



Vaccination in Pregnancy

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ABSTRACT

Vaccination during pregnancy is an integral part of obstetric care as it protects the mother as well as the newborn from infections by passage of antibodies to the neonate. Pregnancy increases susceptibility to certain bacterial and viral infections. Vaccination in pregnancy raises a lot of concern regarding safety of the mother and fetus however inactivated vaccines and toxoids are considered safe in pregnancy. The supportive recommendations from healthcare workers increases acceptance of the vaccines and obstetricians play a key role in overcoming the barrier and building confidence. The following article provides insights into routine vaccinations given during pregnancy, vaccinations recommended in special circumstances and those contraindicated in pregnancy. It also analyses the barriers of vaccination in current scenario in the country and gives a brief window of what the future holds.

Key words: Vaccines, Immunization, Pregnancy

INTRODUCTION

Many vaccine-preventable diseases can be avoided by immunizing the mother.

Vaccination during pregnancy is an integral part of obstetric care.^[1] Pregnancy increases susceptibility to many bacterial and viral infections which lead to morbidity and mortality of both mother and fetus. Inactivated vaccines and toxoids are considered safe during pregnancy.

Vaccination during pregnancy protects the mother as well as the newborn from infections as the antibodies are passed to the neonate who is protected for the first few months of life until it is time for his own vaccination.^[2]

Maternal IgG antibodies are actively transferred to fetus, mainly after 32 weeks of gestation.^[3,4] Hence, there is a high level of protection due to these antibodies in fetus born at term compared to preterm.

Other factors influencing the transfer of maternal IgG are placental integrity, total maternal IgG and its subtype, and timing of immunization compared to delivery.^[5]

Conventionally, vaccination was the responsibility of pediatricians and physicians. Now, obstetricians have a key role to play for both the mother and neonate. Immunization history

should be obtained and vaccines advised as a part of antenatal care. The success of maternal and neonatal tetanus by immunization adds hope for many diseases in future.

TETANUS

- A newborn suffers from neonatal tetanus when anti-tetanus antibodies are not transferred passively from the mother.
- The infection usually spreads through unhealed umbilical stump.
- In 2006, the World Health Organization (WHO) position paper on tetanus recommended three doses of diphtheria-tetanus-pertussis vaccine in infancy, with boosters in childhood and adolescence and a sixth dose at first pregnancy. When the immunization status is unknown, the mother should receive two doses of vaccine 4 weeks apart and preferably 2 weeks before delivery.^[6,7]
- If a mother received two doses in her last pregnancy and conceives within 3 years, only one booster dose is recommended.
- The WHO also recommends a third dose of tetanus toxoid 6 months after the second one to extend protection for at least 5 years.
- A serum antibody titer of >0.01 U/mL provides protection. The wide coverage of vaccine has been successful in the elimination of maternal and neonatal tetanus in low- and middle-income countries by 94–96%.^[8]
- The vaccine also prevents premature births.
- Elimination of neonatal tetanus is defined as <1 case/1,000

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live births in every district of every country. India was finally free of maternal and neonatal tetanus in 2015. Eradication of tetanus is not possible because the spores are widespread in the environment.^[9]

- If a case of neonatal tetanus is identified, the mother should be given tetanus toxoid as early as possible and the baby to be treated as per national guidelines.
- The mother should receive second dose of toxoid 4 weeks after the first and a third dose 6 months after the second.

DIPHTHERIA

Although the disease burden has declined due to childhood vaccination, India still contributes substantially to the global scenario. India has moved toward Tetanus-Diphtheria vaccine, instead of only tetanus. In pregnancy, this will benefit both mother and the neonate against two diseases.^[10]

PERTUSSIS (WHOOPIING COUGH)

The highest risk of complication and hospitalization is among the neonates who are too young to be vaccinated. Adolescents and adults act as reservoirs for disease transmission as the immunity imparted by the vaccine wanes off. Family members and caregivers transmit the infection to the baby.

