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Immunization of pregnant women: Future of early infant protection

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Children in early infancy do not mount effective antibody responses to many vaccines against commons infectious pathogens, which results in a window of increased susceptibility or severity infections. In addition, vaccine-preventable infections are among the leading causes of morbidity in pregnant women. Immunization during pregnancy can generate maternal immune protection as well as elicit the production and transfer of antibodies cross the placenta and via breastfeeding to provide early infant protection. Several successful vaccines are now recommended to all pregnant women worldwide. However, significant gaps exist in our understanding of the efficacy and safety of other vaccines and in women with conditions associated with increased susceptible to high-risk pregnancies. Public acceptance of maternal immunization remained to be improved. Broader success of maternal immunization will rely on the integration of advances in basic science in vaccine design and evaluation and carefully planned clinical trials that are inclusive to pregnant women.

Introduction

Infectious diseases remain a major cause of morbidity and mortality in children between the ages of 0 to 4 y More than 5 million child-related deaths occur worldwide from vaccine-preventable diseases.[1] Vaccination can avert the occurrence of severe infections and alleviate their devastating consequences. However, newborn infants do not efficiently develop protective immunity in response to many vaccines.[2] Scheduled vaccination against common infections, such Hepatitis B, pertussis and Haemophilus influenzae, usually commences at a few months to several years after birth,[3] leaving a critical window of vulnerability. For this reason, immunization of pregnant women has emerged as an alternative strategy to combat neonatal infection. It relies on the transfer of maternal vaccine-induced humoral immunity to the fetus during gestation and breastfeeding to confer early immune protection until routine vaccination of the child is initiated. In addition, maternal immunization also generates immune protection to the pregnant mother, who are at increased risk of a variety of infections due to the unique immune alternations that occur during pregnancy.[4-6] Several successful maternal vaccines, such as Tetanus-Diphtheria-Pertussis (Tdap) vaccine and inactivated influenza vaccine (IIV), are now universally recommended by the Center for Disease Control and prevention (CDC) to all pregnant women.[7] However, significant gaps exist in our knowledge of the efficacy and safety of many other vaccines with existing or novel formulations. This review surveys the current profile of maternal vaccine recommendations from the World Health Organization (WHO) and the CDC, vaccine use, and discusses the scientific and clinical advances and challenges in understanding the benefits and risks of maternal vaccination, with the goal of shedding light on the direction of developing safer and more efficient maternal vaccines to combat a broader range of infections.

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Literature Search Strategy

We synthesized an outline of the review based on current recommendations and concerns of maternal vaccination. Following the outline a systematic literature search was performed (up to February 2015) in PUBMED using keywords and terms: "maternal vaccination" and "vaccine antibody production," "vaccine safety" and "neonatal Fc receptor;" which were relevant to each section of our search outline. The search was performed without limitations to species and diseases. Articles were cited based on relevance and quality as interpreted by all authors. Moreover, relevant abstracts from recent meetings were also included. Based on the reviewed information and recent progress in vaccinology and reproductive immunology, we formulated a perspective on future directions for maternal vaccination.

Current Recommendation and Optimal Schedule

The World Health Organization (WHO) and the Advisory Committee on Immunization Practices (ACIP) at the CDC

consider maternal immunization a high priority. **Table 1** shows the present guidelines in the United States for immunization of pregnant women are issued from the ACIP. Since there is no evidence of adverse pregnancy outcomes when given inactive vaccines (viral, bacterial and toxoid), both organizations recommend vaccinating during pregnancy especially when there is explicit risk to exposure.[8] Maternal vaccination aims protect the both the mother and neonate. As of 2013, 2 vaccines for pertussis and influenza are recommended by the ACIP and WHO to be administered to all women of reproductive age before, during or after pregnancy.

