Vaccinations in pregnancy

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Abstract

Vaccinations are a cost-effective means of preventing disease. They may be recommended primarily for maternal benefit or for prevention of intrauterine fetal or early neonatal infection. Increasingly they are a recognized technique of providing protection through passive immunity to the newborn infant. The MBRRACE-UK 2014 report, covering 2009–2012 during the H1N1 epidemic, demonstrated that one in eleven maternal mortalities were directly from influenza virus. More than half of these could have been prevented by the flu vaccine in pregnancy. Research is ongoing in the development of additional vaccines for infections that can cause detrimental effects to pregnant women and their infants. Theoretical concerns regarding adverse effects to the fetus and lack of efficacy have, in general, not been confirmed by clinical evidence. Nevertheless live attenuated vaccines remain contraindicated due to risk of fetal infection. As with any clinical decision, advice on antenatal vaccination should be based on the balance of risks and benefits to mother and fetus. This article aims to guide such decisions by discussing the issues surrounding commonly used vaccines and presenting current UK guidelines.

Keywords attenuated vaccines; fetal immunity; live vaccines; maternal vaccination; vaccination during pregnancy; vaccine risks

Introduction

Vaccination is one of the most cost-effective techniques available in preventative medicine and has the potential to reduce neonatal and maternal morbidity and mortality. As with any other intervention during pregnancy, vaccination programmes may be complicated by safety, social and organizational concerns. For many medical conditions, pregnant women are consistently under treated or under investigated, largely due to both physician and patient concerns of the potential harm to the fetus. As vaccines are used for prevention of diseases, there is often the misconception that vaccines should be deferred until after pregnancy. However, women and their babies can come to harm during pregnancy or in the postpartum period if they develop diseases that could have been prevented by safe vaccination. Despite widespread educational campaigns to encourage certain vaccinations in pregnancy, uptake still remains suboptimal. This article aims to provide up to date guidance for practitioners advising women on vaccination during pregnancy.

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General principles

Purpose of immunization

The rationale for vaccinations in pregnancy may be either protection of the mother, protection of the fetus/neonate or both. Access to healthcare provides an opportunity to identify and treat women with inadequate immunization status for vaccinations unrelated to pregnancy. Vaccination may also be indicated to protect against pathogens which are particularly severe during pregnancy. By preventing maternal infection, vaccinations may protect the fetus from intrauterine infections and their potentially teratogenic consequences. Early neonatal vaccination promotes a variable response and so maternal vaccination is an accepted technique of passively immunizing the newborn at an age when vaccination may be unsuccessful. By delaying neonatal vaccination until it will be more effective and simultaneously immunizing the mother, there may also be cost savings.

Safety

There is growing safety data on vaccination in pregnancy with vaccines such as those for influenza and pertussis vaccine in widespread use in recent years. Traditionally, manufacturers were reluctant to include pregnant women in clinical trials for fear that the trial would implicate their vaccine in the normal fetal loss rate. Most older data used to guide women and clinicians are the product of vaccine registries which collated information from women receiving the vaccine inadvertently during pregnancy. Whilst providing reassurance, these lacked the rigorous control of a clinical trial. With recent recommendations of vaccinating all pregnant women with the influenza and pertussis vaccines, there is a growing body of reassuring safety data.

Live attenuated vaccines are contraindicated in pregnancy due to theoretical risk of transmission across the placenta. Administration of vaccines, live or otherwise, however has not been associated with adverse clinical outcomes, except in one Brazilian study of inadvertent maternal rubella vaccination. This found a greater rate of prematurity and low birth weight in neonates where there was proven transplacental transfer of the attenuated virus. As the risk of adverse outcomes appears to be low, live vaccines may occasionally be recommended for an individual if the disease risk is high.

Women who receive live vaccines should be counselled to avoid pregnancy for four to twelve weeks following inoculation, but should a vaccine be received inadvertently, this is not an indication for termination. Clinicians are not advised to routinely test for pregnancy prior to vaccine administration, provided the woman is confident she is not pregnant.

Yellow fever and smallpox are the only vaccines contraindicated postpartum or when breastfeeding. Smallpox, however, is no longer recommended for the general public and is only for researchers who work with smallpox.