Antenatal vaccination prevents pertussis in mothers and their infants by passive transfer of maternal anti-pertussis antibodies. The probability of the mother infecting her newborn is also reduced.

TETANUS DIPHTHERIA ACELLULAR PERTUSSIS (T-DAP) VACCINE

- The T-dap vaccine includes tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.
- This provides protection against three bacterial infections – tetanus, diphtheria, and pertussis. Antenatal immunization protects both the mother and the baby.
- The recommendation is to immunize all pregnant women with a single dose of T-dap in the third trimester, preferably between 27 and 36 weeks of gestation irrespective of prior Td or T-dap vaccination.^[11,12] This maximizes passive transfer of antibody to the infant.
- However, it may be given at any time during pregnancy.
- This has to be repeated in every pregnancy regardless of previous immunization status as the protection against pertussis is short-lived.
- T-dap vaccine can be considered instead of the second dose of tetanus toxoid to extend protection against diphtheria and pertussis in addition to tetanus.
- Family members are usually the source of pertussis transmission in infants.^[13] Hence, T-dap is also important for health-care professionals and any person (siblings, grandparents, child-care providers) having close contact with an infant aged less than 1 year.
- This is termed as cocooning and a good strategy against infantile

pertussis.^[14]

- Post-partum vaccination with T-dap, if missed during pregnancy, also offers some protection to the infant.
- T-dap is in use since 2012 in various countries such as the US, the UK, Australia, and New Zealand.
- The vaccine is well tolerated in pregnancy.
- Pain and swelling at the injection site, fever, and body ache are the only side effects.

INFLUENZA IN PREGNANCY

The virus undergoes frequent antigenic change.

Pandemic flu can occur due to antigenic drift of its surface proteins. A 2011 Lancet meta-analysis reports 20 million influenza-related acute lower respiratory infections.

- Pregnant women with influenza virus infection are seven times more likely to be hospitalized and four times more likely to need ICU care.
- Furthermore, there is an increase in miscarriage rates, stillbirths, and early neonatal deaths.
- There is an increased risk of premature and complicated birth.^[2]
- The best solution for flu prevention is immunization. The CDC recommendation is to immunize all pregnant women with inactivated influenza vaccine during flu season. There is no place for live-attenuated vaccine in pregnancy. The influenza vaccination is beneficial for both seasonal influenza and influenza pandemics.^[15]
- It is recommended for mothers from 26 weeks onward and in case of pandemic, the vaccine can be given earlier to protect the mother.^[14] Transfer of maternally derived antibodies occur.
- The strains included in the vaccine are selected based on epidemiologic and virological surveillance by the WHO's Global Influenza Surveillance and Response System (GISRS).
- WHO monitors the evolution of viruses and recommends the viruses to be included in the vaccines twice a year (Northern and Southern hemisphere formulations). Influenza vaccine formulations change up to twice annually.^[16]
- Table 1 gives all the vaccine recommendations in pregnant women.

VACCINES IN PREGNANCY UNDER SPECIAL CONDITIONS

SARS-CoV-2 Vaccination in Pregnancy: A unique Opportunity for Equity

Vaccination is highly effective in reducing the severity of COVID-19 infection, hospitalization, and death.

Protective antibodies are found in umbilical cord blood and breast milk which shows protection to the neonate. Vaccines available in India are:

- Covishield – produced by Serum Institute of India (SII) in collaboration with Astra-Zeneca. This is an adenovirus-based viral vector vaccine.

