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Screening for HIV Infection in Pregnancy

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1. Introduction

Approximately 100 to 200 infants annually in the United States are infected with HIV (CDC, 2007). Most were born to mothers who were unaware of their infected HIV status or who did not receive preventative services during their pregnancy to reduce transmission rates. Therefore, in 2006, the CDC updated its guidelines for screening of various populations for HIV, including pregnant women. Obstetricians and gynecologists are ideally suited to such screening of their patients during annual exams and prenatal visits.

1.1. Screening for HIV infection during prenatal care

Screening only patients who reported risk factors for the HIV infection will miss many infected women. Therefore, the current recommendation is for implementation of universal opt-out screening for HIV as early in pregnancy as possible (Branson et al., 2006). In this universal opt-out screening method, a patient is informed that HIV testing will be performed as a routine part of her prenatal care, unless she declines testing. She should be given written or oral information about HIV, including an explanation of the infection, the meaning of positive or negative test results, and measures that can be used to reduce perinatal transmission. She should also be given the opportunity to ask further questions. However, no informed consent is required. If a patient declines screening, this should be documented in the medical record, and screening should be offered at subsequent prenatal visits (Branson et al., 2006; ACOG, 2008). Retesting is recommended with each new pregnancy. Although these are the recommendations endorsed by the CDC and ACOG, healthcare providers must be aware of the laws regarding screening in their own states, which may differ from the above guidelines. Further information on state HIV testing laws can be obtained from state and local health departments.

Chou et al, estimated that the number needed to screen (NNS) in an area with 0.15% prevalence would be between 3,500 to 12,170 to prevent 1 case of perinatally-acquired HIV infection. In a high risk area with a prevalence of 5%, the NNS would be from 105 to 365 to prevent 1 case of perinatally-acquired infection (Chou et, 2005).

At this time, both conventional and rapid screening tests for HIV are available to the health-care provider. Conventional testing consists of a screening test with an enzyme immunoassay (ELISA), followed by confirmatory testing of a positive result with Western blot or immunofluorescent antibody (IFA) testing. The sensitivity and specificity of this method of testing is greater than 99%. False positive results are rare even in the setting with low prevalence. Final results may not be available for several days to weeks. With rapid testing, a blood or saliva test for HIV antibodies is performed, and the results are often available within an hour. Confirmatory testing of a preliminary positive result is still required before a diagnosis of HIV can be made. A negative result with either the conventional or rapid screening test indicates a woman does not have HIV, and no further testing is needed, unless one suspects the patient was recently infected with HIV but has not produced an antibody response to the virus (ACOG, 2008; Rahangdale & Cohan, 2008). If the initial screening test is positive, but the confirmatory test is negative, the patient should be considered not infected, and no further testing is necessary.

1.2. Rescreening in the third trimester

Studies from several countries have demonstrated that pregnant women seem to be at increased risk for acquisition of HIV over their non-pregnant counterparts (Moodley et al., 2009; Gray et al., 2005; Sansom et al., 2003). Theories for this range from behavioral actions of the woman or her partner that put her at increased risk, to physiologic changes associated with pregnancy, including changes to the genital tract mucosa to changes in cellular immunity that may lead to increased susceptibility to HIV with pregnancy. Evidence has demonstrated that the rate of seroconversion during pregnancy may be as high as 2 to 3 percent in some areas (Moodley et al., 2009; Gray et al., 2005; Sansom et al., 2003). A study by Sansom, *et al* demonstrated that in a population with an HIV incidence of approximately 1 in 1000 person-years, the cost of repeat testing was offset by the savings in medical costs for prevention of an infected infant (Sansom et al., 2003). For the above reasons, repeat HIV testing is recommended in certain populations in the third trimester, preferably before 36 weeks gestation (Branson et al., 2006; ACOG, 2008). These populations include:

- Women living in areas with a high incidence of HIV/AIDs, including the 20 states with the highest incidence among women of child-bearing age
- Women who receive their healthcare in facilities where at least 1 in 1000 women screened for HIV are found to be infected
- Women who engage in high-risk behavior that puts them at risk for HIV acquisition (injection drug use, exchange of sex for drugs or money, diagnosis of another sexually transmitted infection in the past year, a sex partner who engages in injection drug use or high-

risk behaviors or is infected with HIV, or women who have had a new or more than one sexual partner during their pregnancy)

