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Management of Varicella Infection (Chickenpox) in Pregnancy

This Clinical Practice Guideline has been prepared by the Maternal Fetal Medicine Committee, reviewed by the Infectious Diseases Committee and the Family Physician Advisory Committee, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To review the existing data regarding varicella zoster virus infection (chickenpox) in pregnancy, interventions to reduce maternal complications and fetal infection, and antepartum and peripartum management.

Methods: The maternal and fetal outcomes in varicella zoster infection were reviewed, as well as the benefit of the different treatment modalities in altering maternal and fetal sequelae.

Evidence: Medline was searched for articles and clinical guidelines published in English between January 1970 and November 2010.

Values: The quality of evidence was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care. Recommendations for practice were ranked according to the method described in that report (Table).

Recommendations

1. Varicella immunization is recommended for all non-immune women as part of pre-pregnancy and postpartum care. (II-3B)
2. Varicella vaccination should not be administered in pregnancy. However, termination of pregnancy should not be advised because of inadvertent vaccination during pregnancy. (II-3D)
3. The antenatal varicella immunity status of all pregnant women should be documented by history of previous infection, varicella vaccination, or varicella zoster immunoglobulin G serology. (III-C)
4. All non-immune pregnant women should be informed of the risk of varicella infection to themselves and their fetuses. They should be instructed to seek medical help following any contact with a person who may have been contagious. (II-3B)
5. In the case of a possible exposure to varicella in a pregnant woman with unknown immune status, serum testing should be performed. If the serum results are negative or unavailable within 96 hours from exposure, varicella zoster immunoglobulin should be administered. (III-C)
6. Women who develop varicella infection in pregnancy need to be made aware of the potential adverse maternal and fetal sequelae, the risk of transmission to the fetus, and the options available for prenatal diagnosis. (II-3C)
7. Detailed ultrasound and appropriate follow-up is recommended for all women who develop varicella in pregnancy to screen for fetal consequences of infection. (III-B)

8. Women with significant (e.g., pneumonitis) varicella infection in pregnancy should be treated with oral antiviral agents (e.g., acyclovir 800 mg 5 times daily). In cases of progression to varicella pneumonitis, maternal admission to hospital should be seriously considered. Intravenous acyclovir can be considered for severe complications in pregnancy (oral forms have poor bioavailability). The dose is usually 10 to 15 mg/kg of BW or 500 mg/m^2 IV every 8 h for 5 to 10 days for varicella pneumonitis, and it should be started within 24 to 72 h of the onset of rash. (III-C)
9. Neonatal health care providers should be informed of peripartum varicella exposure in order to optimize early neonatal care with varicella zoster immunoglobulin and immunization. (III-C) Varicella zoster immunoglobulin should be administered to neonates whenever the onset of maternal disease is between 5 days before and 2 days after delivery. (III-C)

INTRODUCTION

Varicella zoster virus is a highly contagious DNA virus of the herpes family. It is transmitted by respiratory droplets and by direct personal contact with vesicular fluid. The primary infection is characterized by fever, malaise, and a pruritic rash that develops into crops of maculopapules, which become vesicular and crust over before healing. The incubation period lasts 10 to 21 days, and the disease is infectious 48 hours before the rash appears and continues to be infectious until the vesicles crust over.[1]

Chickenpox (or primary VZV infection) is a common childhood disease. In this population it usually causes mild infection, and mortality rates in the United States are as low as 0.4 per 1 million population.[2] It is estimated that > 90% of the antenatal population are seropositive for VZV IgG antibody[3] and therefore almost invariably immune to infection. Because of this high frequency of immunity, contact with chickenpox among pregnant women rarely results in primary maternal VZV infection, which is estimated to complicate up to 2 to 3 of every 1000 pregnancies.[4] Therefore in Canada, with about 350 000 pregnancies per year,[5] 700 to 1050 cases of chickenpox in pregnant women are expected to occur annually.

Following the primary infection, the virus may remain dormant in sensory nerve root ganglia but can be reactivated to cause a vesicular erythematous skin rash in a dermatomal distribution known as herpes zoster or shingles. As shingles in pregnancy is not associated with viremia and does not appear to cause fetal sequelae, it is not discussed in these guidelines.

ABBREVIATIONS

IgG	immunoglobulin G
VZIG	varicella zoster immunoglobulin
VZV	varicella zoster virus

POSSIBLE SEQUELAE OF VARICELLA INFECTION IN PREGNANCY: MATERNAL

The mortality rate for chickenpox increases with age. Thus in early adulthood it is associated with mortality rate that is 15 times higher than the childhood mortality rate.[6] According to the Centers for Disease Control and Prevention, the case fatality rate increases from 2.7 per 100 000 persons aged 15 to 19 years, to 25.2 per 100 000 persons aged 30 to 39.[7] Mortality rates are higher in pregnant women than in non-pregnant adults, and death usually results from respiratory disease. It is estimated that 5% to 10% of pregnant women with varicella infection develop pneumonitis.[8] Risk factors for the development of varicella pneumonitis in pregnancy include cigarette smoking and > 100 skin lesions.[9] Most of the complications of adult chickenpox, such as pneumonitis occur on day 4 or later.[10] In one prospective study,[11] 12 out 21 pregnant patients who were diagnosed with varicella pneumonitis and treated with acyclovir in the second or third trimester of pregnancy required intubation and mechanical ventilation. The strongest correlate with maternal death was onset of disease in the third trimester, with no deaths among the second-trimester subjects.

