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Prenatal Invasive Procedures in Women With Hepatitis B, Hepatitis C, and/or Human Immunodeficiency Virus Infections

This guideline has been prepared by the Genetics Committee, reviewed by the Infectious Disease 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 risk of in utero infection through prenatal invasive procedures in women with hepatitis B, hepatitis C, and/or human immunodeficiency virus (HIV) infections.

Outcomes: Fetal and neonatal morbidity and mortality.

Evidence: Published literature was retrieved through searches of Medline, CINAHL, and the Cochrane Library using appropriate controlled vocabulary (amniocentesis, chorionic villus sampling, cordocentesis, fetal and neonatal infection) and key words (hepatitis B, hepatitis C, HIV). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies from 2002 to 2012 published in English or French. (Studies from 1966 to 2002 were previously reviewed in Clinical Practice Guideline No. 123.) Searches were updated on a regular basis and incorporated in the guideline to February 2014.

Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table).

Recommendations

1. For women infected with hepatitis B, hepatitis C, and/or human immunodeficiency virus, the use of non-invasive methods of prenatal risk assessment is recommended, using tests with high sensitivity and low false-positive rates, such as serum screening combined (or not) with nuchal translucency, anatomic ultrasound, and non-invasive molecular prenatal testing. (III-B)

Key Words: Pregnancy, genetics, amniocentesis, chorionic villus sampling, viral hepatitis, human immunodeficiency virus, prenatal diagnosis

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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.[35]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[35]

2. For women infected with hepatitis B, hepatitis C, and/or human immunodeficiency virus undergoing an amniocentesis, every effort should be made to avoid inserting the needle through, or very close to, the placenta. (II-2B)
3. Little information is available on other prenatal diagnostic and therapeutic invasive procedures; the risks and benefits of such procedures should therefore be assessed prior to their use. (III-C)
4. The rate of neonatal hepatitis B infection attributable to amniocentesis ranges up to 1.4% in newborns of mothers positive for hepatitis B surface antigen. However, the rate of neonatal infection attributable to amniocentesis in newborns of mothers with a positive hepatitis B *e* antigen status may be as high as 16%. Although there is no statistically significant difference between the rates of infection in newborns exposed to amniocentesis or not exposed to amniocentesis in these two maternal populations, knowledge of the mother's hepatitis B *e* antigen status may be valuable in counselling women about the risks associated with amniocentesis. (II-2A)
5. Amniocentesis in women infected with hepatitis C does not appear to significantly increase the risk of vertical transmission, but women should be counselled that very few studies have properly addressed this possibility (II-2C). More research on this topic is recommended. (III-L)
6. Amniocentesis in women infected with human immunodeficiency virus on combination antiretroviral therapy does not appear to significantly increase the risk of vertical transmission, particularly if the viral load is undetectable, but women should be counselled that data on this issue is limited. (II-2B)
7. For women not on combined antiretroviral therapy, the risk of vertical transmission is increased by performing an amniocentesis. When possible, combined antiretroviral therapy should be initiated and the procedure postponed until the viral load is undetectable. Other case management should be individualized in consultation with infectious diseases specialists and obstetricians. (III-B)

INTRODUCTION

These guidelines are designed to address the risks of in utero infection (vertical transmission) through prenatal invasive procedures in women infected with hepatitis B, hepatitis C, and/or HIV so that obstetric care providers may better counsel these women about their options.

ASSESSMENT OF RISK AND AMNIOCENTESIS

For women infected with hepatitis B, hepatitis C, or HIV, the addition of non-invasive methods of prenatal risk screening, such as serum screening combined (or not) with nuchal translucency, and anatomic ultrasound, provide the best risk assessment possible to properly inform women of their risk of chromosomal anomalies. The best available test should be used to keep the false-positive rate to a minimum. None of these infections seems to be associated with a significant increase in vertical transmission when amniocentesis is performed in the settings described below. The use of NIPT using cell-free DNA technology could be based on the same indications as in women without these chronic infections.

Women whose risk of vertical transmission is significantly higher than in those not exposed to an invasive procedure (such as HIV-infected women not on cART) should be considered for NIPT prior to any confirmatory invasive testing, after being counselled on the benefits and limitations of the test. NIPT provides higher sensitivity (close to 100%) and a lower false-positive rate (around 1%) when screening for trisomy 13, 18, or 21 in a high-risk population than the most frequently used screening

methods (such as serum based screening or first trimester screening). Because of its lower false-positive rate, it can therefore reduce the number of amniocenteses performed. Currently NIPT does not routinely screen for other chromosomal anomalies that are found more often in women who screen positive with the first-line screening approaches. It is often used as a secondary test prior to invasive testing or as a primary test in a high-risk population based on age or previous history.[1] Data on the accuracy of the test in a general population is limited. It has not been studied specifically in a population with a chronic viral infection or on antiretroviral medications.

In planning for an amniocentesis for women infected with hepatitis B, hepatitis C, and/or HIV undergoing amniocentesis, every effort should be made to avoid inserting the needle through the placenta, as was the case in all the series described in this guideline.