- Women with signs or symptoms of acute HIV infection

1.3. Screening of women with undocumented HIV status

Studies indicate that between 40 and 85 percent of infants infected with HIV are born to mothers whose HIV infection status is unknown prior to delivery (ACOG, 2008). If a woman without documentation of HIV status presents to labor and delivery, opt-out rapid HIV testing should be performed at time of her initial presentation. A positive result should prompt immediate treatment with antiretroviral prophylaxis without awaiting the result of confirmatory testing. If subsequent confirmatory testing shows the woman to be HIV negative, treatment may be discontinued. Similarly, if a woman has an unknown HIV status in the postpartum period, her infant should be tested by rapid screening. Antiretroviral treatment should be initiated with a positive result, as the benefits of such treatment are maximized when started within 48 hours of delivery (ACOG, 2008; Rahangdale & Cohan, 2008). Again, treatment may be stopped if confirmatory testing is negative.

The above recommendation for prenatal screening for HIV infection is summarized in table 1.

Timing	Screening test	Confirmatory Test
Initial prenatal care visit	Enzyme immunoassay (ELISA)	Western blot or immunofluorescent antibody (IFA) testing
Third trimester of pregnancy	Repeat ELISA in women at high risk for acquisition of HIV infection	Western blot or IFA testing
At time of labor and delivery for women with undocumented HIV status	Rapid HIV antibody screening test.	Western blot or IFA testing

Table 1. CDC and ACOG recommendation for screening for HIV infection during pregnancy.

2. Evidences supporting the effectiveness of current interventions to decrease mother-to-child transmission of HIV infection

Research in HIV infection reported several key factors in the transmission of the virus from the mother to the infant. The risk factors for transmission can be divided into: virologic/immunologic, maternal health status/behavior, and obstetrical factors (McGowan et al, 2000). High maternal plasma HIV-1 viral load, low maternal CD4 T-lymphocyte count, multidrug-resistant HIV genotype will increase the transmission rate. Certain maternal behavior (illicit drug use, cigarette smoking, breast feeding) or maternal health status (increased base-

line weight or malnutrition or vitamin A deficiency) can increase the rate of mother-to-child transmission. Some obstetrical factors (vaginal delivery, prolonged rupture of membrane, fetal scalp electrode placement, chorioamnionitis, perineal lacerations, prematurity) can increase the vertical transmission rate (McGowan et al, 2000).

Other reports on perinatal transmission of HIV infection suggested that approximately 70% of the infections transmitted to the infant during the labor and delivery process; only 30% of the cases occurred during the antepartum period (Kourtis et al, 2006). Current interventions to prevent perinatal transmission of HIV infection included: prophylaxis therapy with anti-retroviral medication, scheduled cesarean delivery and avoidance of breast feeding. These interventions resulted in decreasing transmission rate to 2% (Cooper et al, 2002). We will examine the evidence supporting these interventions.

2.1. Prophylaxis with antiretroviral agents

The Pediatric AIDS Clinical Trials Group (PACTG) 076 conducted a randomized controlled study and in 1994 published its landmark results demonstrating a reduction in perinatal HIV transmission by two-third with the antiretroviral medication Zidovudine (ZDV). HIV-infected mothers in the study group received a three-part regimen of antiretroviral medication. They received ZDV during pregnancy, intravenous ZDV during labor, and their infant received ZDV orally for 6 weeks (Conner et al, 1994). This trial reported a decrease in transmission rate from 26% in the placebo group to 8% in those patients who received ZDV. Later in the year of 1994, FDA approved the use of ZDV for reducing perinatal HIV transmission and the U.S. Public Health Service Task Force (USPHSTF) and CDC published their recommendations for the administration of this regimen in an effort to reduce mother-to-child transmission of the HIV infection (CDC, 2006).

