

Immunization in Pregnancy

This clinical practice guideline has been reviewed by the Infectious Diseases Committee and reviewed and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

PRINCIPAL AUTHORS

Andrée Gruslin, MD, Ottawa ON
 Marc Steben, MD, Montreal QC
 Scott Halperin, MD, Halifax NS
 Deborah M. Money, MD, Vancouver BC
 Mark H. Yudin, MD, Toronto ON

INFECTIOUS DISEASES COMMITTEE

Mark H. Yudin, MD (Chair), Toronto ON
 Marc Boucher, MD, Montreal QC
 Beatrice Cormier, MD, Montreal QC
 Andrée Gruslin, MD, Ottawa ON
 Deborah M. Money, MD, Vancouver BC
 Gina Ogilvie, MD, Vancouver BC
 Caroline Paquet, RM, Trois-Rivières QC
 Audrey Steenbeek, RN, Halifax NS
 Nancy Van Eyk, MD, Halifax NS
 Julie van Schalkwyk, MD, Vancouver BC
 Thomas Wong, MD, Ottawa ON

Disclosure statements have been received from all members of the committee.

guidelines developed by the Canadian Task Force on Preventive Health Care.

Benefits, Harms, and Costs: Implementation of the recommendations in this guideline should result in more appropriate immunization of pregnant and breastfeeding women, decreased risk of contraindicated immunization, and better disease prevention.

Recommendations

1. All women of childbearing age should be evaluated for the possibility of pregnancy before immunization. (III-A)
2. Health care providers should obtain an immunization history from all women accessing prenatal care. (III-A)
3. In general, live and/or live-attenuated virus vaccines are contraindicated during pregnancy, as there is a, largely theoretical, risk to the fetus. (II-3B)
4. Women who have inadvertently received immunization with live or live-attenuated vaccines during pregnancy should not be counselled to terminate the pregnancy because of a teratogenic risk. (II-2A)
5. Non-pregnant women immunized with a live or live-attenuated vaccine should be counselled to delay pregnancy for at least four weeks. (III-B)
6. Inactivated viral vaccines, bacterial vaccines, and toxoids are considered safe in pregnancy. (II-1A)
7. Women who are breastfeeding can still be immunized (passive-active immunization, live or killed vaccines). (II-1A)
8. Pregnant women should be offered the influenza vaccine when pregnant during the influenza season. (II-1A)

J Obstet Gynaecol Can 2008;30(12):1149–1154

Abstract

Objective: To review the evidence and provide recommendations on immunization in pregnancy.

Outcomes: Outcomes evaluated include effectiveness of immunization, and risks and benefits for mother and fetus.

Evidence: The Medline and Cochrane databases were searched for articles published up to June 2007 on the topic of immunization in pregnancy.

Values: The evidence obtained was reviewed and evaluated by the Infectious Diseases Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) under the leadership of the principal authors, and recommendations were made according to

Keywords: Pregnancy, immunization, live vaccine, live-attenuated vaccine, inactivated viral vaccine, bacterial vaccine, contraindications

INTRODUCTION

Immunization programs are among the most cost-beneficial health interventions. As women who are considering pregnancy or who are already pregnant present for health care consistently, obstetrical care providers are well placed to review their immunization status and recommend vaccination strategies. This can significantly reduce the occurrence of preventable diseases, benefiting not only the patient and her infant but also the rest of the population.

As pregnancy is considered to be an immunologically competent status, a full and unaltered response to immunization is expected.^{1,2} However, given the theoretical risks to the fetus following administration of vaccines, it is essential that

This document reflects emerging clinical and scientific advances on the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Local institutions can dictate amendments to these opinions. They should be well documented if modified at the local level. None of these contents may be reproduced in any form without prior written permission of the SOGC.