Limited information is available on procedures other than amniocentesis in this population, therefore this guideline focuses specifically on that procedure.

Recommendations

1. For women infected with hepatitis B, hepatitis C, and/or human immunodeficiency virus, the use of non-invasive methods of prenatal risk assessment is recommended, using tests with high sensitivity and low false-positive rates, such as serum screening combined (or not) with nuchal translucency, anatomic ultrasound, and non-invasive molecular prenatal testing. (III-B)
2. For women infected with hepatitis B, hepatitis C, and/or human immunodeficiency virus undergoing an amniocentesis, every effort should be made to avoid inserting the needle through, or very close to, the placenta. (II-2B)
3. Little information is available on other prenatal diagnostic and therapeutic invasive procedures; the risks and benefits of such procedures should therefore be assessed prior to their use. (III-C)

ABBREVIATIONS

cART	combined antiretroviral therapy
CVS	chorionic villus sampling
DNA	deoxyribonucleic acid
HBeAg	hepatitis B *e* antigen
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
NIPT	non-invasive molecular prenatal testing
RNA	ribonucleic acid

HEPATITIS B

In women presenting for prenatal care, hepatitis B has a prevalence of 0.34% to 1.1%.[2–4] The rate of vertical transmission in HBsAg-positive women without immunoprophylaxis is approximately 15%, and may be as high as 90% in those women who are HBsAg- and HBeAg-positive. With appropriate immunoprophylaxis, the rate of vertical transmission drops to 1.5% for women who are HBsAg-positive and to 10% for women who are HBsAg- and HBeAg-positive.[5] Genetic amniocentesis has been reported in 115 HBsAg positive-women.[6–9] Most amniocenteses were performed with care to avoid a transplacental approach. All the infants of these pregnancies received hepatitis B vaccination and immunoprophylaxis commencing at birth. The overall rate of vertical transmission was 2.9%. This rate of immunoprophylaxis failure is consistent with rates seen in women who have not undergone amniocentesis.[10] In one series, 3 infants (30%) of mothers who were HBeAg-positive demonstrated postnatal seroconversion following an amniocentesis, compared with 14% for those whose HBeAg-positive mothers did not have an amniocentesis ($P > 0.05$).[9] These findings would suggest that the risk of fetal hepatitis B infection through amniocentesis is low. However, knowledge of the mother's HBeAg-status may be valuable when counselling on the risks associated with amniocentesis, as the transmission rate may be higher in HBeAg-positive women.

No available studies report on vertical transmission in this population using other prenatal invasive procedures (such as CVS or fetal blood sampling) or assess preventive strategies (such as hepatitis B immunoglobulin and antiviral therapies) prior to invasive prenatal procedures.

Recommendation

4. The rate of neonatal hepatitis B infection attributable to amniocentesis ranges up to 1.4% in newborns of mothers positive for hepatitis B surface antigen. However, the rate of neonatal infection attributable to amniocentesis in newborns of mothers with a positive hepatitis B *e* antigen status may be as high as 16%. Although there is no statistically significant difference between the rates of infection in newborns exposed to amniocentesis or not exposed to amniocentesis in these two maternal populations, knowledge of the mother's hepatitis B *e* antigen status may be valuable in counselling women about the risks associated with amniocentesis. (II-2A)

HEPATITIS C

The prevalence of hepatitis C varies greatly between populations. Generally, the prevalence in women of

reproductive age is 1% to 2%.[11,12] A British Columbia study reported a prevalence of HCV infection of around 0.9% in the pregnant population, although only half of those women would have been detected through testing based on risk-factors.[13] In women in the Canadian federal penitentiary system, however, the prevalence is 40%,[14] and in antenatal clinics in Scotland it is 0.6%.[14] The rate of vertical transmission is approximately 5% to 10%.[15–18] The exact timing of vertical transmission is unknown, but elective Caesarean section does not appear to be preventive.[18] The risk of vertical transmission appears to be increased in women whose hepatitis C is associated with active liver disease, in those whose level of HCV RNA is greater than 10^6/mL, and in women co-infected with HIV.[15,18] Only a few series discuss the use of amniocentesis in pregnant women infected with HCV. One series reported the use of amniocentesis in 22 women with hepatitis C, of whom 16 had HCV RNA identified in their serum. All women (median age 39 years) underwent amniocentesis in the 4th month of pregnancy.[19] The amniotic fluid samples were tested using polymerase chain reaction for HCV RNA. Of the 16 viremic women, HCV RNA was detected in the amniotic fluid of only one, whose placenta was anterior. On postnatal testing, none of the children from these pregnancies, including the child from the pregnancy with HCV RNA-positive amniotic fluid, was found to be HCV RNA-positive.[19] A case–control study, published as an abstract only, of factors involved in vertical transmission reported a similar rate of amniocentesis in infected (8/51) and non-infected (28/110) children.[20] In contrast, a case series of 44 vertically infected children reported a history of amniocentesis in 10 (22.5%) of the pregnancies, a rate higher than seen in the general population.[21] Finally, Minola et al. reported a case of a twin pregnancy in which only one sac was sampled, and only that one fetus was infected at 12 months of age.[22] Although the 2 best studies are somewhat reassuring, little is learned from these series, as the various methodologies do not allow for a meta-analysis. In summary, amniocentesis in women infected with hepatitis C does not significantly increase the risk of vertical transmission, but women should be counselled that very few studies have properly addressed this possibility, nor have factors that could affect the transmission rate been well studied.