POSSIBLE SEQUELAE OF VARICELLA INFECTION IN PREGNANCY: FETAL

Fetal effects of varicella can manifest as either congenital varicella syndrome (embryopathy) or neonatal varicella (no embryopathy, but chickenpox infection within the first 10 days of life). Since the first described cases in 1947, the overall number of neonates that have been reported to have congenital varicella syndrome is as low as 41 per year in the United States, 4 per year in Canada, and 7 per year in the United Kingdom and Germany.[12,13] Maternal varicella during the first half of pregnancy may cause congenital malformations or deformations by transplacental infection. Some of these manifestations include chorioretinitis, cerebral cortical atrophy, hydronephrosis, and cutaneous and bony leg defects, often presenting as a partial limb reduction.[14] Rates of infection are approximately 0.4% before 13 weeks and 2% between 13 and 20 weeks.[4,15] In a systematic review by the Motherisk program (Canadian data), with all available cohort studies, the risk was 0.7% in the first trimester, 2% in the second, and 0% in the third trimester.[16] In most of the cohorts, there was no clinical evidence of congenital varicella embryopathy after 20 weeks' gestation.[17] Yet, Tan and Koren reviewed the literature and identified 9 case reports of fetal varicella syndrome occurring in weeks 21 to 28 of gestation.[12] In 8 out of these 9 cases there were serious adverse effects in the central nervous system, an incidence as high as the rates of central nervous system involvement in earlier trimesters.[13]

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
	E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	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.[36]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[36]

Findings that can be seen on ultrasound include musculoskeletal abnormalities seen as asymmetric limb shortening or malformations, chest wall malformations, intestinal and hepatic echogenic foci, intrauterine growth restriction, polyhydramnios, fetal hydrops, or fetal demise. Cerebral anomalies documented with ultrasound include ventriculomegaly, hydrocephalus, microcephaly with polymicrogyria, and porencephaly. Congenital cataract and microphthalmos are the most common ocular lesions but are not readily visible on ultrasound.[18] In most of the relevant studies, ultrasound findings suggestive of congenital varicella syndrome were detected in the majority of the affected fetuses.[19,20]

PERIPARTUM EXPOSURE

Exposure of the baby to the virus just before or during delivery poses a serious threat to the neonate, which may develop a fulminant neonatal infection (neonatal varicella). Rarely, these neonates can develop disseminated visceral and central nervous system disease, which is commonly fatal. Neonatal infection occurs primarily when symptoms of maternal infection occur less than 5 days before delivery to 2 days after.[21] This period correlates with the development of maternal IgG and is therefore too short to provide transplacental passive immunization to the fetus and neonate. When varicella zoster immune globulin is administered to the mother, 30% to 40% of newborns still develop infection; however, the number of complications is reduced.[22]

PREVENTION OF MATERNAL COMPLICATIONS

The efficacy of antiviral therapy in treating varicella pneumonia in adults has not been uniformly established through randomized clinical trials, and its efficacy has been debated.[23] However, in one study, oral acyclovir was shown to be more effective than placebo in reducing the duration of fever and symptoms of varicella infection in immunocompromised children and immunocompetent adults if commenced within 24 hours of development of the rash.[24,25] As a result it is generally recommended that children at high risk and adults with a substantive varicella infection (> 100 lesions) and/or respiratory co-factors should be treated with oral antivirals. Pregnant women with varicella pneumonitis should definitely be treated with oral antivirals and, if level of illness warrants, with IV antivirals.

PREVENTION OF INTRAUTERINE INFECTION

Definition of Significant Exposure

Direct contact exposure is defined as direct contact that lasts an hour or longer with an infectious person while indoors. Substantial exposure for hospital contacts consists of sharing the same hospital room with an infectious patient or prolonged, direct, face-to-face contact with an infectious person (e.g., health care workers). Brief contacts with an infectious person (e.g., contact with X-ray technicians or housekeeping personnel) are less likely than more prolonged contacts to result in VZV transmission.

Persons with continuous exposure to household members who have varicella are at greatest risk for infection.[7]

Vaccine

An attenuated live-virus vaccine (Varivax) was approved for use in 1995.[26] Two doses, given 4 to 8 weeks apart, are recommended for adolescents ≥ 13 years of age and for adults with no history of varicella. This results in 97% seroconversion.[27] The vaccine, however, is not recommended for pregnant women or for those within a month of pregnancy. Nevertheless, a pregnancy registry listing 362 vaccine-exposed pregnancies has reported no case of congenital varicella syndrome or other congenital malformation.[28] Therefore, termination of pregnancy should not be recommended because of inadvertent vaccination during pregnancy.