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of Evidence Assessment*	Classification of Recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.¹⁷

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.¹⁷

the obstetrical care provider counsel the pregnant woman with respect to the risks and benefits of vaccines, as well as potential exposure to the diseases the vaccines are expected to prevent. Appropriate information and counselling must also be provided in cases of inadvertent vaccination in pregnancy. This document reviews active and passive immunization, indications for and contraindications to such interventions in pregnancy, and suggested precautions. Finally, specific vaccines are discussed and recommendations made for their use in pregnancy (Table 2).

General Comments

Prenatal care providers should obtain a thorough immunization history. In many cases, women present for prenatal care having not had their immunization status reviewed since they completed the school-age vaccination schedule. Ideally, women should have their vaccination status optimized pre-pregnancy, so there would be no concern about coverage in pregnancy. However, if this is not possible, planning for vaccination in pregnancy with killed or recombinant vaccines or planning for vaccination post partum with live-attenuated vaccines is appropriate. Prenatal care

providers should also be aware of the risks, if any, of inadvertent vaccination during pregnancy.

The overall objective of immunization in pregnancy is to induce a state of immunity such that the woman and the fetus are protected following exposure to the offending organism. In addition, this offers an opportunity for protection of the neonate for the first 6 to 12 months of life. Vaccines may be prepared from various sources, including the inactivated agent, live attenuated agent, and modified and single antigen recombinant forms of the offending organism.

Immunizations can be either active or passive, depending on the characteristics of the agent used. Passive immunization is a process whereby the agent used has been obtained from serum from either a person or an animal already adequately immunized. From this process, antibodies can be obtained either as whole serum or as concentrated IgG and may be administered to the host to confer immediate protection. Active immunization relies on the administration of antigens and results in a prompt but transient IgM response in the host. This is followed by a rise in IgG antibody production that will be more or less sustained, explaining why for some vaccines, booster doses may be required for long-term immune memory. Of note, oral vaccines will stimulate IgA initially as opposed to IgM (parenteral).

Given the theoretical fetal risks associated with maternal immunization, an evaluation of potential risks of exposure to the infectious agent, as well as benefits of vaccination

ABBREVIATIONS

CRS	congenital rubella syndrome
HPV	human papilloma virus

should be performed before this intervention is considered. The type of vaccine required must also be taken into consideration as some may be clearly contraindicated.

REVIEW OF SPECIFIC VACCINE CATEGORIES

Live and Live-Attenuated Vaccines

In general, live and/or live-attenuated virus vaccines are contraindicated during pregnancy, as there is a primarily theoretical risk to the fetus. However, it is important to mention that, to date, there is no evidence to demonstrate a teratogenic risk from any currently available vaccines (e.g., mumps, measles, rubella varicella).^{3,4}

Rubella vaccine

The rubella virus is moderately infectious and clinically manifests as fever, malaise, lymphadenopathy, and upper respiratory symptoms followed by the appearance of a typical rash. Complications are more common in the adult and include arthralgia, arthritis, encephalitis, neuritis, and thrombocytopenic purpura. CRS is particularly severe and more common if it occurs early in pregnancy, with up to 85% of infants affected if infected in the first trimester. CRS may result in deafness, cataracts, cardiac defects, microcephaly, mental retardation, hepatosplenomegaly, bone damage, and thrombocytopenia. Furthermore, the effects may be delayed by several years, and children may present with diabetes or a progressive encephalopathy. The best way to eradicate CRS is to immunize all susceptible women and women without adequate proof of immunization. The obstetrical care provider is in a good position to identify susceptible women and to provide immunization post partum. The rubella vaccine alone and in combination (MMRII) is a live vaccine and therefore contraindicated during pregnancy. It is therefore suggested that women should delay pregnancy by one month following such immunization.