In the late 1990s, additional antiretroviral medications were developed and the combined use of three or more of these drugs was found to greatly inhibit viral replication and allow improvement of the immune system. The combination of these medications was known as highly active antiretroviral therapy (HAART). In 1998, USPHSTF and CDC issued recommendation regarding HAART: pregnant women should receive HAART if they required the treatment for their disease status and all HIV-infected pregnant women should be offered HAART. USPHSTF and CDC at that time acknowledged that the benefits and risks to the fetus are uncertain (CDC, 1998). Four large U.S. and European cohort studies all concluded that regimens with two or more antiretroviral drugs were more effective than the one-drug regimen for reducing vertical transmission of the HIV infection (Cooper et al, 2002, Arch Pediatr Adolesc Med 2002, Clin Infect Dis 2005, Mandelbrot et al, 2001).

For women diagnosed late in pregnancy and were not able to receive a full course of antiretroviral treatment, a short course of antenatal treatment, although less effective, also was proven to decrease perinatal transmission (Lallemant et al, 2000, Shaffer et al, 1999, Petra study 2002, Wiktor et al, 1999, Dabis et al, 1999, Chou et al, 2005). There was some reduction in the HIV infection transmission even when treatment was abbreviated to only antiretroviral regimen during labor (Moodley et al, 2003, Taha et al, 2003, Guay et al, 1999). However,

neonatal prophylaxis alone in a mother who did not receive antiretroviral prophylaxis therapy was less effective in preventing HIV infection (Taha et al, 2003).

2.2. Scheduled cesarean delivery

A meta-analysis of 15 prospective cohort studies by the International Perinatal HIV Group (The International Perinatal HIV Group, 1999) included 8,533 mother-neonate pairs. Vertical HIV transmission was reduced by 50% when the mode of delivery was elective cesarean delivery. The effect of both antiretroviral therapy prophylaxis and cesarean delivery further reduced HIV transmission by 87 percent when compared with other modes of delivery (either vaginal delivery or non-elective cesarean delivery) and no antiretroviral therapy. However, in women who received HAART and achieved low HIV viral load levels (defined as less than 1,000 copies/ mL), current data is insufficient to determine whether elective cesarean delivery would offer further risk reduction. ACOG concluded that scheduled cesarean delivery should be discussed and recommended for HIV-infected women whose HIV-1 RNA viral load exceeds 1,000 copies/mL. Scheduled cesarean delivery was recommended as early as 38 weeks gestation to reduce the risk of labor or of prematurely ruptured membranes (ACOG, 1999).

2.3. Avoidance of breastfeeding

Breastfeeding was associated with an HIV transmission rate of 14% to 16% based on the results of two meta-analyses of observational studies (Dunn et al, 1992, John et al, 2001). A review of the literature did not reveal any randomized, controlled trials evaluating the HIV transmission rate associated with breastfeeding in the United States. A large, prospective cohort study in Italy included 3,770 babies and concluded that HIV infection rates were significantly higher in babies who were breastfed after the authors adjusted for other factors, including antiretroviral use (adjusted odds ratio, 10.20 [CI, 2.73 to 38.11]) (Arch Pediatr Adolesc Med., 2002, Chou et al, 2005).

In a study in Africa, women who breastfed and did not receive antiretroviral therapy had a probability of transmitting the HIV infection of 36.7% (CI, 29.4% to 44.0%) at 24 months and an infant mortality rate of 24.4% (CI, 18.2% to 30.7%). Those who formula fed their babies had a transmission probability of 20.5% (CI, 14.0% to 27.0%) and an infant mortality rate of 20.0% (CI, 14.4% to 25.6%) (Nduati et al, 2000).

As a result, in many countries, including the United States where formula feeding is readily available and inexpensive, breastfeeding is not recommended for infants of HIV-infected women (WHO, 2000).

3. Potential harms/risks as the result of prenatal HIV screening

We will next explore the potential risks as the results of prenatal HIV screening and the potential harms of the recommended interventions to reduce perinatal transmission of HIV infection (Table 2).