Children under the age of 6 months, and pregnant women are at the greatest risk for hospitalization and death due to pertussis and influenza.[9,10] In the United States (US), the earliest recommended immunization series for pertussis is 2 months of age, which is depended on passive maternal antibody exchange. At the time of birth, pregnant women have relatively low concentration of maternal pertussis antibodies.[11-13] Expectant mothers can be vaccinated for pertussis preferably between 27 and 36 weeks of gestation in the US,[14] between 28 and 32 (up to 38) weeks in the United Kingdom (UK),[15] and between 28 and 38 weeks in New Zealand.[16] In the UK and New Zealand, the vaccination is funded by governmental initiatives. In Australia, third trimester Dtap vaccination is also recommended for women during each pregnancy,[17] although the vaccine is currently not funded under the Australian National Immunization Program, but is free under some state and territory initiatives. Vaccination resulted in high concentrations of pertussis antibodies for the first 2 months of life which did not alter infant response to routine recommended vaccinations.[10,18] Pertussis vaccination reports show no negative consequences to neonate regardless of maternal vaccination schedule and benefits the fetus fold2- through passive immunity and cocooning where the neonate is protected through contact immunization.[10,19] However, a major concern about maternal pertussis vaccination is blunting of the infants response to their routine vaccinations.

Unlike pertussis, there is considerable evidence that pregnant women are at increased risk for more serve illness, miscarriages, premature and stillborn births associated with influenza infection.[9] Due to the maternal exposure to influenza, WHO recommends that pregnant women should have the highest priority, since children under the age of 6 months are not eligible to receive influenza vaccines.[1] ACIP recommends influenza vaccination as early as the first trimester, when other risk factors, such as chronic disease, can complicate over the course of the flu.[20] Reports have shown that prenatal vaccinations reduce the incidence of hospitalization up to 48% in children for 12 months in the US and upwards of 63% have been reported in Bangladesh.[21,22] Moreover, several other inactivated vaccines, including Hepatitis A and B and meningococcal, are recommended for

Table 1. Current recommendations of maternal immunization by the Center of Disease Control in the United States

Vaccine	Type / Form	Before pregnancy	During pregnancy	After pregnancy
Hepatitis A	Inactivated	Yes, if indicated	Yes, if indicated	Yes, if indicated
Hepatitis B	Inactivated	Yes, if indicated	Yes, if indicated	Yes, if indicated
HPV	Inactivated	No (under study)	No (under study)	Yes, if indicated (to 26 y of age)
Influenza	Inactivated	Yes	Yes	Yes
	Live attenuated	Yes, if under 50 and healthy; avoid conception for 4 weeks	No	Yes, if under 50 and healthy; avoid conception for 4 weeks
MMR	Live attenuated	Yes, if indicated; avoid conception for 4 weeks	No	Yes, if indicated. To be given immediately postpartum if susceptible to rubella
Meningococcal	Polysaccharide	Yes, if indicated	Yes, if indicated	Yes, if indicated
	Conjugate	Yes, if indicated	Yes, if indicated	Yes, if indicated
Tdap	Toxoid Inactivated	Yes, if indicated	Yes, vaccinate during each pregnancy between 27–36 weeks of gestation	Yes, immediately postpartum if not given previously
Tetanus/Diphtheria	Toxoid	Yes, if indicated	Yes, if indicated (Tdap preferred)	Yes, if indicated
Varicella	Live attenuated	Yes, if indicated; avoid conception for 4 weeks	No	Yes, give immediately postpartum if susceptible
Anthrax	Subunit	Yes, if indicated	No, unless risk of exposure is significant	No, unless risk of exposure is significant
BCG	Liveattenuated	Yes, if indicated	No	No
Japanese Encephalitis	Inactivated	Yes, if indicated	Insufficient data for recommendation	Insufficient data for recommendation
MPSV4	Polysaccharide	Yes	No, unless risk of exposure is significant	No, unless risk of exposure is significant
Rabies	Inactivated	Yes, if indicated	No, unless post-exposure	No, unless post-exposure
Typhoid	Liveattenuated	Yes, if indicated	Insufficient data for recommendation	Insufficient data for recommendation
Smallpox	Liveattenuated	Yes, if indicated	No, unless post-exposure	No, unless post-exposure
Yellow Fever	Liveattenuated	Yes, if indicated	No, unless risk of exposure is significant	No, unless risk of exposure is significant

women before, during or after pregnancy when risk factors exist.[7] Therefore, more case-by-case studies are needed that use inactivated vaccines with novel adjuvants to assess potential risks.[23]

