seasonal influenza immunization and a relative increase in the proportion of the IgG4 subclass [84,89,90]. Fewer studies have examined the impact of pregnancy on the antibody response to pertussis immunization. Two studies reported similar antibody responses to pertussis immunization in pregnant and non-pregnant women [91,92]. However, one of the two studies reported lower T cell responses to pertussis antigens in pregnant as compared to non-pregnant women [92]. A recent study involving a larger sample size observed lower antibody responses to pertussis toxin and filamentous hemagglutinin in pregnant as compared to non-pregnant women [93]. Factors responsible for the discordant results obtained in different studies are unclear but are possibly attributable to the relatively small size of the population included in most studies and to differences in tested vaccines and in participant characteristics, including pre-vaccination antibody titers that are an important determinant of vaccine responses [94]. The persistence of antibodies following maternal immunization will influence the optimal timing of immunization and the requirement to repeat immunization during consecutive

pregnancies. Pertussis antibodies decay rapidly supporting the need to immunize during each pregnancy, as is recommended in an increasing number of high income countries [95,96]. Antibody decay following immunization with adjuvanted pandemic influenza vaccine was similar in pregnant and non-pregnant women [88]. The impact of pregnancy on the quality of the antibody response to vaccines remains largely uncharacterized. A study showed that the avidity of cord blood antibodies is higher following pertussis immunization at 27–30 weeks as compared to after 31 weeks of gestation, a difference that is likely related to the time needed to increase antibody avidity following booster immunization rather than to an impact of gestational stage [97]. The impact of pregnancy on the glycosylation profile and on the functional properties of vaccine-induced antibodies remains to be investigated.

The evidence that pregnancy induces changes in circulating antigen-presenting cells and in the composition of the microbiome suggests that innate immune responses and inflammatory reactions to vaccines may also be influenced. In one study, pregnant women given seasonal influenza vaccine had increased plasma levels of inflammatory cytokines during the first days after vaccination but these responses were similar to those in non-pregnant women [85]. In a recent study, pregnant women were more likely to report moderate and severe pain at the injection site following pertussis immunization as compared to non-pregnant women but the occurrence of other local and systemic reactions following vaccination was similar in both groups [93].

With the exception of maternal human immunodeficiency virus (HIV) infection, the impact of maternal diseases on responses to vaccination remains largely uncharacterized. In South Africa, maternal HIV infection was associated with lower seroconversion rates after seasonal influenza vaccination but vaccine efficacy was comparable to that observed in HIV-uninfected pregnant women [16]. HIV infection was also associated with lower immunogenicity of a candidate glycoconjugate Group B streptococcus vaccine in pregnant women [98]. Immunogenicity of pandemic A/H1N1 influenza vaccination in HIV-infected pregnant women correlated positively with pre-vaccination immunity and negatively with HIV replication [99]. Hypergammaglobulinemia is commonly observed in pregnant women living in low income countries but its impact on antibody responses to vaccines has not been characterized.

Transfer of maternal antibodies to the newborn infant

Transfer of maternal antibodies to the fetus and newborn infant across the placenta and breastmilk provides protection against infectious pathogens to which the mother has been exposed. In addition, recent studies indicate that

maternal antibodies also contribute to infant gut homeostasis by shielding commensal bacteria, impacting the development of the gut immune system and to the prevention of allergic responses in early life [100–102].

Of the immunoglobulins in the maternal circulation, only IgG is transferred transplacentally [68,103]. Studies suggest that maternal IgE could be transported complexed with IgG [104]. Transfer of antibodies is an active process beginning at the end of the first trimester of pregnancy. By the end of the second trimester, transplacental antibody ratios are about 50% and are greater than 100% at birth in full-term newborns [105,106]. As a result, infants born prematurely have lower levels of maternal antibodies, increasing risk for vaccine-preventable diseases [107]. IgG subclass is an important determinant of transfer across the placenta. Antibody transfer ratio is highest for IgG1 and lowest for IgG2 [68,103,106]. Transfer of IgG is also influenced by their antigen specificity [107]. Transfer of polysaccharide antigen-specific IgG is lower than protein antigen-specific IgG, a difference that is likely related to the lower transfer of IgG2. However, there is considerable variation in transfer ratios among protein antigen-specific and polysaccharide antigen-specific antibodies, suggesting that other factors than IgG subclass may play a role. Among them, IgG glycosylation could be involved. Indeed, IgG of different antigen-specificities have different glycosylation profiles and some studies suggest selective transfer of IgG expressing specific glycovariants [108,109].