	Maternal risks	Fetal risks
Prenatal screening		
Screened positive	Discrimination from their partner Social ostracization from family and friends Anxiety and depression Abandonment and abuse from family and friend	
Screened falsely positive	Anxiety Social discrimination Relationship problems Unnecessary antiretroviral prophylaxis during labor	Potential risk for elective termination of pregnancy
Interventions to decrease perinatal transmission		
ART prophylaxis	Hepatic toxicity and hypersensitivity reaction (with Nevirapine) Development of drug resistance Gestational diabetes (with combination therapy including protease inhibitors)	Risks of neural tube defects with Sustive (Efavirenz) with first trimester exposure. ? Potential risk of mitochondrial toxicity and disorder Inconsistent data regarding increasing risk for preterm birth and low-birth weight
Scheduled cesarean delivery at 38 weeks	Post-operative morbidities, including: postpartum fever, hemorrhage, endometritis, urinary tract infection.	A trend toward higher risk of respiratory distress syndrome among neonates born by cesarean section (when compared to those born via vaginal delivery)

Table 2. Potential harms / risks from prenatal screening and strategic interventions to decrease perinatal transmission of HIV infection:

According to Katz, prenatal screening for HIV in pregnancy aims to test a presumably healthy population to discover asymptomatic women who are actually infected with HIV infection. These pregnant women might not have or perceive that they have risk factors for the HIV infection. This is different than the usual situation when a woman acknowledges her risk for the infection and requests the screening test. Most women would agree to be screened as they believe that they are doing everything they can for the health for their baby but they might not realize the full implication of a positive HIV test result on their lives. In some instances, they do not perceive that they are at risk for the infection and thus could be quite unprepared to receive the positive diagnosis. This could result in adverse effect on their emotional health, their pregnancy, and the family. Thus health care provider should

always be well prepared to provide the appropriate emotional support for a possibility of abnormal result (Katz, 2000).

Women tested positive for HIV infection can experience significant problems with discrimination from their partner, social ostracization from their family and members of the community (Provisional Committee on Pediatric AIDS, 1995, Samson et al, 1998). They were found to have higher anxiety and depression scores and many women fear abandonment or abuse, therefore, did not disclose their HIV status to their friend or families. (Lester, 1995) although no increased risk for intimate partner violence was noted according to one cohort study (Koenig et al, 2002, Chou et al, 2005)

Data on consequences of false-positive HIV infection diagnoses in pregnant women are mainly anecdotal as reported by Sheon et al. The potential risks from false-positive results included: elective termination of pregnancy, anxiety, social discrimination and relationship problems with their partner (Sheon et al, 1994, Chou et al, 2005).

False positive results from rapid HIV testing during labor result in 4 women receiving unnecessary antiretroviral prophylaxis out of 4,849 women tested (Bulterys et al, 2004).

4. Risks of Antiretroviral Therapy (ART) to fetus

4.1. Potential teratogenic effects of ART

Efforts continue to increase our knowledge of the potential teratogenic effects of the antiretroviral agents administered in pregnancy. The Antiretroviral Pregnancy Registry Steering Committee published their recent report of antiretroviral exposures during pregnancy from January 1989 through July 2007. They did not identify an increased risk of birth defects in those exposed to any of the antiretroviral therapy in the first trimester. The risk of birth defects among women exposed to antiretroviral therapy in first trimester was 2.8 per 100 live births, which is not different from the risk of birth defects in women exposed to these agents in the second or third trimester (2.6 per 100 live births), nor the CDC's reported background rate of birth defects of 2.72 per 100 live births (www.APRegistry.com, 2007, Bardeguetz, 2009).

Four retrospective reports associated Sustiva (Efavirenz) with neural tube defects in infants born of mothers exposed to this medication in the first trimester (Bardeguetz, 2009). There are discrepant results with regard to mitochondrial toxicity and disorders in children exposed in utero to antiretroviral therapy. Two deaths believed to be due to mitochondrial disorder were reported in children exposed in utero to nucleoside analogues (in specific, a combination of Zidovudine and Lamivudine regimen) (Blanche et al, 1999). However, European Collaborative report and systematic review of U.S. cohorts reports did not find evidence of clinical symptoms, or deaths due to mitochondrial dysfunction among HIV-negative infants exposed to antiretroviral agents in utero (Bardeguetz, 2009).