Efficacy

Pregnancy is a time of immunomodulation and concerns exist about the ability to mount an adequate vaccine response during pregnancy. So far the evidence does not support this hypothesis. It has been shown that IgG is actively transported across the placenta primarily in the third trimester, providing the neonate with protective levels of antibody, whereas T cell immunity does not appear to be transferred. The efficacy of antibody transfer is affected by many variables. In terms of the vaccine itself, placental transport favours IgG1 antibodies over IgG2 and so vaccines that promote the former response will result in better protection of the neonate. IgG1 antibodies tend to be induced by protein antigens, whereas polysaccharide antigens promote an IgG2 response. Conjugate vaccines may therefore favour an IgG1 response and provide better neonatal protection. Maternal factors that may influence placental transfer of IgG include placental abnormalities, such as those caused by malaria or HIV, which reduce antibody transfer.

Some pregnant women may be taking immunomodulatory medication for medical conditions such as inflammatory bowel disease. They may have reduced seroconversion rates and immune responses to vaccines because of these medications. They should still receive the same vaccines as other pregnant women (live vaccines contra-indicated). The vaccine may have reduced efficacy which the clinician should be mindful of. Neonates that are exposed *in utero* to biologics should not receive live attenuated vaccines for the first six months of life. They can receive other vaccines safely. Therefore, with regards to routine vaccinations, this means the avoidance of BCG and rotavirus vaccinations.

Timing (Table 1)

Pre-conception vaccination is optimal, providing the benefits of vaccination without any theoretical risk to the fetus. Unfortunately, as at least 40% of UK pregnancies are unplanned, this is often not feasible and the first clinical interaction is usually once conception has occurred. A decision then needs to be made whether to vaccinate during pregnancy or wait until postpartum. The key deciding factor in this situation should be whether the woman or offspring is at high risk of the infectious agent during the pregnancy or puerperium. If not, the full maternal benefit of vaccination can be gained by postpartum administration without any potential risk posed by pregnancy. Loss to follow up may, however, be high.(Table 1)

Should the balance of risks favour antenatal vaccination, then there is the question of optimal timing. The first trimester is the time of organogenesis and has the highest teratogenic risk, so should be avoided if possible. It is also the time of greatest fetal loss, so interventions in this period risk implication in unrelated adverse outcomes. If the primary purpose is prevention of maternal disease, administration should occur as soon as possible after the commencement of the second trimester. In situations where the main driver is fetal protection, the dynamics of placental immunoglobulin transfer must be considered. As pregnancy progresses, active transport of maternal antibodies increases such that at 33 weeks' gestation, fetal levels match those of the mother and by term they exceed them. 30–32 weeks is considered optimal for vaccination, marrying the maximal immune response at two weeks post-inoculation with a time of efficient placental transfer, whilst allowing leeway for premature delivery.

UK routine vaccination schedule

Age	Vaccine
2 months	DTaP/IPV/Hib/HepB (6in1)
	Pneumococcal
	Rotavirus
	Men B
3 months	DTaP/IPV/Hib/HepB (6in1)
	Rotavirus
4 months	DTaP/IPV/Hib/HepB (6in1)
	Pneumococcal
	Men B
12–13 months	Hib/Men C
	MMR
	Pneumococcal booster
	Men B
2–8 years (annual)	Influenza
Pre-school (3yrs and 4 months)	MMR
	DTaP/IPV or dTaP/IPV (4in1)
12–14 years (girls only)	HPV (2 doses within 12 months)
14 years	Td/IPV (3in1)
	MenACWY
65 and over	Influenza (annual)
	Pneumococcal
70 years	Shingles
Boosters	Tetanus: every ten years or upon sustaining a soil contaminated wound. 5 doses should provide lifetime protection
	IPV: every ten years. 5 doses should provide lifetime protection

DTaP: diphtheria, tetanus and acellular pertussis; IPV: inactivated polio vaccine; Hib: haemophilus influenzae type B; HepB: hepatitis B; Men B: meningitis B; Men C: meningitis C; MMR: measles, mumps and rubella; HPV: human papilloma virus; Td: tetanus and diphtheria; MenACWY: meningitis A, C, W and Y. BCG vaccine from birth for high risk groups.