Inadvertent vaccination in pregnancy was reportable to the Centers for Disease Control and Prevention between 1971 and 1989. Analysis of the accumulated data revealed that subclinical infection was detected in 1% to 2% of fetuses but that there was no evidence of CRS in any of the 321 women inadvertently vaccinated who elected to continue their pregnancies.⁵ Therefore, in such situations, women should be reassured that ending the pregnancy is not necessary on the basis of fetal risks following maternal immunization. However, given the small theoretical fetal risk, immunization with the rubella vaccine is best delayed until after delivery. Neither breastfeeding nor anti-Rho(D) administration is a contraindication to immunization.

Varicella vaccine

Although varicella is relatively uncommon in the pregnant population (0.7 per 1000), it can result in very significant maternal and fetal morbidity and mortality. Despite improvements in clinical care, varicella may be complicated by pneumonia in up to 28% of pregnant women, and this remains associated with a risk of mortality. In a recent report of 198 cases of varicella in pregnancy, 16 deaths were reported, all in the group complicated by pneumonia.⁶ Furthermore, varicella in early pregnancy is associated with a 1% risk of congenital infection, which carries serious sequelae such as cerebral cortical atrophy, mental retardation, and dermatomal specific limb abnormalities.⁷ Maternal varicella occurring five days before to two days after delivery is associated with severe neonatal varicella in 17% to 30% of infants and a case fatality rate as high as 31%.⁸

These facts highlight the importance of adequate immunization in women of childbearing age and the influence obstetrical care practitioners can exert on the prevention of varicella in mother and fetus.

Immunity to varicella should be reviewed in the context of maternal health care, and vaccination should be recommended as soon as appropriate. Since the varicella vaccine is an attenuated virus vaccine (two preparations are available in Canada and both are live), it should not be given in pregnancy. A program of administration to susceptible post partum women should be developed. A second dose is recommended and should be administered approximately four weeks after the first.⁹

Breastfeeding is not a contraindication to vaccination, nor is household contact with a newborn.

A study of 362 women inadvertently exposed to varicella vaccine in pregnancy between 1995 and 2000 identified no cases of congenital varicella.¹⁰ It therefore does not constitute a reason to recommend pregnancy termination. Instances of inadvertent varicella immunization during pregnancy or of pregnancy occurring within three months after immunization should be reported to the pharmaceutical company.*

Non-pregnant women who are vaccinated should delay conception by one month.

Following exposure of a pregnant woman to varicella, a history of previous vaccination or of chickenpox itself should be sought, as it has been shown to correlate with immune status. In the absence of such a history, the mother's immunity should be determined. Susceptible women should then be offered varicella zoster immune globulin within 96 hours

*Immunization with Varivax III should be reported to Merck Frosst Canada, Medical Services (1-800-684-6686). Immunization with Varilrix should be reported to GlaxoSmithKline (1-800-387-7374).

Table 2. Indications for vaccine use in pregnancy

Vaccine	Indication for use in pregnancy	Comment
Live		
Measles	Contraindicated	No known fetal effects, but theoretical increased risk of preterm labour and low birthweight with live vaccine
Mumps	Contraindicated	As above-see text
Rubella	Contraindicated	As above-see text
Varicella	Contraindicated	No known fetal effects. Not reason for termination Varicella zoster immunoglobulin to be considered if pregnant woman exposed to virus
Poliomyelitis Sabin/ Salk	To be considered in high-risk situations (inactivated preparation)	Consider if pregnant woman needs immediate protection (high-risk situation/travel) No known fetal effects
Yellow fever	Generally contraindicated unless high-risk situation	No data on fetal safety, although fetuses exposed have not demonstrated complications Not a reason for pregnancy termination If travel to high-risk endemic area unavoidable, suggest vaccination
Influenza	Indicated in pregnancy, primarily for protection at > 20 weeks when risk is greatest	No adverse effects in over 2000 fetuses exposed Influenza may be associated with greater morbidity in pregnancy, so immunization recommended
Rabies	No indication of fetal anomalies	Risks from inadequate treatment significant Pregnancy not contraindication to post-exposure prophylaxis
Vaccinia	Contraindicated	Has been reported to cause fetal infection
Non-Live		
Hepatitis A	Low theoretical risk	Appropriate in the presence of medical indication
Hepatitis B	No apparent fetal risk	Vaccine recommended for pregnant women at risk
Pneumococcus	Indicated in high-risk patients	No safety data available, but no adverse effects reported; high-risk patients should therefore be vaccinated
Meningococcus	Safe and efficacious in pregnancy	Vaccine to be administered using same guidelines as for non-pregnant patients
Cholera	No data on safety	To be used if high-risk situation only (e.g., outbreak)
Plague	No data on safety	Vaccination to be considered only if benefits outweigh risk
Typhoid Some preparations are live	No data on safety	To be considered only in high-risk cases (e.g., travel to endemic areas)
Diphtheria/tetanus	No evidence of teratogenicity	Susceptible women to be vaccinated as per general guidelines for non-pregnant patients
Japanese encephalitis (inactivated Japanese encephalitis vaccine)	No data on safety	Not to be given routinely in pregnancy, as theoretical risk exists Consider only if travel where risk exposure is high (benefit > risk)