Live attenuated vaccines are generally not recommended for use in pregnancy due to the potential risk of introducing to the developing fetus a live pathogen that could acquire secondary mutations causing the reversion to virulence, and the concern over attenuated pathogens causing severe complications in immunocompromised pregnant women. In general, there is a lack of widely conclusive safety studies. Certain live attenuated vaccines, such as Measles-Mumps-Rubella, Yellow Fever and Pneumococcus, are only administered if there is a high risk of exposure to disease in which the mother or child could be in danger (**Table 2**).

Global profile of vaccine usage in the obstetric population

Successful implementation of maternal immunization primarily relies upon the ability of medical professionals to actively educate and implement immunization services to the general public. Even with encouraging data from post licensure studies of the safety of maternal influenza and Tdap vaccines, there are still uncertainties among the public in the understanding of maternal immunologic protection and traditional immunization schedule. For example, in Europe, only 62% of the countries recommend a seasonal influenza vaccine to pregnant woman; moreover, among these countries, only a third recommend influenza vaccination for all pregnant women.[24] While in the United States, maternal influenza vaccination rate has been estimated to be around only 50%.[25] Currently there is little information available regarding the rate of Tdap and other vaccinations. To increase the number of pregnant women getting vaccinated, care providers play an important role in promoting vaccine acceptance. Women have reported their doctors as being their most trusted source for information. Therefore, a major barrier in vaccinating pregnant women is the lack of provider recommendation. Additional issues include that obstetric care providers are not set up to routinely administer vaccines as part of antenatal care provision in all models of care, and that not all recommended maternal vaccines are provided free in all countries, which further hampers acceptance, especially by low-income populations. Given the increased risk of vaccine-preventable diseases during pregnancy, an avant-garde means is needed to increase vaccine coverage. For example, the uses of modern technologies, such as "educational text messages," is an innovative systematic strategy to prompt women to communicate with their providers.[26] Likewise, healthcare professionals should assume responsibility for keeping themselves abreast of the scientific knowledge on the protective efficacy and possible adverse effect in the short- and long-term health status of various pregnant and pediatric populations as it pertains to maternal vaccinations.[27]

Table 2. Summary based on CDC and WHO of the potential risk of vaccine-preventable diseases on pregnancy

Vaccine	Disease	Diseases in pregnant women	Risk of disease to fetus	Disease in young infants
Non-adjuvant vaccines	Influenza	In severe cases, hospitalization and death during the 2nd and 3rd trimester	Possible increased abortion rate due to complication related to severity of the disease in the mother	Increased rate of hospitalization in children < 6 months of age
Adjuvant vaccines				
MMR	Rubella	Not altered by pregnancy	Miscarriage and congenital rubella syndrome (CRS)	
	Measles	More severe disease	Increased miscarriage rates and premature birth	Possible severe disease in newborns, higher risk of Subacute sclerosing panencephalitis (SSPE) in children < 2 y of age
	Mumps	Not altered by pregnancy	Increased miscarriage rate in the 1st trimester and fetal death	
Polysaccharide vaccine	Meningococcal	Significant morbidity and mortality; unaltered by pregnancy	Unknown	Infant may develop significant morbidity and mortality
Conjugated vaccine				
Tdap	Pertussis	Unaltered by pregnancy	Unknown	Young infants at higher risk for severe disease and complication
Tetanus toxoid vaccines	Tetanus/Diphtheria	High morbidity and mortality; unaltered by pregnancy	Unknown	Neonatal tetanus with high mortality (60%)
Vaccinia "live-attenuated"	Smallpox	Possible fatality in severe cases	Possible miscarriage or premature birth	Contraindicated for infants less than 1 y of age
Yellow Fever[a] "live-attenuated"	Yellow Fever	Significant morbidity and mortality; unaltered by pregnancy	Unknown	Unknown

[a]Vaccination given to pregnant women during epidemics and when traveling to endemic areas cannot be avoided.