Table 1

Vaccinations with specific relevance to pregnancy (Table 2)

Influenza

Influenza in pregnancy and postpartum has a higher morbidity and mortality than in the general population, especially in the third trimester. MBRRACE-UK, the confidential enquiry into maternal mortality, reported that one in eleven maternal deaths from 2009 to 2012 were directly caused by influenza infection in pregnancy. At least half of these could have been prevented by influenza vaccination in pregnancy.(Table 2)

Influenza vaccination has been recommended in the UK for all pregnant women since 2010, for both maternal and fetal benefit. It may be given in any trimester and should be administered postpartum to those who did not receive it antenatally. Current influenza vaccine uptake rates during pregnancy in the UK are still suboptimal but are improving (increased from 44.9% in 2016–2017 to 47.2% in 2017–2018).

Two types of influenza vaccines are available: inactivated intramuscular vaccine (trivalent or quadrivalent), which is recommended, and a live attenuated intranasal vaccine that is contraindicated. The inactivated vaccine has been used in pregnancy for many years, with extensive investigation not revealing any link to fetal or maternal complications. In women who received the intranasal vaccine inadvertently there have been no reported adverse events. Neither vaccine is

Summary of vaccinations in pregnancy

Vaccine	Type	Safety	Comments
Vaccines with specific relevance to pregnancy			
Influenza	Inactivated (intramuscular)	No evidence adverse outcomes	Recommended for all pregnant women in any trimester
	Live attenuated (intranasal)	Contraindicated	
Pertussis	Given as Boostrix-IPV® (Diphtheria and tetanus toxoids, acellular pertussis and inactivated poliomyelitis)	No evidence adverse outcomes	Recommended for all pregnant women between 16 and 32 weeks during vaccine programme
Tetanus and diphtheria	Toxoids	No evidence adverse outcomes	Give as per non-pregnant women Exchange one dose in later pregnancy for Boostrix-IPV®
MMR	Live attenuated	Contraindicated	Give pre-conceptually if possible All pregnant women should have rubella IgG measured and be vaccinated postpartum if non-immune
Varicella	Live attenuated	Contraindicated	
HPV	Inactivated	No evidence adverse outcomes	Not recommended
Vaccines where indications are unchanged in pregnancy			
Pneumococcal	Polysaccharide	No evidence adverse outcomes	
Hib	Conjugate	No evidence adverse outcomes	
Meningococcal C	Conjugate	No evidence adverse outcomes	
	Polysaccharide	Insufficient data but low theoretical risk	
Meningococcal B	Recombinant	Insufficient data but low theoretical risk	
Hepatitis A	Inactivated	Insufficient data but low theoretical risk	
Hepatitis B	Recombinant	No evidence adverse outcomes	Consider accelerated course in high risk groups
BCG	Live attenuated	Contraindicated	
Anthrax	Live attenuated	Contraindicated	
	Inactivated	Contraindicated for prevention Advised post exposure	
Travel vaccines			
Polio	Inactivated	Some theoretical safety concerns but UK guidelines recommend	Exchange one dose in later pregnancy for Boostrix-IPV®
	Live attenuated	Contraindicated	
Rabies	Inactivated	No evidence adverse outcomes	
Typhoid	Inactivated	Insufficient data but low theoretical risk	
	Live attenuated	Contraindicated	
Japanese Encephalitis	Inactivated	Insufficient data but low theoretical risk	
Plague	Inactivated	Insufficient data but low theoretical risk	
Cholera	Inactivated	Insufficient data but low theoretical risk	
Yellow fever	Live attenuated	Low rate fetal infection from vaccination but no evidence major adverse outcomes	Risk of disease usually outweighs risk of vaccine so recommended on travel to endemic area Not recommended if breastfeeding

Table 2

contraindicated in breastfeeding or in household contacts of pregnant women, although clinicians often avoid the live vaccine postpartum due to theoretical risks of viral shedding.

Vaccination is also important for neonatal protection. Infants under six months have the highest rate of hospitalization and death from influenza. No vaccine is licensed for this group, leaving them reliant on passive protection from their mothers. Maternal immunization is recommended to reduce the incidence of neonatal influenza with protection lasting up to six months. The majority of infantile influenza originates from household contacts, so vaccinating the mother will have a dual effect by reducing maternal disease and hence infant pathogen exposure. Some argue for vaccination of all close contacts of infants for this reason: a technique known as cocooning; but this is not currently common practice in the UK.

The influenza vaccine is recommended in each pregnancy as a slightly different vaccine is manufactured every year to reflect the predicted strains of influenza for the coming flu season. Most years, the influenza vaccine is thought to be about 50% effective due to varying strains of influenza causing the illness. Some years the flu vaccine is not an effective match to the actual influenza virus causing the flu illness (due to antigenic drift of the virus) so Healthcare workers still need to be vigilant for signs of influenza in vaccinated women.

