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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. Data from the International Network of Obstetric Survey Systems relating to the COVID-19 pandemic showed that for all countries studied (the UK, the Netherlands, Norway, Denmark, Finland and Italy), at least 80% of pregnant women admitted to critical care were unvaccinated. In the UK this figure was 98%. 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 could have been prevented by the flu vaccine in pregnancy. Research is ongoing to develop additional vaccines for infections that 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 preventative medicine techniques and has the potential to reduce neonatal and maternal morbidity and mortality. As with any intervention during pregnancy, vaccination programmes may be complicated by safety, social and organisational concerns. For many medical conditions, pregnant women are consistently under treated or under investigated, largely due to both physician and patient concerns regarding potential harms to the fetus. As vaccines are used for disease prevention, there is often the misconception that vaccines should be deferred until after pregnancy. However, pregnant women and their babies can come to harm 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. Never has this been more evident than with respect to COVID-19 vaccination in pregnancy: a lack of involvement of pregnant and breastfeeding women in research and inconsistent messaging in the early part of the COVID-19 vaccination programme in the UK, have led to considerable vaccine hesitancy amongst pregnant women. This article aims to provide up to date guidance for practitioners advising women on vaccination during pregnancy.

General principles

Purpose of immunization

The rationale for vaccination in pregnancy may be either protection of the mother, protection of the fetus/neonate, or both. A period where women are accessing healthcare more regularly 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 infection and 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. Delaying neonatal vaccination until it will be more effective and simultaneously immunizing the mother, may achieve cost savings.

Safety

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 and are of no use for novel vaccines. The adverse impact of omitting pregnant and breastfeeding women from vaccine research has been highlighted during the COVID-19 pandemic. Widespread real-world use of vaccines during pregnancy in recent years, including influenza, pertussis and COVID-19, has resulted in a growing body of reassuring safety data on vaccination in pregnancy.

Live attenuated vaccines are contraindicated in pregnancy due to theoretical risk of transplacental transmission. 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.

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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 contra-indicated postpartum, or when breastfeeding. Smallpox, however, is no longer recommended for the general public (only for researchers who work with smallpox).

Efficacy

Pregnancy is a time of immunomodulation and concerns exist about the ability to mount adequate vaccine responses during pregnancy. So far, the evidence does not support this hypothesis.

With regards to passive immunity for the baby, IgG is actively transported across the placenta, primarily in the third trimester, providing the neonate with protective levels of antibodies. The efficacy of transfer is affected by many variables: placental transport favours IgG1 antibodies over IgG2, 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. Placental abnormalities, such as those caused by malaria or HIV, may reduce antibody transfer. T cell immunity does not appear to be transferred.

Some pregnant women may be taking immunomodulatory medications, for example in inflammatory bowel disease. They may have reduced seroconversion rates and immune responses to vaccines. They should still receive the same (non-live) vaccines as other pregnant women. The vaccine may have reduced efficacy, which the clinician should be mindful of. Neonates exposed *in utero* to biologics in the third trimester should not receive live attenuated vaccines for the first six months of life (avoid BCG and rotavirus vaccinations). They can receive other vaccines safely.

Timing (Table 1)

Pre-conception vaccination is optimal, providing the benefits of vaccination without any theoretical risk to the fetus. As at least 40% of UK pregnancies are unplanned, this is often not feasible and the first clinical interaction is usually post-conception. 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 risks to the fetus. Loss to follow up may, however, be high.

Should the balance of risks favour antenatal vaccination, then there is the question of optimal timing. As the first trimester is the time of organogenesis and has the highest teratogenic risk, traditionally vaccination during this time has been avoided. As it is also the time of greatest fetal loss, any intervention in this period risks implication in unrelated adverse outcomes. Where the primary purpose is prevention of maternal disease, administration has been recommended as soon as possible after commencement of the second trimester. However, there is no evidence of teratogenicity in any of the safety data for vaccinations used commonly in pregnancy: therefore, for conditions where the risks of infection in pregnancy are considerable (e.g. COVID-19), particularly if a course of vaccinations are required to achieve immunity, this advice should be waived. 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.