Transport of maternal IgG to the fetus involves crossing several placental layers, including syncytiotrophoblasts, the fetal endothelium and the stroma that separates the two cell layers [103,106]. The neonatal Fc receptor (FcRn) is the main receptor transporting maternal IgG across syncytiotrophoblasts. Following endocytosis from the maternal circulation, the Fc segment of IgG binds the FcRn at acidic pH. The endosome is then transported to the basal surface of the syncytiotrophoblast where IgG dissociate from the FcRn at physiologic pH. As the FcRn is not expressed by fetal endothelial cells, other receptors have to participate in the transport of IgG to the fetal circulation. Studies suggest that the FcγRIIb2 expressed by fetal endothelial cells could be involved but its role in maternal antibody transfer is still debated [110,111]. A better understanding of the molecular and cellular basis of maternal antibody transfer across the placenta would help designing vaccines inducing antibodies with optimal transferability to the fetus.

Timing of maternal immunization

For maternal vaccine delivery, the decision of when to vaccinate during pregnancy needs to consider several variables, including limited antenatal care for many women in developing countries leading to a need for

an increased vaccination window, the need to protect preterm infants who would not benefit from vaccination late in pregnancy, and the optimal timing for antibody affinity maturation and transplacental transfer. In the United States, current recommendations are to administer pertussis-containing vaccines during pregnancy from 27 to 36 weeks gestation, which then requires about 2 weeks to have a serologic response, followed by transplacental antibody transfer [112]. This recommendation leads to an at-risk group of infants who are born earlier than 30 weeks gestation, who are also at highest risk for severe disease due to pertussis. It also potentially limits protection of infants born closer to term when maternal immunization is performed shortly before delivery. A recent prospective observational study examined concentrations of anti-pertussis toxin and anti-filamentous hemagglutinin IgG in newborns of women who received second versus third trimester vaccination [113]. Overall, higher concentrations of cord blood antibodies to both pertussis toxin and filamentous hemagglutinin were detected following second trimester versus third trimester vaccination. Although maternal vaccine responses were not measured, the data were interpreted as the consequence of the longer duration of antibody transfer following vaccination during the second trimester of pregnancy. Immunization against pertussis is recommended from the second trimester of pregnancy in several countries, including the United Kingdom and Belgium, but currently not in the United States [112,114].

For influenza vaccination in pregnancy, the recommendation in industrialized countries is to vaccinate any time during pregnancy during influenza season. There are many countries where influenza circulates many months during the year, including subtropical Asia and sub-Saharan Africa. In these settings, influenza vaccination may be considered as a year-round vaccination strategy and has been shown to be efficacious in a randomized clinical trial of maternal influenza vaccination in Nepal [14]. In this study, women were additionally randomized to second or third trimester vaccination to evaluate the effect on infant influenza vaccine efficacy [115]. The results from this study showed that there was no significant difference in influenza vaccine efficacy by second or third trimester vaccination, and there was a nonsignificant trend towards improved birth weight with earlier vaccination. Cord blood anti-hemagluttination inhibition titers against A/H3N2, A/H1N1 and B antigens was not different between the two groups, though the numbers of samples tested were small. Therefore, available data regarding pertussis and influenza vaccine timing in pregnancy suggest that earlier vaccination is not associated with decreased efficacy against disease in mothers and infants. As vaccination from the second trimester of pregnancy offers the advantage to protect preterm infants and to increase the potential window for vaccination in settings where it may be challenging to access pregnant women, further studies should be conducted to consolidate these observations in different populations. Limited information is available

regarding the impact of timing of vaccination during pregnancy for other vaccines. The principle that optimal transfer of maternal antibodies requires sufficient time between maternal immunization and delivery is likely to apply. In a study of *Haemophilus influenzae* type B conjugate vaccine, transmission of antibodies was greatest in mothers vaccinated more than 4 weeks before delivery [116].

Impact of chronic maternal infections on antibody transfer

Chronic maternal infections, such as HIV and malaria, reduce the transfer of maternal IgG [117–120]. Studies conducted across different populations reported an association between reduced transfer of maternal IgG and placental malaria [117,121–124]. Trophozoites cause direct invasion of the placenta and could thereby alter IgG transfer. However, a recent study in Papua New Guinea indicated that this decreased transfer may not be directly related to placental malaria but rather due to hypergammaglobulinemia [125]. Hypergammaglobulinemia results from chronic inflammation and polyclonal B cell activation. It is generally considered that hypergammaglobulinemia impairs maternal antibody transfer by saturating the FcRn [106]. However, studies reported a variable impact of maternal hypergammaglobulinemia on transplacental transfer according to IgG subclass and antigen-specificity, suggesting that other factors involving placental receptors and cells or biophysical characteristics of IgG may be involved [117,121]. Little is know regarding the impact of hypergammaglobulinemia on transfer of IgG induced by vaccination during pregnancy.