Pertussis

In the 1950s, routine childhood vaccination was introduced and there was a dramatic reduction in cases of pertussis to a nadir in the late 1970s. Since then case numbers have steadily increased and, in 2012, there was a pertussis outbreak. In the UK there were nearly 10,000 cases (which is more than ten times than previous years) with infants under three months most at risk. In 2013 and 2014, case numbers continued to be high and it was recommended that the temporary vaccination programme in pregnancy be extended for at least another 5 years. Infants under three months are too young to be protected by their routine vaccinations, which are given at two months when their immune system is mature enough to mount a sufficient response. The vast majority of the deaths during the 2012 pertussis outbreak were in infants younger than 3 months. A large observational study of pregnant women vaccinated since the start of the outbreak showed no increase in pregnancy adverse outcomes. In the first year of the pertussis vaccine programme in the UK, the risk of pertussis in infants less than 3 months born to vaccinated mothers was reduced by more than 90%.

Women should receive a single pertussis vaccination during pregnancy. Antipertussis antibodies have been shown to decline after one year so the vaccine is recommended in each pregnancy. The Department of Health advise vaccination between 16 and 32 weeks' gestation. Women may be vaccinated after 32 weeks but this may not offer as high a level of passive protection to the baby. Pertussis vaccination may safely be given with the influenza vaccine, regardless of previous immunization status and women should be warned that cumulative doses increase the likelihood of injection site reactions and fever. Should vaccination during the pregnancy not be possible, it should be performed postpartum. As there is no exclusive pertussis vaccination, the vaccine used in UK adults since 2014 is Boostrix-IPV® which also protects against diphtheria, tetanus and polio (dTAp/IPV). With maternal pertussis vaccination, the infant gains passive immunity from immunoglobulin transfer across the placenta. Protection by cocooning also occurs with maternal vaccination as infant pathogen exposure is reduced through close contact immunization. The USA currently recommends immunization of all close contacts in addition to the maternal vaccination programme, but this advice has not been adopted in the UK.

Several studies have shown blunted pertussis antibody production at two, three and four months following active immunization to infants of mothers vaccinated in pregnancy. It is not clear, however, how closely antibody levels correlate with clinical protection and on-going studies are not sufficiently powered to assess clinical outcomes. Current evidence suggests a short blunting of the infant response, but that the benefit of protection in neonates outweighs possible increased risk later in infancy, when the burden of mortality is lower. A mathematical model with a conservative estimate of 20% efficacy of maternal antibodies and a generous estimate of 60% risk increase later in infancy due to blunting still found vaccination during pregnancy to be more cost-effective than postpartum vaccination.

Tetanus

Neonatal tetanus accounts for a large, though happily diminishing, global health burden and has an untreated mortality approaching 100%. In response to neonatal tetanus deaths reaching 6.7 per 1000 live births, the World Health Assembly prioritized elimination of this disease in 1989 and in 1999 the WHO launched the Maternal and Neonatal Tetanus Elimination Initiative. Since then there has been a 96% reduction in neonatal cases as per WHO 2015 estimates. Eradication is impossible due to environmental spores, so the target is for elimination of the disease; defined as less than one case per 1000 live births. Fourteen countries still had this to achieve in March 2018; predominantly in Sub-Saharan Africa and Asia.

Neonatal and maternal tetanus is most commonly contracted through unhygienic birth practices or poor umbilical cord care and so the WHO has focused on these areas, as well as robust vaccination programmes. Maternal tetanus antibodies are placentally transferred, providing protection to the neonate until their active immunization at two months. Protection is sufficient even with vaccination prior to conception. Millions of doses have been administered worldwide with no evidence of increased risk to the mother or fetus.

In the UK, if a woman is up to date with tetanus immunizations, no action is required during pregnancy. Currently, however, all pregnant women should receive tetanus vaccination as a by-product of the pertussis vaccination programme, which uses Boostrix-IPV®: a pertussis, polio, tetanus and diphtheria combination vaccine. Should a woman be due her tetanus booster or require one for wound-management purposes, this should be given in the same way as for any adult. During the temporary pertussis vaccination programme, however, the Boostrix-IPV® vaccine should be used in preference to the usual combination vaccine of tetanus, diphtheria and polio, ensuring protection against pertussis and convenience for the woman by minimizing the number of injections required. For the reasons described above, Boostrix-IPV® should ideally be given between 16 and 38 weeks and may be delayed until this time if safe to do so. Insufficiently vaccinated women with high-risk wounds should

receive Boostrix-IPV®, with or without immunoglobulin, immediately regardless of gestation. Women with unknown or no tetanus immunization, should receive the routine three dose course of vaccinations and those with incomplete vaccination should complete the course but do not need to restart it. Again, one of the doses should be replaced with Boostrix-IPV®, preferably between 16 and 38 weeks, to provide pertussis protection.