Table 1: Vaccines recommended for all pregnant women

| Vaccine | Vaccine type | Pregnancy recommendation |
|--|--|---|
| T-dap | Tetanus and diphtheria—inactivated toxoids; | 1 dose T-dap from 27 to 36 weeks, regardless of previous immunization |
| Tetanus Toxoid/Tetanus Diphtheria (Incomplete immunization/unknown status) | acellular pertussis—inactivated subunit Inactivated toxoids | 2 doses 4 weeks apart (2 nd dose can be T-dap) |
| Influenza | Inactivated viral subunit | 1 dose during flu season, any gestational age |
| Vaccines recommended under special circumstances | Vaccines contraindicated in pregnancy | |
| COVID-19 (pandemic) | | |
| Hepatitis A | Measles Mumps Rubella | |
| Hepatitis B | Varicella | |
| Pneumococcal | Human Papilloma virus | |
| Meningococcal | Bacillus Calmette Guerin | |
| Yellow fever | | |
| Japanese encephalitis | | |
| Typhoid | | |
| Rabies | | |
| Anthrax | | |

- Covaxin – Produced by Bharat Biotech Ltd. This is an indigenous vaccine and is an inactivated (killed) whole virus vaccine.
- Sputnik V

Ministry of Health and Family Welfare, Government of India, approved vaccination of pregnant women against COVID-19 on 2nd July, 2021. The dosage and side effects are similar to that of general population.^[17]

Counseling will help overcome the fear of vaccination in pregnancy.

Hepatitis A

- Hepatitis A is RNA virus and the vaccines are formalin-inactivated.
- The safety of vaccination during pregnancy is not known.
- However, due to the fact that the vaccine is inactivated, the risk to the fetus is expected to be low.
- The vaccine is indicated in special circumstances when the benefits outweigh the risks – chronic liver disease, hemophilia, intravenous drug abuse, working with primates, and travel to endemic regions.
- Finally, if exposed to Hepatitis A infection, immunoglobulin should be administered.
- It is highly effective and prevents acute infection.

Hepatitis B

- Hepatitis B is a DNA virus and the vaccine is recombinant formulation based on hepatitis B surface antigen envelope protein.
- Three doses are highly effective in disease prevention.
- The vaccine is recommended for pregnant women who are at high risk during pregnancy.
- It is an inactivated subunit vaccine, the risks to the baby are very low.
- High-risk groups are women with multiple sex partners during the previous 6 months, those who inject drugs/partner injects drugs, regular blood transfusion, liver disease, chronic kidney disease, and women traveling to high-risk countries.
- The vaccine is also advisable for women at risk of contact with

body fluids like doctors, nurses, and lab staff and those who are evaluated or treated for sexually transmitted disease.^[18]

- The antibodies protect the newborn.

Meningococcal Disease

Meningococcal disease is caused by *Neisseria meningitidis*, a bacterium. It has a high mortality rate, despite treatment and the survivors have significant sequelae. Two inactivated vaccines are effective against meningococcal disease – conjugate vaccine and a polysaccharide vaccine.

The meningococcal vaccine is recommended during pregnancy to mothers at high risk for the disease.

The risk factors^[1] are living in close contact such as dormitories, functional and anatomical asplenia, immunosuppression, complement deficiency, and travel to high-risk endemic areas.

The vaccine is safe during breastfeeding.

PNEUMOCOCCAL DISEASE

Pneumococcal disease is responsible for pneumonia, bacteremia, meningitis, and otitis media.

Thirteen-valent pneumococcal conjugate vaccine and 23-valent polysaccharide vaccines are recommended for mothers who have-risk factors.

The vaccine can be given during breastfeeding.

The risk factors which recommend for vaccine usage are chronic heart disease, chronic lung disease, asthma, diabetes mellitus, congenital or acquired immunodeficiencies, sickle cell disease and other hemoglobinopathies, anatomic or functional asplenia, chronic liver disease, smoking, alcoholism, cirrhosis of liver, and chronic renal failure.^[19]

TRAVEL VACCINATIONS

International travel is increasing, and the specialty of travel medicine is emerging to protect the health of travelers through the use of immunization and appropriate drugs.

Pregnant women planning international travel need to fulfill country-specific recommendations.

The vaccine-preventable diseases encountered are Yellow fever, Japanese encephalitis, and typhoid fever.

YELLOW FEVER

Yellow fever is caused by an RNA flavivirus and is spread by mosquitoes. The disease spectrum varies from mild-to-severe symptoms which include multiorgan failure, hemorrhage, and death. The disease is endemic in South America and sub-Saharan Africa.