Of infants exposed in utero to Zidovudine who were followed at 4 years to 6 years of life. The reports were reassuring. Normal growth, cognitive, and developmental function were noted in these infants at 4 years old. They did not sustain any tumors or deaths from cancer at 6 years old.

4.2. Association between ART and preterm birth and low-birth weight

Inconsistent results were noted among the reports studying the effects of combination antiretroviral therapy on two obstetrics outcomes: preterm birth and low birth-weight. Lorenzi et al in 1998 first reported the association between combination antiretroviral therapy with preterm birth in a retrospective Swiss study of 30 women (Lorenzi et al, 1998). Subsequently, other European studies reported a similar association between combination antiretroviral therapy and preterm birth (The European Collaborative Study (ECS) and Swiss Mother + Child HIV Cohort Study (Mo-CHiV), 2000, Grosch-Woerner et al, 2008). However, this association was not found in U.S. studies until a recent study by Cotter et al. The authors prospectively collected the data from 1990 through 2002 on 999 women receiving antiretroviral regimen during pregnancy. They concluded that women who received combination therapy that included a protease inhibitor had an increased risk of preterm delivery (Cotter et al, 2006).

In a largest analysis to date, Tuomola et al did not find an increased rate of premature birth or low birth-weight infants among 2,123 HIV infected pregnant women from seven clinical studies who received combination ART and gave birth from 1990 through 1998.

5. Risks of ART to mothers

A large prospective study evaluating the rates of maternal toxicity, pregnancy complications, and peripartum morbidity among HIV-infected pregnant women receiving prenatal care and ART concluded that adverse events were rare. Gestational diabetes was noted to be highest among women who received combination therapy including protease inhibitors either before or during first trimester (Watts et al, 2004). Reports of potential risks of hepatic toxicity and hypersensitivity reaction were noted in pregnant women receiving the drug Nevirapine (Bardequez, 2009).

Another valid concern is the potential development of drug resistance when ART was administered to the mother for a short period during pregnancy. Drug resistance was noted in 20 – 69% of women who received only intrapartum prophylaxis with single-dose nevirapine. This could decrease the choice of medications for these women should they later need treatment for their disease. Although, there are reports that this observed resistance dissolved over time. (Bardequez, 2009). Limited exposure to zidovudine alone did not alter maternal disease progression, time until development of AIDS or death, or development of genotypic zidovudine resistance (Bardequez et al, 2003).

6. Potential maternal risks from scheduled cesarean delivery

Cesarean deliveries could result in significant complications when compared to vaginal delivery even for HIV-negative women (Allen et al., 2003; Makoha et al., 2004). HIV-infected women with an immunodeficient state could potentially at risk for post-operative infectious

morbidities. Most studies report that HIV-infected women are at higher risk for post-operative complications, mostly infectious, than the uninfected women (Coll et al., 2002; Grubert et al., 1999; Vimercati et al., 2000). The rate of complications is higher in those with severe immunodeficiency (Jamieson et al., 2007).

Read et al conducted a largest prospective observational study which included 1,186 HIV-infected women from The Women and Infants Transmission Study. The authors evaluated the postpartum morbidity among these infected women according to their mode of delivery. When compared to women who delivered vaginally, women who underwent scheduled cesarean delivery had an increased rate of postpartum fever (14.3%), hemorrhage (7.1%), endometritis (5.4%), urinary tract infection (5.4%), and any postpartum morbidity (26.7%) (Read et al, 2001).

7. Potential neonatal risks from scheduled cesarean delivery at 38 weeks gestation

In the absence of medical or obstetrical indications, ACOG recommends against scheduled cesarean delivery at less than 39 weeks of gestation, due to the increased risk of respiratory morbidity in the neonate born prior to this gestational age (ACOG, 2001). Neonatal morbidity is high even among those neonates born via cesarean delivery a few days younger than 39 weeks (Tita et al, 2011). However, both ACOG and U.S. Public Health Service recommend scheduled cesarean delivery at 38 weeks for HIV-infected women with viral load greater than 1,000 copies/ml (ACOG, 2001; Public Health Service Task Force, 2010). The scheduled cesarean delivery date is set at one week earlier than the usually required gestational age of 39 weeks to avoid onset of spontaneous labor and rupture of membranes which could increase perinatal transmission of HIV. Livingston et al and the IMPACT Protocol 1025 Study Group evaluated the risk of neonatal respiratory distress syndrome according to the mode of delivery and gestational age at delivery. They reported that the mode of delivery was not associated with respiratory distress syndrome. However, there was a trend toward a higher risk of respiratory distress syndrome among neonates delivered by either elective or non-elective cesarean section when compared to those delivered vaginally. Two out of 227 neonates born via scheduled cesarean delivery at 38 weeks gestation had respiratory distress syndrome (Livingston et al., 2010).