Varicella Zoster Immunoglobulin

As prevention is the most effective strategy for the reduction of maternal complications associated with varicella infections, immunoglobulin prophylaxis is an important objective for susceptible, exposed pregnant women.[23]

VZIG has been shown to lower varicella infection rates if administered within 72 to 96 hours after exposure.[4] The effectiveness of VZIG when given beyond the 96 hours after initial exposure has not been evaluated. Protection is estimated to extend through 3 weeks, which corresponds with the half-life of the immunoglobulin. The principal indication for the use of VZIG in pregnant women is reduction of the maternal risks of varicella infection-related complications associated with adult disease.[4] If the mother does not acquire varicella infection, this eliminates risk for the neonate, but this has not been studied as an end point because of the low frequency of cases. The dose is 125 units per 10 kg given intramuscularly, with a maximum dose of 625 units. VZIG is recommended[7] for all susceptible pregnant women.[29]

To determine if an exposed pregnant woman is susceptible, a history of varicella infection should be taken, and, if this is positive, the woman can be assumed to be immune. If the history is negative and no varicella antibody testing was done in early pregnancy, antibody testing with enzyme-linked immunosorbent assay or fluorescent antibody to membrane antigen should, if possible, precede use of VZIG. However, in settings where pregnant women might be tested too late and/or results may not be available quickly, using VZIG before antibody testing results are available might be practical.

The value of VZIG in averting fetal varicella is primarily in its ability to prevent maternal infection, but it may have some effect in decreasing the risk of fetal infection even in those women who go on to develop varicella. In a study of 1373 women who had varicella during pregnancy, 9 cases of congenital varicella syndrome were identified, all occurring after maternal varicella during the first 20 weeks of gestation. However, no cases of congenital varicella syndrome were reported in any of the 97 women in whom varicella occurred after post-exposure prophylaxis with anti-VZIG.[4,30,31]

The most frequent adverse reaction following VZIG administration is local discomfort at the injection site, with pain, redness, and swelling occurring in approximately 1% of people.[32] Less frequent adverse events include gastrointestinal symptoms, malaise, headache, rash, and respiratory symptoms, which occur in approximately 0.2% of recipients. Severe events, such as angioneurotic edema and anaphylactic shock, are rare (occurring in < 0.1% of recipients). Obstetrical care providers need to be aware of the availability of testing and therapy in their local environment. As both testing and therapy are time sensitive, it is important to know the turnover time for the test in local laboratories, and how to arrange VZIG administration. As VZIG is a blood product, patient consent is required.

TREATMENT

Acyclovir

Acyclovir is a synthetic nucleoside analogue that inhibits replication of human herpes viruses, including VZV. Acyclovir crosses the placenta readily and can be found in fetal tissues, cord blood as well as in the amniotic fluid. It may inhibit viral replication during maternal viremia, limiting transplacental passage of the virus.[33,34]

Safety

Data published since acyclovir became available do not indicate increased adverse effects related to its use in pregnancy.[35]

Efficacy

When compared with placebo, oral acyclovir reduces the duration of fever and symptoms of varicella infection in immunocompromised children and immunocompetent adults if commenced within 24 hours of development of the rash.[24,25] In instances of serious, viral-mediated complications (e.g., pneumonitis), the American Academy of Pediatrics states that intravenous acyclovir should be considered.[7] It is not given as prophylaxis to exposed women during pregnancy.

Recommendations

1. Varicella immunization is recommended for all non-immune women as part of pre-pregnancy and postpartum care. (II-3B)
2. Varicella vaccination should not be administered in pregnancy. However, termination of pregnancy should not be advised because of inadvertent vaccination during pregnancy. (II-3D)
3. The antenatal varicella immunity status of all pregnant women should be documented by history of previous infection, varicella vaccination, or varicella zoster immunoglobulin G serology. (III-C)
4. All non-immune pregnant women should be informed of the risk of varicella infection to themselves and their fetuses. They should be instructed to seek medical help following any contact with a person who may have been contagious. (II-3B)
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6. Women who develop varicella infection in pregnancy need to be made aware of the potential adverse maternal and fetal sequelae, the risk of transmission to the fetus, and the options available for prenatal diagnosis. (II-3C)
7. Detailed ultrasound and appropriate follow-up is recommended to all women who develop varicella in pregnancy to screen for fetal consequences for infection. (III-B)
8. Women with significant (e.g., pneumonitis) varicella infection in pregnancy should be treated with oral antiviral agents (e.g., acyclovir 800 mg 5 times daily). In cases of progression to varicella pneumonitis, maternal admission to hospital should be seriously considered. Intravenous acyclovir can be considered for severe complications in pregnancy (oral forms have poor bioavailability). The dose is usually 10 to 15 mg/kg of BW or 500 mg/m^2 IV every 8 h for 5 to 10 days for varicella pneumonitis, and it should be started within 24 to 72 h of the onset of rash. (III-C)
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