of exposure in an attempt to prevent the disease or reduce the severity of the infection in the mother. The recommended dosage is 125 units/10 kg to a maximum of 625 units. Although there may also be some benefit to the fetus, this remains to be investigated in a clinical trial.

Benefits versus risks

Given the possible risks, live and live-attenuated vaccines should not be given in pregnancy unless there are special circumstances and the benefits clearly outweigh the theoretical risks. For example, if a pregnant woman **must** travel to an endemic area for yellow fever, the vaccine may need to

be administered, even though it is a live attenuated vaccine, when the risk of exposure is high and the travel cannot be postponed. A recent report of 304 pregnant women exposed to yellow fever immunization in early pregnancy demonstrated that such exposure was not associated with an increase in major fetal malformation.¹¹

Inactivated Viral Vaccines, Bacterial Vaccines, and Toxoids

These vaccines are considered safe in pregnancy. The possible benefit of immunizing pregnant women must always be balanced against the potential risks of the vaccine. As there

is no evidence to suggest a risk to the fetus or to the pregnancy from maternal immunization with these agents, the benefit of their use generally far outweighs the theoretical risks.

Influenza vaccine

Influenza is a highly contagious acute respiratory infection. It is manifested clinically as an abrupt onset of malaise, headache, and myalgia followed by a cough, fever, and sore throat.

There is literature that suggests that pregnant women are at increased risk of complications from influenza.^{12,13} Pregnancy is associated with significant cardiovascular and respiratory demands, as evidenced by increases in stroke volume, heart rate, and oxygen consumption. This is highlighted in a 1998 study, which reported that the need for hospitalization was four times greater in pregnant than non-pregnant women with influenza.¹⁴

The risks were in fact calculated to be equivalent to those of non-pregnant women with high-risk conditions, for whom immunization has traditionally been recommended. Older data^{12,13} also suggest increased maternal risk, as previous reports of pandemics showed that morbidity and mortality was greater in pregnant women. Although the data are limited and more research is needed to clarify the maternal-fetal risks of influenza, current recommendations support immunization of pregnant women with the inactivated vaccine. There is debate about the appropriateness of immunization in the first trimester, so it may be prudent to delay immunization until the second trimester unless there is an immediate risk of transmission. Influenza is not known to be teratogenic. No adverse effects on perinatal outcome were observed in a cohort of 252 women vaccinated at a mean gestational age of 26.1 weeks.¹⁵ Current Canadian recommendations advocate universal immunization of pregnant women against influenza.

Another reason for immunization in pregnancy is the protection of the newborn after birth, which can be accomplished with passive immunity (transfer of maternal antibodies). Further, the most common way for infants to acquire influenza is from household contacts, so immunization of the mother can prevent her from acquiring influenza and potentially passing it on to her child.