Vaccinations with specific relevance to pregnancy (Table 2)

COVID-19

COVID-19 infection in pregnancy is clearly associated with adverse outcomes for mother and baby. To 31 October 2021, MBRRACE-UK have reported 34 maternal deaths from COVID-19. Critical care admission is more likely than in non-pregnant age-matched controls: in England, Wales and Northern Ireland in 2020 there were 613,936 pregnancies, with a female population aged 16–49 years of 13,158,711. The duration of pregnancy plus the puerperium is 46 weeks, giving an annual pregnancy rate in women of childbearing age of 5.3%. Between 01/09/2020 and 27/01/2022 4631 women aged 16–49 were admitted to critical care with COVID-19. Of these 937 (20.2%) were pregnant or recently pregnant, suggesting a potential four-fold increase in the risk of critical care admission for pregnant women versus non-pregnant age-matched controls.

The data from Scotland suggest a considerable increase in extended perinatal mortality (to 28 days postpartum) amongst babies born to women with a COVID-19 infection within 28 days before birth: 22.6/1000 births, compared to a background rate, during the pandemic, of 5.9/1000 births. There are significant associations between COVID-19 infection in pregnancy and intrauterine growth restriction and preterm birth.

The mRNA vaccines (Pfizer-BioNTech and Moderna) are safe in pregnancy: no safety concerns have been revealed in real-world data in over 177,000 pregnancy women in the US and 84,000 women in England. The first dose of the AstraZeneca COVID-19 vaccination has, rarely, been associated with vaccine-induced immune thrombocytopenia and thrombosis (VITT), and so, at the time of writing, is not recommended for adults under 40 or pregnant women.

Vaccination appears to be protective against adverse outcomes. Scottish and UK Obstetric Surveillance System datasets both show that 98% of critical care admissions were unvaccinated. In the Scottish data, all the perinatal mortality in women with a recent or current COVID-19 infection occurred in unvaccinated women. The JCVI strongly recommends the mRNA vaccines at any stage of pregnancy if indicated (if unvaccinated, to complete a course or to receive a booster dose).

Influenza

Influenza in pregnancy and postpartum has a higher morbidity and mortality than in the general population, especially in the

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

third trimester. MBRRACE-UK, the confidential enquiry into maternal mortality, reported that one in eleven maternal deaths from 2009 to 2012 were due to influenza infection. At least half could have been prevented by influenza vaccination in pregnancy. These data included the swine flu epidemic, and happily in recent years the maternal death rates from influenza have been lower (in 2016–18 only two maternal deaths reported).

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. Unfortunately, current influenza vaccine uptake rates during pregnancy in the UK are suboptimal and potentially declining (reduced from 47.2% in 2017–2018 to 43.7% in 2019–20 and 43.6% in 2020–1).

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 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 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: they rely on passive immunity, generated by maternal immunization, 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. 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 vaccine is not an effective match to the actual influenza virus causing illness (due to antigenic drift) so health care

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	
COVID-19	mRNA (Pfizer/BioNTech and Moderna)		
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 foetal 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
Ebola	Live attenuated	Contraindicated Small dataset suggests no increase in adverse outcomes with vaccination	High rates of adverse maternal and fetal outcomes with infection, so should be considered if high risk of exposure

Table 2

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: 14 infant deaths were reported in England and Wales (the vast majority in infants under three months). Infants under three months are too young to be protected by their routine vaccinations, which are commenced at two months once their immune system is mature enough to mount a sufficient response. Vaccination of women in pregnancy (with a single dose) was therefore recommended. Observational and case-control studies have shown high vaccine effectiveness for infants (91%), and no increase in adverse pregnancy outcomes. The Joint Committee on Vaccination and Immunization (JCVI) has now incorporated this emergency vaccination programme into the routine schedule. The latest data (April–June 2021) suggest 64.5% uptake, with a wide range when disaggregated geographically (29.9%–80.5%).