Yellow fever vaccine is live attenuated. It is safe and effective.

CDC recommends vaccination during pregnancy if her risk of exposure and infection is high and the advantages outweigh the risks of vaccine.

Non-pregnant women of reproductive age group are advised to avoid conception for 4 weeks post-vaccination.

In countries where Yellow fever vaccine is an entry requirement, but the disease is not endemic, pregnancy constitutes medical grounds for exemption from the vaccination requirement.

JAPANESE ENCEPHALITIS

Japanese encephalitis is also caused by RNA flavivirus and spread by mosquitoes. The disease is prevalent in Asia. The mortality rate is high, and the survivors have neurocognitive and psychiatric sequelae.

CDC recommends inactivated Japanese encephalitis vaccine for pregnant women planning longer duration travel to endemic areas, where immunization is more beneficial compared to the risk of infection.

TYPHOID FEVER

Two vaccines are available – a live-attenuated vaccine and a polysaccharide vaccine. In cases of travel to endemic areas, the inactive parenteral vaccine may be administered.

RABIES

- Rabies is caused by Rhabdovirus and the infection is spread through saliva or central nervous system tissue of an infected animal.
- The disease is fatal to both mother and baby.
- Pre-exposure prophylaxis is advised if risk of exposure is high. Inactivated rabies vaccine is available.
- CDC recommends post-exposure prophylaxis to any pregnant woman after a moderate- or high-risk exposure to rabies.
- This includes rabies vaccine and human rabies immunoglobulin.

ANTHRAX

- Anthrax is caused by *Bacillus anthracis*, a spore-forming bacterium. The spores can be aerosolized and remain viable for long periods and considered a deadly biological weapon.

- Pre-exposure vaccination is not advised during pregnancy.
- However, post-exposure vaccination with inactivated subunit should be recommended with anthrax exposure.

VACCINES CONTRAINDICATED DURING PREGNANCY

Live-attenuated vaccines are contraindicated during pregnancy. The virus can cross the placenta and infect the fetus.

MEASLES MUMPS RUBELLA (MMR)

Measles and mumps are both caused by paramyxovirus and Rubella by togavirus. The disease burden has decreased with childhood vaccination and adult booster dosing. The vaccine is live attenuated and possible teratogenic effects of vaccine on fetus exists.^[1] This is not advisable during pregnancy.

Hence, pregnancy status should be ruled out in women of child-bearing age before vaccination. They must be advised contraception for 1 -month post-vaccination.^[20] Accidental administration of MMR vaccine, however, does not call for the termination of pregnancy as no evidence of harm has been documented so far. Preconception screening and MMR administration are advised to avoid congenital rubella syndrome in her subsequent pregnancy. A single dose of vaccine produces antibody levels in 95% of susceptible persons.

Pregnant women who are susceptible to Rubella are vaccinated postpartum as it eliminates the risk of future pregnancies. The virus is excreted in breast milk and causes seroconversion and asymptomatic infection is reported in the neonate.^[21]

VARICELLA

Varicella is caused by Varicella zoster virus of the herpes family. Pregnant women are usually immune to infection and have protective antibodies. Maternal Varicella zoster virus infection is seen in 2–3 cases/1,000 pregnancies.^[22] Varicella immunization is not recommended during pregnancy as the virus can harm the fetus. However, accidental administration during pregnancy does not call for termination.

Pre-pregnancy and postpartum period should be utilized to vaccinate all non-immune women. In case of a possible exposure to Varicella in antenatal period, the immunity should be checked by a history of previous infection, immunization, or immunoglobulin G serology.

If immune status is not known, and the serum status is negative, varicella zoster immunoglobulin should be administered as soon as exposure occurs.

The patient and family must understand the maternal and fetal sequelae of varicella infection and the risk of transmission.

HUMAN PAPILOMA VIRUS (HPV)

- HPV is a small DNA virus and the vaccine is L1 major capsid protein of HPV which form virus-like particles.