Transfer of Maternal Immunity via Placenta and Breastfeeding

Underpinning the idea of maternal immunization is that the transport of vaccine-induced maternal immunoglobulin G (IgG) antibody across the placenta by neonatal Fc receptor (FcRn) expressed on trophoblasts across,[28-30] confers fetal and early infant immune protection (**Fig. 1A**). The amount of IgG transferred across the placenta to the fetus correlates with IgG concentration in the maternal circulation, gestational age, maternal health and IgG subclass, with IgG_1 and IgG_4 preferentially transported over IgG_3 and IgG_2.[31] Therefore, vaccines that contain protein antigens, such as Tdap, that elicit predominant production of IgG_1 and IgG_3 are generally more efficient than polysaccharide vaccines that mainly elicit the production of IgG_2.[32,33] IgG transfer from the mother to the fetus can occur as early as gestational week 13, with the largest amount transferred during the third trimester of pregnancy (**Fig. 1B**).[34,35] Additional passive immunity in the form of vaccine-induced IgA, IgG and IgM secreted into colostrum and breast milk is transferred during breastfeeding.

Benefits of Immunizing Pregnant Women

Maternal immunization presents unique benefits to the mother, fetus and the newborn by inducing active immunity in the mother and the transfer of passive humoral immunity across the placenta to the fetus. The fetus is susceptible to infections during pregnancy, perhaps due to the immaturity of the fetal immune system,[36] and its tendency to mount tolerogenic responses.[37-40] Newborn infants mount sub-optimal immune responses to many viral, bacterial and fungal pathogens, rendering them prone to more severe or prolonged infections than adults.[37,41] The heightened neonatal susceptibility was attributed to a less intact mucosal barrier, a lack of existing immunological memory, the immaturity of the neonatal immune system and its propensity to mount tolerogenic responses.[39,42] Despite recent efforts in breaking neonatal tolerance to induce efficient vaccine response in infants,[43-54] fetal and neonatal tolerance may have important physiological functions by promoting fetal-maternal tolerance, avoiding harmful fetal inflammation during development and suppressing detrimental inflammation during mucosal colonization after birth.[55-58] In England, Amirthalingham et. al (2014) sought to determine the effectiveness of the pertussis vaccination program for pregnant women and infants between January 2008 and September 2014. By comparing vaccine status of mothers in confirmed cases with estimated of vaccine coverage for the national population of pregnant women, they noticed greater than 90% vaccine effectiveness based on national vaccine coverage and confirmed infant cases. They concluded that the vaccines effectiveness is due to both passive antibody transport and reduction of maternal exposure. Therefore, immunizing pregnant women can circumvent the multiple disadvantages of attempting to directly immunize neonates immediately after birth.