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. Anti-pertussis antibodies have been shown to decline after one year so the vaccine is recommended in each pregnancy. Vaccination is advised between 16 and 32 weeks' gestation, and can be given at the same time as the influenza vaccine. Vaccination beyond 32 weeks may not offer as high a level of passive protection to the baby. Cumulative doses increase the likelihood of injection site reactions and fever. Should vaccination during 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).

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. Subsequently there has been a substantial reduction in mortality, with an estimated 25,000 neonatal deaths in 2018, down from 200,000 in 2000 (88% reduction) and 787,000 in 1988. 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. In December 2020, 12 countries still had to achieve this target; 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 immunisations, no action is required during pregnancy. However, all pregnant women will receive tetanus vaccination as a by-product of the pertussis vaccination programme (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, regardless of gestation. Ideally, 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. 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 32 weeks, to provide pertussis protection.

In low- and middle-income countries, guidelines differ but the WHO recommends 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 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 and 2019 (989 and 808 cases in England and Wales). The data for 2020 is much improved (79 cases), but is confounded by the precautions undertaken as a result of the COVID-19 pandemic.

All three diseases are associated with adverse fetal outcomes; measles increases the risk of prematurity, miscarriage, and possibly stillbirth. In the mother, measles may also be more severe in pregnancy and can develop into a potentially fatal

pneumonitis. 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.

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 (for example if they are due to undergo fertility treatment). 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 with infection before 28 weeks. Compared to rubella, this congenital syndrome is much rarer. It 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 contraindicated in pregnancy. Preconception consideration of vaccination is therefore recommended by the Royal College of Obstetricians and Gynaecologists (RCOG). 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.

Should 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 dataset 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 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 RCOG 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 aciclovir. These neonates are at high risk of varicella infection 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 any 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 (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. Women due the pneumococcal vaccine should receive it in the second or third trimester of pregnancy (there is insufficient safety data for 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, 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 low- and middle-income countries, however, which carry most of the disease burden.

Meningococcal B and C

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–Guérin (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 any theoretical risks 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, chloroquine, proguanil and Malarone® (atovaquone and proguanil) appear 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.

Polio

As with 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.

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.

Ebola

Ebola virus causes serious disease and there have been a number of outbreaks in recent years (most recently in the Democratic Republic of Congo). People can become infected through contact with blood, body fluids or organs of an infected person. There is currently no effective treatment for Ebola virus disease (EVD), but there are now two licensed vaccines: ERVEBO® (previously known as rVSV-ZEBOV) is a recombinant vesicular stomatitis virus-based vaccine expressing a Zaire Ebolavirus glycoprotein. This is a single dose vaccine now approved by the European Medicines Agency and the United States Food and Drug Administration. In the US three groups are eligible: EVD responders, biosafety level 4 workers and healthcare personnel involved in the care and transport of patients with EVD. The European Medicines Agency has approved a second vaccine, delivered in two doses given 8 weeks apart (Zabdeno® and Mvabea®) for individuals 1 year and older.

As both are viral vector vaccines, they would normally not be recommended in pregnancy. Pregnant women continue to be excluded from vaccination strategies at present. Small numbers of pregnant women have inadvertently been exposed to the ERVEBO® vaccine: no statistically significant differences in pregnancy outcome are reported. In EVD 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 EVD is high, the benefit of the vaccine would likely outweigh the risk.

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. 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 RCOG 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.

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 in pregnancy 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, pertussis and COVID-19 vaccination to continue to save lives: never has consistent messaging around vaccination safety in pregnancy been more important than during the current viral pandemic. ◆

FURTHER READING

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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.
- All pregnant women in the UK should be offered pertussis vaccination for neonatal protection.
- COVID-19 vaccination is safe in pregnancy, and so should not be withheld if indicated. It can be given at any stage of pregnancy.
- All healthcare providers should use every encounter with a pregnant woman as a health promotion opportunity and should encourage maternal vaccination