In the developing world, guidelines differ with the WHO recommending two doses given one month apart in the first pregnancy, the third dose given at least 6 months later and then one dose in each subsequent pregnancy (or intervals of at least one year) to a total of five doses. The first two vaccinations provide over 80% protection against neonatal tetanus.

Measles, mumps and rubella (MMR)

Women in the UK should have been fully immunized against measles, mumps and rubella in childhood, with the two doses of vaccine providing lifelong immunity. Whilst vaccination had reduced the incidence of these conditions in the UK, unfounded publications linking the vaccine to autism decreased vaccine uptake and has led to resurgence of these diseases. There was a sharp rise in the number of measles cases in the UK from 2001 to 2013 with a decrease in numbers after this. However, the case numbers were high again in 2018 (with 913 laboratory confirmed cases).

All three diseases are associated with adverse fetal outcomes; measles increases the risk of prematurity, miscarriage, and possibly stillbirth. First trimester mumps can lead to intrauterine death. In addition to miscarriage and fetal death, the fetuses of women infected with rubella before 20 weeks' gestation have a 20–85% risk of congenital rubella syndrome: a devastating constellation of auditory, visual, cardiac and neurological abnormalities. There is no known effective preventative treatment for congenital rubella syndrome in women infected with rubella during pregnancy. In the mother, measles may also be more severe in pregnancy and could develop into a potentially fatal pneumonitis.

For these reasons it is imperative that, whenever possible, pregnant women have immunity to these diseases. Unfortunately, MMR vaccine is contraindicated in pregnancy as it is a live attenuated vaccine. It is therefore highly recommended that women planning a pregnancy have IgG antibody titres measured and are vaccinated prior to conception if non-immune. Women who receive vaccination should be advised to wait for 28 days before trying to conceive. Women are routinely tested for immunity to rubella in early pregnancy and those with inadequate immunity are advised to avoid contact with those with rubella and to receive postpartum vaccination.

Although the vaccine is contraindicated in pregnancy and there is evidence of placental transfer of the attenuated virus, a large number of women have been monitored following inadvertent vaccination with no evidence of congenital rubella syndrome. Pregnant women who receive the vaccine should therefore be reassured that termination of pregnancy is not necessary. The attenuated virus may be transmitted in breastmilk but this does not cause significant clinical disease and is routinely recommended postpartum for women with insufficient immunity. The virus is not shed after vaccination and so close contacts of pregnant women may be immunized as normal.

Varicella zoster

Chickenpox infection in pregnancy carries both maternal and fetal risks. For the mother the risk of pneumonitis and other complications are increased and for the fetus there is a risk of congenital varicella syndrome if infection occurs before 28 weeks. Compared to rubella, this congenital syndrome is much rarer and consists of segmental areas of skin deformity, limb hypoplasia, neurological and ophthalmological abnormalities. Should maternal varicella occur in the perinatal period, there is a risk of severe neonatal varicella with a high mortality rate.

Varicella vaccination does not form part of the routine UK immunization programme, but the vast majority of adults have natural immunity from childhood infection. The vaccine is live attenuated and hence is contraindicated in pregnancy. Preconception consideration of vaccination is therefore recommended by the Royal College of Obstetricians and Gynaecologists. Immunity can be assessed by a history of chickenpox which is 97–99% predictive of protective antibodies. In women without a definite history of the disease, IgG can be measured and, if seronegative, preconception vaccination considered, with two doses one month apart. UK guidelines suggest delaying pregnancy for three months post-vaccination, whereas in the USA one month is recommended.

If the vaccine be administered during pregnancy or in the preceding three months, no intervention is needed. Despite theoretical concerns, the vaccine registry has not demonstrated any link with adverse outcomes, although the data set is small. Recently vaccinated individuals rarely transmit the virus to close contacts, and the theoretical risk of doing so is outweighed by the reduced chance of wild type transmission. Contacts of pregnant women may therefore be vaccinated as normal, but should be warned to avoid high risk groups (non-immune pregnant women, infants, immunocompromised people) should they develop a varicella-like rash, when the risk of transmission is higher.