Other Vaccines

Human papilloma virus

In Canada, the quadrivalent HPV vaccine was approved in July 2006 for the prevention of infection by HPV strains that are responsible for 70% of cervical cancers and 90% of genital warts. In February, 2007, after serious consideration, the National Advisory Committee on Immunization issued recommendations for the use of Gardasil for females aged 9 to 26.

Gardasil vaccine is manufactured using recombinant technology and uses a specific subunit of the virus L1, which then assembles into non-infectious virus-like particles. It specifically targets HPV 6, 11, 16, and 18, which are known to be associated with cervical, vulvar, and vaginal cancers and genital warts.

Although the vaccine is not recommended for use during pregnancy, there is no evidence that it is teratogenic.¹⁶ If a woman becomes pregnant part way through the vaccine series, it is recommended that the rest of the series be deferred until after pregnancy. The vaccine can be administered to women who are breastfeeding.¹⁶

SIDE EFFECTS AND CONTRAINDICATIONS

Vaccines may cause various side effects, which should not all be interpreted as contraindications. Side effects can be divided in five categories: (1) immediate/early, (2) local, (3) systemic, (4) allergic, and (5) long-term.

1. Immediate/early effects include fainting and vasovagal reactions. These are differentiated from anaphylactic shock (see below). Patients who have received the vaccine should be kept in the waiting room for observation for 5 to 10 minutes.
2. Local effects are mild and are the most common. They include soreness, erythema, and swelling.
3. Systemic effects are less common and include malaise and fever.
4. Mild allergic reactions can also occur. In general, these will be in reaction to exposure to avian proteins (eggs, such as in yellow fever) or to traces of neomycin/streptomycin (MMR). Anaphylactic reactions are exceedingly rare. They should be recognized immediately and treated following local protocols with injection of sc epinephrine (1:1000).
5. Long-term complications such as Guillain-Barre syndrome can occur but usually at rates lower than that seen for spontaneous disease.

Unfortunately, too often, vaccines are withheld on the basis of what is thought to be a contraindication.

The items on this list DO NOT represent contraindications to immunization

- Mild acute illness with or without low-grade fever
- Autoimmune disorder, multiple sclerosis
- Family history of convulsions, epilepsy
- Recent exposure to an infectious disease
- Current antimicrobial therapy or convalescence from recent illness
- Household contact with pregnant woman
- Breastfeeding

- Prior reaction to immunization with mild/moderate tenderness, redness, swelling, or fever of less than 40°C
- Personal history of allergies, excluding anaphylaxis, to neomycin/streptomycin or egg protein
- Family history of adverse reaction or allergies to vaccines
- Positive TB skin test

Two of these circumstances deserve additional discussion: household contact vaccination and breastfeeding. Although individuals immunized with live virus vaccines can shed the virus, they will not transmit it; therefore, household contacts of pregnant women can be safely vaccinated without risks to the mother and her fetus. Breastfeeding is also considered safe following immunization of the mother, and it has not been shown to adversely influence the maternal immune response. Therefore, breastfeeding does not represent a contraindication to any immunization: passive-active immunization, live vaccines, or killed vaccines.

Recommendations

The quality of evidence reported in this document has been assessed using the Evaluation of Evidence criteria in the Report of the Canadian Task Force on Preventive Health Care¹⁷ (Table 1).

1. All women of childbearing age should be evaluated for the possibility of pregnancy before immunization. (III-A)
2. Health care providers should obtain an immunization history from all women accessing prenatal care. (III-A)
3. In general, live and/or live-attenuated virus vaccines are contraindicated during pregnancy, as there is a, largely theoretical, risk to the fetus. (II-3)
4. Women who have inadvertently received immunization with live or live-attenuated vaccines during pregnancy should not be counselled to terminate the pregnancy because of a teratogenic risk. (II-2)
5. Non-pregnant women immunized with a live or live-attenuated vaccine should be counselled to delay pregnancy for at least four weeks. (III)
6. Inactivated viral vaccines, bacterial vaccines, and toxoids are considered safe in pregnancy. (II-1)
7. Women who are breastfeeding can still be immunized (passive-active immunization, live or killed vaccines). (II-1)
8. Pregnant women should be offered the influenza vaccine when pregnant during the influenza season. (II-1)