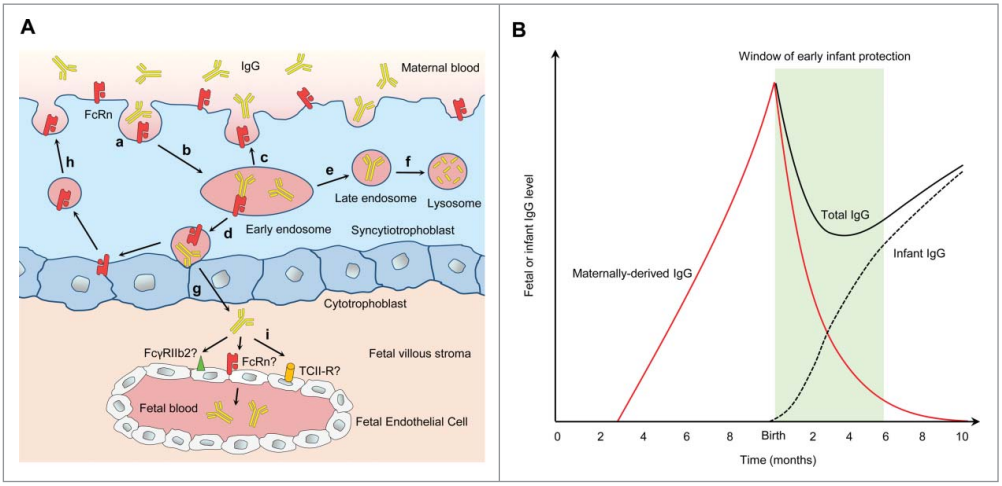

Figure 1. Transport of maternal IgG via the placenta to the fetus and its function in early infant immune protection. (**A**) Villous syncytiotrophoblasts are in direct contact with the maternal blood and express FcRn. Syncytiotrophoblasts internalize maternal IgG (**a**) into early endosomes, where the acidic pH induces IgG to bind FcRn with high affinity (**b**). IgG-FcRn complexes can either be recycled back to the maternal blood, where IgG dissociates (**c**) or undergo transcytosis to the fetal side of the syncytiotrophoblast surface (**d**). Unbound IgG in early endosomes can be recycled back to the maternal blood (**c**) or targeted to late endosomes (**e**) and subsequently lysosomes for degradation (**f**). Transcytosed IgG is released from FcRn under neutral pH (**g**) and enters the fetal villous stroma. FcRn on the fetal side of syncytiotrophoblasts can be retrieved back to the maternal side for additional rounds of IgG transport (**h**). FcγRIIb2, FcRn, or possibly transcobalamin II receptor (TCII-R) expressed on the fetal endothelium may mediate the transport of IgG into fetal circulation, but the exact mechanism and the relative contribution of these pathways remain unknown (**i**). (**B**) The placental transfer of maternal IgG to the fetus is detectable as early as gestational week 13[35] With increased placental FcRn expression, IgG transport steadily increases as the pregnancy progresses, with the largest amount transferred during the third trimester. Although maternal IgG wanes after birth, it provides the infant with immune protection during a critical window after birth (green) before the infant produces significant amount of antibodies upon vaccination.

Another important, albeit less obvious, benefit of maternal vaccination may involve the function of maternal antibodies in promoting the immune maturation and modulation in infants. Animal studies found that maternally derived antibodies have a profound and long-lasting effect in promoting the development of infant B cells and their antibody diversification and production, as well as the selection against potentially autoreactive B cell populations.[59-61] Maternal antibodies acquired from milk during breastfeeding can provide mucosal protection by neutralizing pathogenic virulence factors in the intestinal lumen and inhibiting the adhesion and invasion of pathogens.[62,63] They may further facilitate

mucosal antigen sampling and the development of immune tolerance for commensal microbes and food antigens during the critical window shortly after birth. In this case, maternal antibodies may contribute to the association of breastfeeding with reduced childhood disorders, such as allergic diseases.[64]

Risks of Immunizing Pregnant Women

Concern over pregnancy outcome and infant health

In the past, researchers have been reluctant to include pregnant women in clinical studies because of the potential harm to the fetus. Though this is amicable, their exclusion has limited the growth of knowledge about vaccine safety and efficacy for pregnant women and the fetus.[65] As mentioned before, major risks of immunizing pregnant women include the possibility of introducing to the developing fetus a live pathogen, which could acquire secondary mutations leading to a reversion to virulence. Live attenuated vaccines may also cause potentially severe complications in immunocompromised pregnant subjects. Therefore, they are generally contraindicated in pregnant women. As recommended by the CDC and WHO, in case of a live viral vaccine, such as MMR and varicella, being inadvertently administered to a pregnant woman, or should a woman becomes pregnant within 4 weeks after vaccination, she should be counseled about the theoretical concern for the fetus, although inadvertent administration of these vaccines should not be considered a reason to terminate pregnancy.[66] There is no evidence showing an increased risk of vaccinating pregnant women with inactivated vaccines or toxoids. Therefore, their benefit outweighs the potential risk if the vaccine-preventable infection poses a significant risk to the pregnant woman, the fetus and baby.