Non-vaccinated women exposed to varicella during pregnancy should be tested for IgG and should receive varicella immunoglobulin if non-immune. This is safe in pregnancy and reduces maternal morbidity, but has not been shown to have any direct fetal benefit when given antenatally. The Royal College of Obstetricians and Gynaecologists recommends that neonates born to mothers who develop chickenpox within the period seven days before to seven days after delivery should receive prophylaxis with immunoglobulin with or without acyclovir. These neonates are at high risk of developing varicella infection of the newborn despite high titres of passively acquired maternal antibody.

Human papilloma virus (HPV)

HPV is an inactivated viral vaccine, which theoretically should be safe in pregnancy. Vaccination during pregnancy is not recommended however, as the vaccine provides no benefit to the fetus and the maternal risk during pregnancy is not sufficient to warrant potential fetal risk. HPV vaccination should be deferred until postpartum, including any outstanding vaccinations in a partially completed course. In view of the demographic targeted and because formal pregnancy testing is not required prior to administration, it is likely that many women will receive the vaccine inadvertently during pregnancy. When this occurs

women should be reassured that there is no evidence of teratogenicity and that no intervention is necessary. Phase III clinical trials analysing over 2500 exposed pregnancies did not find any significant increase in adverse outcomes and pregnancy registries also support this conclusion. Vaccinating women who are breastfeeding is considered safe.

Vaccinations where indications are unchanged in pregnancy (see Table 2)

Pneumococcal

In the UK pneumococcal vaccination is only received by infants, those over 65 and those in a risk group due to long term health conditions, for example sickle cell disease. Pregnancy is not an indication for vaccination. Therefore, women due the pneumococcal vaccine should receive it in the second or third trimester of pregnancy (there is not enough information about safety in the first trimester) unless preconception vaccination is possible, which would be preferable. Controlled studies have demonstrated safety and efficacy in pregnancy and, as a polysaccharide vaccine, theoretical concerns are minimal. Research is ongoing into the role of placental antibody transfer in potential neonatal protection. However, a Cochrane database systematic review has stated that there is insufficient evidence at present to determine if the vaccine in pregnancy could reduce infant infections.

Haemophilus influenzae type B (Hib)

This conjugate vaccine is safe and efficacious in pregnancy and should be used if there are any specific indications for it, such as those unimmunized diagnosed with Hib infection (as disease can recur), functional or anatomical asplenia, immunodeficiency, or complement deficiency. Other than in these situations, most adults do not require vaccination, even during pregnancy. Herd immunity provides some neonatal protection prior to active immunization, so there is no indication for maternal vaccination for neonatal benefit. It may be relevant in the developing world however, which carries most of the disease burden.

Meningococcal C and meningococcal B

Meningococcal C vaccine should be administered using the same guidelines as for non-pregnant women. Meningococcal C vaccine is available in conjugate and polysaccharide vaccine forms, both of which are immunogenic in pregnancy. The polysaccharide vaccine has been administered extensively in pregnancy with no adverse effects. There is limited data for the conjugate vaccine to date, but it is reassuring so far. Meningococcal B vaccine was introduced to the UK immunization schedule in 2015. This vaccine is a recombinant DNA vaccine. There is insufficient data on this vaccine in pregnancy so far but there have been no reports of any safety concerns so far and the vaccine should not be withheld when there is a clear risk of meningococcal infection.

Hepatitis B

There is no requirement for routine hepatitis B vaccination in pregnancy, but high-risk groups such as intravenous drug users or healthcare workers should be vaccinated, as they would be outside of pregnancy. Hepatitis B vaccine is a recombinant vaccine and is safe and efficacious in pregnancy. For women at especially high risk, an accelerated vaccination course of three vaccines over 1 month is suggested.

Bacillus calmette guerin (BCG)

This is a live attenuated vaccine and is contraindicated in pregnancy, although limited research has not revealed adverse outcomes. As its efficacy in adults is poor, however, the protection it provides to the mother would rarely outweigh the theoretical risk to the fetus. The BCG vaccine is now recommended only for neonates in at risk groups in the UK (infants living in areas where the annual incidence of TB is 40/100,000 or greater or infants who have a parent or grandparent who was born in a country where the annual incidence of TB is 40/100,000 or greater).