8. Conclusion

Current evidence supports prenatal HIV screening. The benefits from screening appear to outweigh the small risks / harms to the fetus and mothers from the treatment interventions which significantly reduce perinatal-acquired HIV infection. We concluded the chapter by discussing the obstacles to the HIV prenatal screening and prevention interventions. Prenatal

tal screening for HIV infection and implementation of Protocol 076 were lauded as a major public health success story and resulted in a significant decline in the number of children infected with HIV from their mother. However, in the United States, there are still about 100–200 infants born every year with perinatally acquired HIV infection (CDC, 2007). Lack of prenatal care remains one of the obstacles to prevention of perinatal transmission of HIV. In the United States about 5 to 10% of women do not pursue prenatal care or receive insufficient care (Kogan et al., 1998). HIV infected women, in particular, often do not receive prenatal care. In New York City, 50% of women infected with HIV who delivered in at a municipal hospital did not receive prenatal care (Minkoff et al., 1990). Of the HIV-infected women surveyed in Philadelphia, only one third reported adequate prenatal care, and 20% did not receive any care (Turner et al., 1996).

Even more worrisome, at the Medical Center of Louisiana in New Orleans, LA, 50% of the HIV-infected parturients who did not have prenatal care but presented to the hospital for labor and delivery did not disclose their HIV status to their physicians (CDC, 2004). Could it be because the HIV-infected women did not know of the available interventions that they put their infants at risk for the infection?

Several authors attempt to understand why HIV-infected women opted out of prenatal care and available interventions to decrease vertical transmission. Rothpletz-Puglia et al solicited opinions from a group of HIV-negative women about the process of prenatal HIV screening. The authors reported that fear was a big factor for declining testing. The women are afraid to find out they are HIV-infected. They are frightened to discover a partner's infidelity. They are fearful of being judged by their health care provider or of being denied medical care if they tested positive (Rothpletz-Puglia et al, 2001).

Lancioni et al. reported that HIV-infected women did not participate in prenatal care because they fear disclosing their status to their caretakers and being judged by them for continuing the pregnancy (Lancioni et al., 1999). In a recent report by Lindau et al, HIV-infected women who were interviewed were aware of the benefits of prophylaxis treatment yet most received insufficient or no prenatal care. They knew of their HIV infection diagnosis but most did not disclose their status to their caretaker when they presented for delivery at hospitals capable of providing prophylaxis treatment. They attributed health care providers' lack of sensitivity, violations of confidentiality, disdain for HIV infection and substance abuse as reasons for their non-participation in prenatal care, avoidance of treatment for HIV infection, and non-disclosure of their HIV status. Denial and fear were other barriers to HIV prophylaxis treatment (Lindau, 2006).

We agreed with Lindau et al that may be what is needed to further reduce perinatal transmission beyond the conventional models for prevention is to understand the HIV-infected women's point of view, their fears and concerns and to eliminate the disrespect treatment as perceived by them from the health care providers. It is hope that we can create a medical environment where these women will be confident of our compassion and care to disclose their status and to want to seek prenatal care and HIV prophylaxis treatment (Lindau, 2006).

Lastly, not only obstetricians and gynecologists need to follow the CDC and ACOG guidelines in providing opt-out prenatal screening for HIV they must receive appropriate training for pre and post screening counseling and must ensure patient confidentiality. More importantly, at every screening they must be prepared for positive results: they must be compassionate toward those tested positive and must have resources available for their emotional support beyond providing the standard medical interventions to decrease vertical transmission.

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