CONCLUSION

The development of new vaccines and the accumulating information about vaccine safety ensure that

obstetrician-gynaecologists can provide immunizations and/or advice about immunization for their pregnant patients. This is most important in disease prevention, and obstetrician-gynaecologists must play an active role in vaccine administration. Furthermore, it is imperative that more research efforts be focused in the area of immunization in pregnancy.

REFERENCES

1. Miller JK. The prevention of neonatal tetanus by maternal immunization. *J Trop Pediatr Environ Child Health* 1972;18(2):159–67.
2. Heinonen OP, Shapiro S, Monson RR, Hartz SC, Rosenberg I, Slone D. Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. *Int J Epidemiol* 1973;2(3):229–35.
3. Munoz FM, Englund JA. Vaccines in pregnancy. *Infect Dis Clin North Am* 2001;15(1):253–71.
4. Heinonen OP, Slone D, Shapiro S. Immunizing agents. Kaufman DW, ed. *Birth defects and drugs in pregnancy*. Littleton, MA: Publishing Sciences Group;1997:314–21.
5. Centers for Disease Control and Prevention. Measles, mumps and rubella vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations for the advisory committee on immunization practices (ACIP). *MMWR Recomm Rep* 1998;47(RR-8).
6. Gershon AA. Chicken pox, measles and mumps. In: Remington JS, Klein JO, eds. *Infectious diseases of the fetus and newborn infant*. Philadelphia: WB Saunders;2001:683.
7. Harger JH, Ernest JM, Thurnau GR, Moawad A, Thom E, Landon MB, et al.; National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Frequency of congenital varicella syndrome in a prospective cohort of 347 pregnant women. *Obstet Gynecol* 2002;100(2):260–5.
8. Denicola LK, Hanshaw JB. Congenital and neonatal varicella. *J Pediatr* 1979;94(1):175–6.
9. National Advisory Committee on Immunization. *Canadian immunization guide 2006*. 7th ed. Available at: <http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php>. Accessed January 2008.
10. Shields KE, Galil K, Seward J, Sharrar RG, Cordero JF, Slater E. Varicella vaccine exposure during pregnancy: data from the first 5 years of the pregnancy registry. *Obstet Gynecol* 2001; 98(1):14–9.
11. Cavalcanti DP, Salomão MA, Lopez-Camelo J, Pessoto MA; Campinas Group of Yellow Fever Immunization During Pregnancy. Early exposure to yellow fever vaccine during pregnancy. *Trop Med Int Health* 2007;12(7):833–7.
12. Harris JW. Influenza occurring in pregnant women: a statistical study of thirteen hundred and fifty cases. *JAMA* 1919;72(978):980.
13. Freeman DW, Barno A. Deaths from Asian influenza associated with pregnancy. *Am J Obstet Gynecol* 1959;78:1172–5.
14. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffen MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. *Am J Epidemiol* 1998;148:1094–102.
15. Munoz FM, Greisinger AJ, Wehmanane OA, Mouzoon ME, Hoyle JC, Smith FA, et al. Safety of influenza vaccination during pregnancy. *Am J Obstet Gynecol* 2005;192:1098–106.
16. Dawar M, Dobson S, Deeks S. Literature review on HPV 6, 11, 16 and 18: disease and vaccine characteristics. Public Health Agency of Canada 2007. Available at: http://www.phac-aspc.gc.ca/naci-ceni/lr-sl_2-eng.php. Accessed April 2008.
17. Woolf SH, Batista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. *CMAJ* 2003;169(3):207–8.