Anthrax

Anthrax vaccination is compulsory for some US military personnel and data has been collected from inadvertent pregnancy exposures. The vaccine exists in live attenuated and inactivated forms. The live form is contraindicated in pregnancy. The inactive form has previously been linked with a possible increase in birth defects, however more recent evidence failed to detect an association. However, the vaccine is not recommended as a preventative measure due to theoretical concerns. Women known to be exposed to anthrax should receive the inactivated vaccine and antibiotics, as the risk of disease is greater than the risk from the vaccine.

Travel vaccines

Travel to areas endemic for tropical disease is not advised in pregnancy, but is sometimes unavoidable. In this situation the balance of risks and benefits for each vaccine should be assessed and it may be helpful to seek advice from a travel medicine specialist. Women should receive general advice on sun exposure and adequate hydration, venous thromboembolism risk on long flights, travel insurance requirements, and, of course, bite avoidance and malaria prophylaxis if relevant. Mefloquine and chloroquine and proguanil are safe in pregnancy.

Diphtheria

Diphtheria is not particularly associated with pregnancy or the neonatal period, and hence recommendations for pregnancy are the same as for any adult. Diphtheria and tetanus vaccines are always given in combination and therefore if advice for tetanus vaccination is followed patients will automatically receive adequate diphtheria protection. Situations which require specific diphtheria vaccination should be managed as per any other adult. As with tetanus however, one dose should be exchanged for Boostrix-IPV® to protect against pertussis during the current outbreak.

Polio

Similarly to diphtheria, new cases of polio no longer represent a significant disease burden in the UK and there are no additional requirements for pregnancy over any other adult. There are two forms of polio vaccines; inactivated vaccines and oral live attenuated vaccines. The latter are contraindicated in pregnancy although data from population studies failed to show adverse pregnancy or neonatal effects. The former may be combined with tetanus and diphtheria alone or tetanus, diphtheria and pertussis together in the Boostrix-IPV® vaccine. Pregnant women should receive polio boosters as per clinical indication for any adult.

Hepatitis A

The safety of this vaccine is unknown but, as an inactivated vaccine, the theoretical risk is low. Pregnant women in risk groups are therefore advised to be vaccinated and exposed women should receive both the vaccine and immunoglobulin regardless of pregnancy.

Rabies

This inactivated vaccine has not been implicated in any adverse outcomes and therefore pregnant women should receive vaccination as per any other adult. Pregnant women should also receive pre- or post-exposure prophylaxis with the vaccine and immunoglobulin if the risk of exposure is high as the potential consequences of inadequately managed rabies exposure are severe.

Yellow fever

Although this is a live attenuated vaccine, the risk of the vaccine is usually outweighed by its benefits due the severity of this disease. This vaccine is thought to be less effective in pregnancy with lower seroconversion rates compared to non-pregnant women. A study showed a slight increased risk for minor skin malformations in infants but not major malformations in women vaccinated during pregnancy. There have been two serious adverse events in breastfed babies following vaccination and, therefore, breastfeeding is discouraged. Pregnant women who decide against vaccination should receive a medical waiver if traveling to a country where it is an entry requirement, although this waiver may not be accepted.

Typhoid, Japanese Encephalitis, plague and cholera

Women may receive these inactivated vaccines if indicated, although there is inadequate data to comment on safety. It is assumed the risk is low as with other inactivated vaccines. There is a live attenuated oral typhoid vaccine (Ty 21a), which is contraindicated. The Vi capsular polysaccharide inactivated typhoid vaccine can be given. IXIARO® is the Japanese Encephalitis vaccine that is licensed and is inactivated. There is no safe and efficient vaccine for plague currently, although research is on-going into subunit vaccines. Current vaccines require multiple doses to achieve protection. Officially, cholera vaccine requirements no longer exist for any country. It is only now considered for those at high risk of cholera exposure without adequate access to clean sanitation, such as aid workers working in disaster relief or backpackers travelling to remote areas.

Relevant potential future vaccines

Respiratory syncytial virus (RSV)

RSV causes significant morbidity and mortality in infants less than six months, with hospitalisations peaking in the second month of life. No vaccines are currently sufficiently immunogenic for clinical use, but these are in development. Previous potential vaccines have not offered protection to infants less than six months. It has been shown, however, that infants with high RSV antibody levels are conferred clinical protection. This may be achieved by administration of human monoclonal antibody to high-risk neonates. There are currently phase II and III clinical trials underway testing maternal immunization in the third trimester for neonatal benefit (recombinant subunit preF antigen protein and post-F nanoparticles). In a similar way to pertussis, once an appropriate vaccine is available, maternal immunization for neonatal benefit could reduce disease burden.