Studies from low and high income countries reported decreased transfer of maternal IgG in children born to HIV-infected mothers across multiple vaccine and pathogen-specific antigens [119,126,127]. This is particularly significant given the increased infectious morbidity and mortality observed in HIV-exposed uninfected as compared to HIV-unexposed infants [120,128]. This notion is supported by a recent study conducted in Belgium, showing an association between reduced transfer of maternal antibodies, as well as immune activation in the newborn, and risk of hospitalization for infection during the first months of life in HIV-exposed uninfected infants [127]. Few studies have examined the impact of maternal HIV infection on the transfer of antibodies induced by vaccination during pregnancy. Following pandemic A/H1N1 influenza vaccination of HIV-infected pregnant women, cord blood antibody levels were higher than maternal antibody levels in some studies and lower in others [129]. This variability could be related to differences in the activity of maternal HIV infection across studies. Indeed, higher transfer ratios of maternal antibodies were observed in mothers who initiated anti-retroviral therapy before as

compared to during pregnancy [127]. Immunization of HIV-infected pregnant women is an important strategy to protect their vulnerable newborn infants but its efficacy can be limited by reduced vaccine immunogenicity and reduced transfer of maternal antibodies. The impact of HIV infection on the quality of maternal antibodies has not been explored. A better understanding of the impact of HIV in maternal immunity and its transfer to the newborn should help the design of optimal vaccination strategies.

Maternal antibody transfer through breastmilk

Breastfeeding is associated with improvement in a multitude of infant outcomes, particularly in low and middle income countries [130]. Exclusive breastfeeding is recommended by multiple professional groups for the first 6 months of life. Specifically, in relation to infectious risk, breastmilk decreases risk of sepsis and necrotizing enterocolitis in preterm infants, and is associated with decreased risk of respiratory viral infections, acute otitis media, and gastroenteritis [131]. Breastmilk contains secretory IgA and IgG. Other components of breastmilk include lactoferrin, lysozyme, white blood cells (predominantly neutrophils and macrophages), hormones, growth factors, and cytokines which could contribute to antiviral and antibacterial properties [3]. The synthesis of IgA is via plasma cells in the enteromammary and bronchomammary immune system. After exposure to antigens, maternal plasma cells synthesize secretory IgA antibody in the mammary gland and secrete this into milk. The polymeric Ig receptor (pIgR) transports secretory IgA and IgM into breastmilk [132]. Secretory IgA represents the major immunoglobulin in breastmilk, followed by secretory IgM and then IgG. In humans, ingested breastmilk antibodies do not enter the neonatal circulation, but secretory antibodies may prevent microbial colonization and invasion by coating mucosal surfaces [100]. Studies have shown that secretory IgA in colostrum can prevent HIV transcytosis across epithelium by direct neutralization [133]. Breastmilk IgG has also been shown to protect against HIV infection through antibody-dependent cytotoxicity [134]. A correlation between breastmilk IgG against respiratory syncytial virus with protection against acute respiratory infection has recently been reported [135]. Although the role of breastmilk antibodies in protection against disease is not well-studied, pathogen-specific IgA and IgG are induced in breastmilk by maternal immunization and could contribute to protection [3,136,137].

Conclusion

Immunization during pregnancy is an efficient strategy to protect both the mother and the newborn infant against infectious pathogens. As the

momentum for maternal immunization is growing, we have an opportunity to gain fundamental insights in the determinants of maternal immunity against pathogens and of its transfer to the newborn infant. Pregnancy is associated with many dynamic changes in maternal immune cells and molecules that are critical for tolerance of the fetus. These changes could have also been selected to modulate maternal immune components that are transferred to the newborn infant and thereby provide optimal protection against infectious pathogens after birth. Pregnancy modifies the glycosylation profile of maternal IgG and could also influence the production of individual IgG subclasses. Transfer of maternal IgG through the placenta, and potentially through breastmilk, could select antibodies with optimal biophysical and functional profiles. Unraveling these fundamental processes and identifying determinants of the magnitude and quality of vaccine responses in pregnant women offer the potential to optimize maternal immunization strategies. Most of the burden of infectious diseases affecting young infants is in low income countries where prevalence of maternal diseases, including chronic infections, is also highest. A more systematic evaluation and a better understanding of the impact of maternal diseases on vaccine-induced immunity and its transfer to the newborn are required to achieve the broadest impact of maternal immunization worldwide.

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