There are no studies available on other prenatal invasive procedures such as CVS or fetal blood sampling.

Recommendation

5. Amniocentesis in women infected with hepatitis C does not appear to significantly increase the risk of vertical transmission, but women should be counselled that very few studies have properly addressed this possibility (II-2C). More research on this topic is recommended (III-L).

HUMAN IMMUNODEFICIENCY VIRUS

The prevalence of HIV in an obstetric population varies greatly, depending on the population studied. The reported prevalence in British Columbia is 0.03%, while in some inner city populations in the United States, the prevalence is as high as 1.5%.[23,24] The AIDS Clinical Trials Group 076 study clearly demonstrated a 26% vertical transmission rate, which was lowered to 8% in patients who received antepartum, intrapartum, and neonatal zidovudine therapy.[25] Many HIV-positive women are now taking cART.[26] In those, the vertical transmission rate has decreased to less than 1%.[27]

In a French series of 1632 HIV-positive women, of whom only 5% received antenatal zidovudine therapy, the rate of vertical transmission was 19%.[28] Amniocentesis was performed on 13 women and amnioscopy on 26 women, with a vertical transmission rate of 36%. This rate was significantly higher than that observed in women who did not have invasive needling procedures (18%). Five series reporting on a total of 159 women on cART provide contemporary data on this topic. No case of vertical transmission was reported in those series for women having undergone an amniocentesis while on cART.[29] A contemporaneous French cohort of 2528 women on cART who had not had an amniocentesis had a reported 1.2% transmission rate.[30] With this reassuring data, experts now suggest that indicated amniocentesis should not be avoided in women with HIV who are on cART, particularly if their viral loads are low, but that the best non-invasive screening available should be used prior to invasive testing by amniocentesis.

López and Coll suggest that 2 weeks of cART prior to the amniocentesis were sufficient to provide the therapy's observed benefit of reduced vertical transmission.[29] Others recommend waiting for an undetectable viral load before proceeding.[31] These factors should be considered in the choice of antiretroviral, which should be made in consultation with infectious diseases specialists and obstetrical care providers. For example, raltegravir could be used to rapidly decrease a high maternal viral load before the amniocentesis.[32]

Somigliana et al. reported in their series 3 women having undergone CVS and 4 having undergone a cordocentesis, all while on cART.[33] No cases of vertical transmission were reported in those 7 women. With such limited data, however, the use of these procedures cannot be recommended if amniocentesis is an option, because more data is available on amniocentesis.

Recommendations

6. Amniocentesis in women infected with human immunodeficiency virus on combination antiretroviral therapy does not appear to significantly increase the risk of vertical transmission, particularly if the viral load is undetectable, but women should be counselled that limited data is available on this issue. (II-2B)
7. For women not on combined antiretroviral therapy, the risk of vertical transmission is increased by performing an amniocentesis. When possible, combined antiretroviral therapy should be initiated and the procedure postponed until the viral load is undetectable. Other case management should be individualized in consultation with infectious diseases specialists and obstetricians. (III-B)

RISK OF AMNIOTIC FLUID CONTAMINATION AT AMNIOCENTESIS

Contamination of the fetal amniotic cavity with maternal blood during amniocentesis is common.[34] In a study by Giorlandino et al., 20 women underwent a second amniocentesis 2 weeks after the original amniocentesis because of cell culture contamination.[34] At the second amniocentesis all 20 were found to have maternal blood contamination in the amniotic fluid based on red blood cell and hemoglobin concentrations.[34] The amniotic fluids of women undergoing their first amniocentesis were used as matched control subjects and no maternal blood contamination was found at the onset of the procedure. The amount of maternal blood in the amniotic fluid was significantly increased when an anterior placenta was present.[34]

CONCLUSION

There is a critical lack of evidence to determine the impact of prenatal invasive procedures on the risk of vertical transmission in women with hepatitis B, hepatitis C, and/or HIV. For this reason, non-invasive methods of prenatal risk screening that provide the highest sensitivity with the lowest false-positive rate should be used to minimize the number of amniocenteses performed. The available evidence suggests the risk of vertical transmission through amniocentesis in women infected with hepatitis B and hepatitis C is not greatly increased if present at all. In contrast, the risk of vertical transmission of HIV appears to be increased through amniocentesis for women not on cART. For women with HIV treated on cART for at least 2 weeks, the risk of vertical transmission associated with amniocentesis appears to be negligible if present at all. Efforts should be made in all cases to avoid inserting the needle through the placenta.

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