Vaccinations for pertussis and influenza represent good and successful paradigms of maintaining the high safety standard of maternal vaccines, which the safety research of other maternal vaccines can follow. Until recently, both vaccines were extensively tested in non-pregnant populations before being licensed for use in pregnant women.[67] Secondly, large scale post-licensure surveillance on pregnancy outcome and infant health are being carried out following their recommended use in pregnant women by ACIP and WHO. Post-licensure monitoring is necessary, as pre-licensure trials may not have detected rare events or adequately represented special populations. Major challenges (i.e. voluntary follow-ups and retrospective analysis) are speculative with virtually no information against biological agents, such as anthrax, or diseases which are extremely uncommon in the developed world, such as small pox and typhus. In cases where exposure is high, treatment is based heavily on theoretical benefit-to-risk ratio.[7] In 1999, concerns over the link of certain vaccine ingredients, such as thimerosal and mercury, to neurodevelopmental disorders, such as autism, were also raised. A recent comprehensive review concluded that the weight of evidence is that there is no link between the 2 and that better communication of the evidence is warranted.[68] Furthermore, the main brands of vaccines given in pregnancy, including Tdap and influenza, do not contain thimerosal. Many scientific (such as Institute of Medicine and American Congress of Obstetricians and Gynecologists), international (WHO), governmental (CDC) and civil society agencies have been vigilant about reassuring short- and long-term vaccine safety. However, more basic research and post-marketing surveillance systems are needed to ease misconceptions of any potential new vaccine ingredients.[69]

Interference with infant response to vaccination

Certain maternal vaccine-induced antibodies transferred to the fetus have been found to inhibit the neonate's humoral immune response to vaccination.[70] Multiple mechanisms may underlie such inhibitory effects,[62] but they may vary between vaccines, vaccine doses and schedules.[71-73] Human maternal antibodies wane over a period of 6 to 12 months, which correlates with their amount present in the neonates at birth.[74-76] Interference on infant humoral immunity was found to mainly impact primary immunization in early infancy but not subsequent boosting.[77] Therefore, this should not be a deterrent to maternal immunization, especially if vaccination during pregnancy can mitigate high mortality and morbidity of infant infectious diseases. The pros and cons of maternal vaccination effects on infant immune response after scheduled infant immunization need to be carefully and systemically evaluated.

Conclusion and Future Directions

Maternal immunization has emerged as a worldwide public health strategy to protect both pregnant women and infants against infections. To date, the ACIP and WHO have specifically recommend immunization of all pregnant women against influenza and pertussis. Many other countries, such as the UK, Australia and New Zealand, have also similar vaccination recommendation for pregnant women. Despite the success, public acceptance to these recommended maternal vaccines remains to be increased world-wide. To this end, we believe that it is the key to better inform the public of disease risks, vaccine safety and benefits, continue to disseminate the newest scientific knowledge on maternal vaccination to physicians and encourage them to recommend to patients in all models of care, foster the universal implementation of vaccination by physicians and integrate public and private infrastructure and resources to provide financial support for vaccination programs.

In terms of the development of new maternal vaccines, a number of promising new vaccines, such as those against group B streptococcus and respiratory syncytial virus, are in the pipeline or in trial.[78] However, pregnant women have been traditionally excluded from many vaccine trials, which have precipitated a lack of long-term safety and efficacy data for pregnant women and the fetus. It is precisely those initial ethical and practical concerns that have become a bottle neck in maternal vaccine development and have had a direct effect on the quality of care to pregnant women and their ability to make informed decisions on immunization. Furthermore, significant gaps exist in our understanding of the efficacy and safety of vaccines in pregnant women with underlying conditions associated with increased susceptible to high-risk pregnancies. In order break such a vicious cycle, we advocate that consistent efforts are needed to open well-designed vaccine

trials to safely include and monitor pregnant women. As the efficacy of maternal vaccines uniquely relies on the secretion of antibodies at the maternal-fetal interface and in the mammary gland, maternal vaccine development requires a thorough understanding of the mechanisms of mucosal immune regulation and the microbiota influence during pregnancy,[79,80] and mucosal immune assessment, in addition to systemic immune assessment, should be incorporated into vaccine trial protocols. Last, we believe that integration of some recent scientific advances in systems vaccinology, which has demonstrated success in systemically profiling and in certain cases predicting vaccine efficacy,[81-84] will improve greatly the speed, accuracy and safety of vaccines development for the pregnant population.

Disclosure of Potential Conflicts of Interest

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