Group B streptococcus

Group B streptococcus is carried asymptomatically by many women and has the potential to cause devastating neonatal sepsis as well as maternal disease around the time of labour, delivery and the early neonatal period. It is the most frequent cause of severe, early-onset neonatal infection in the UK, but the Royal College of Obstetricians and Gynaecologists does not advocate universal prenatal screening, as there is no convincing evidence of benefit of preventative antenatal treatment. Currently no vaccine is available, but some are in preclinical trials. These could potentially be used in a similar way to tetanus vaccines to protect both the mother and neonate; a recent model estimated that a vaccine could prevent 61–67% of early-onset and 70–72% of late-onset neonatal disease.

Herpes simplex

Herpes simplex virus can cause orofacial and genital infection in adults. The primary infection tends to be the most symptomatic episode. Herpes simplex virus lies dormant in neurons, can reactivate and cause recurrent, mostly asymptomatic, infections. It is an important cause of neonatal infection. 85% of neonatal transmission occurs intrapartum and 5–10% from early postpartum transmission. Neonatal herpes infection can have devastating sequelae such as severe neurological morbidity, multi organ dysfunction or death. Multiple vaccine candidates have been in phase I and II clinical trials but, to date, vaccines developed for herpes simplex virus have proven ineffective. More recently vaccine targets have been focused on preventing the recurrent infections.

Ebola

Ebola virus causes serious disease and there have been a number of much publicised outbreaks in recent years (most recently in Democratic Republic of Congo 2018). People can become infected through contact with blood, body fluids or organs of an infected person. There is currently no effective treatment for this disease although new therapies and vaccines are being tested (rVSV-ZEBOV) and are in phase II and III clinical trials. rVSV-ZEBOV is a recombinant vesicular stomatitis virus-based vaccine expressing a Zaire Ebolavirus glycoprotein. As this is a live attenuated vaccine, it would normally not be recommended in pregnancy. Pregnant women continue to be excluded from vaccination strategies at present. However, in Ebola outbreaks, up to 90% of pregnant women infected die and almost all of the pregnancies of Ebola infected women end in miscarriage or neonatal death. Therefore, if the risk of exposure to Ebola virus disease is high, the benefit of the vaccine would likely outweigh the risk.

Conclusion

Maternal vaccination can prevent and reduce maternal, fetal and neonatal infection and decrease disease burden. Vaccination is a cost-effective intervention and theoretical safety concerns have not been supported by clinical experience. As knowledge of safety and efficacy is coupled with increasing vaccine development and availability, maternal vaccination is becoming a more widely used technique. Healthcare providers should encourage routine maternal influenza and pertussis vaccination to continue to save lives. ◆

Practice points

- If possible, preconception vaccination is ideal, avoiding fetal exposure to potential teratogenicity
- Antenatal vaccination may be for maternal, fetal or neonatal benefit or a combination of the three
- Vaccination for maternal benefit should occur early in the pregnancy to maximize duration of protection. The first trimester is often avoided to prevent implication in unrelated miscarriage
- Vaccination for neonatal protection should ideally occur between 30 and 32 weeks to maximize placental antibody transfer
- Vaccination appears to be as effective in pregnancy as in other women, with the exception of the yellow fever vaccine
- Live vaccines have a theoretical risk of transplacental transmission and fetal infection, although there is minimal evidence of clinical effects. They are therefore contraindicated in pregnancy but may occasionally be used where there is high risk of disease
- Women should never be advised to terminate a pregnancy solely because of inadvertent vaccine administration
- Vaccinations missed during pregnancy should be received postpartum. Only yellow fever and smallpox vaccines are not recommended in breastfeeding;
- All pregnant women in the UK should be offered influenza vaccination for maternal and fetal benefit
- There was a pertussis outbreak in 2012 and a temporary recommendation is that all pregnant women should be offered vaccination for neonatal protection. This temporary recommendation was extended in 2014 for a further five years
- All healthcare providers should use every encounter with a pregnant women as a health promotion opportunity and should encourage maternal vaccination

FURTHER READING

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