- The vaccine is not recommended during pregnancy, and conception is avoided for 1-month post-vaccination.
- However, if a vaccine series is started and then pregnancy is confirmed, vaccination should be delayed and completed after delivery.

BACILLUS CALMETTE GUERIN (BCG)

BCG vaccination should not be given during pregnancy as it is a live vaccine and can harm the fetus.

BREASTFEEDING AND POSTNATAL VACCINATION

For breastfeeding mothers, almost all vaccines (inactivated, live, recombinant, subunit, conjugated vaccines, and toxoids) can be safely administered. Rubella, Hepatitis B, Varicella, Influenza, Tetanus, and HPV vaccinations are advised to all non-immunized postnatal mothers by FOGSI.

Yellow fever vaccination should be avoided but if travel cannot be postponed to endemic areas, vaccination should not be withheld.

VACCINES – SIDE EFFECTS AND CONTRAINDICATIONS

The side effects of vaccine are as follows:

- Immediate effects can be fainting and vasovagal reactions. Patients are usually advised to wait for 15–30 min after receiving a vaccine
- Local effects include erythema and swelling (most common)
- Systemic effects can be malaise and fever
- Mild allergic reactions. This may happen with Yellow fever and influenza vaccine due to egg proteins

Anaphylactic reactions are very rare and should be treated immediately.

General contraindications are:

- Anaphylaxis to a vaccine or vaccine component
- Severe asthma
- History of Guillain–Barre Syndrome (GBS) within 6 months of receiving a vaccine

FUTURE

Vaccines are beneficial during pregnancy in various stages of research and development. Two examples are Group B Streptococcus (GBS) and Respiratory syncytial virus.^[23] Group B Streptococcus is the leading cause of neonatal sepsis and meningitis and the vaccine would be effective in preventing both early and late-onset disease. A polysaccharide conjugate vaccine of GBS is in clinical trials in Europe and Africa. Respiratory syncytial virus causes bronchiolitis and pneumonia in infants and the vaccine would prevent hospitalization and infant mortality due to the disease. The infant will get protection during the first few months of life due to antibody transfer from the mother.

Other potential vaccines targeting Cytomegalovirus, Herpes Simplex virus, and Zika virus will have promising results in future.

OVERCOMING THE BARRIERS

Vaccination during pregnancy raises lots of questions in the minds of the mother and the family regarding the safety concerns, particularly related to the fetus. Other barriers to antenatal vaccination include patients' misconceptions, complexity of the immunization schedules, religious beliefs, and cost. These anxieties and hesitation should be addressed by providing adequate information to the family.

The supportive recommendation from the health-care provider increases acceptance of the vaccine to the extent of 20–100 times. Various surveys have confirmed that the obstetrician plays an important role in the decision-making and in overcoming the barriers and building this confidence. To overcome maternal immunization hesitancy, educational activities should target health-care workers and government officials also along with mothers and their families. The vaccines with proven benefits such as T-dap and influenza should be added to national immunization schedule.

In developing countries like India, where the cost of vaccine is a barrier, the government should include these in routine immunization programs.

CONCLUSION

- Single dose of T-dap vaccine is recommended in the third trimester, preferably between 27 and 36 weeks of gestation irrespective of prior Td or T-dap vaccination.
- All pregnant women should be immunized with inactivated influenza vaccine during flu season at any gestational age, preferably from 26 weeks onwards.
- COVID-19 vaccination is suggested in pregnancy and lactation with dosing similar to general population (present pandemic).
- Women with risk factors and travel needs can be vaccinated with hepatitis A, hepatitis B, pneumococcal, meningococcal, Japanese encephalitis, yellow fever, typhoid, rabies, and anthrax vaccines.
- Women who have inadvertently received a live or live-attenuated vaccine during pregnancy should not be counseled for termination in view of teratogenic risks. Non-pregnant women receiving these vaccines should be advised to delay pregnancy for 4 weeks.

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