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Journals Represented

Mosby–Year Book subscribes to and surveys nearly 900 U.S. and foreign medical and allied health journals. From these journals, the Editors select the articles to be abstracted. Journals represented in this YEAR BOOK are listed below.

Acta Chirurgica Scandinavica
Acta Cytologica
Acta Endocrinologica
Acta Obstetrica et Gynecologica Scandinavica
American Journal of Clinical Nutrition
American Journal of Clinical Pathology
American Journal of Diseases of Children
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American Journal of Hematology
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Annals of the Royal College of Surgeons of England
Archives of Disease in Childhood
Archives of Internal Medicine
Archives of Surgery
Australian and New Zealand Journal of Obstetrics and Gynecology
Biology of the Neonate
British Journal of Cancer
British Journal of Obstetrics and Gynaecology
British Journal of Radiology
British Journal of Surgery
British Medical Journal
Canadian Medical Association Journal
Cancer
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Chinese Medical Journal
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Developmental Medicine and Child Neurology
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Early Human Development
European Journal of Cancer
European Journal of Obstetrics, Gynecology and Reproductive Biology
Family Practice Research Journal
Fertility and Sterility
Gastroenterology
Genitourinary Medicine

Gynecologic Oncology
Gynecologic and Obstetric Investigation
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International Journal of Cancer
International Journal of Cardiology
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Journal of the American Medical Association
Lancet
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Mayo Clinic Proceedings
Medical Care
Medical Journal of Australia
Neurosurgery
New England Journal of Medicine
Obstetrics and Gynecology
Paediatric and Perinatal Epidemiology
Patient Education and Counseling
Pediatric Infectious Disease Journal
Pediatric Radiology
Pediatric Research
Pediatrics
Postgraduate Medical Journal
Postgraduate Medicine
Prenatal Diagnosis
Proceedings of the National Academy of Sciences
Prostaglandins
Psychological Medicine
Radiology
Research Quarterly for Exercise and Sport
Respiration Physiology
Reviews of Infectious Diseases
Southern Medical Journal

Stroke
Surgery, Gynecology and Obstetrics
Urology
World Journal of Medicine

Standard Abbreviations

The following terms are abbreviated in this edition: acquired immunodeficiency syndrome (AIDS), central nervous system (CNS), cerebrospinal fluid (CSF), computed tomography (CT), electrocardiography (ECG), human immunodeficiency virus (HIV), and magnetic resonance (MR) imaging (MRI).

HIV in Pregnancy and Effects on the Fetus and Infant

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Introduction

First recognized in 1981, acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV), was initially associated epidemiologically with men. The virus was believed to be transmitted via homosexual or intravenous drug-using activities. Increasingly, the epidemiologic features of HIV infection have shifted toward populations in which heterosexual activity and/or intravenous drug use predominate as modes of transmission. Accompanying this epidemiologic shift has been a rapid increase in HIV infection in women; since January 1989, 55% of all AIDS have been reported in women (1). As of July 1991, 20,121 cumulative cases of AIDS in women had been reported to the Centers for Disease Control (CDC), in 84% of these women, intravenous drug use or heterosexual contact was reported as the route of HIV exposure (2).

The majority of these HIV-infected women are of childbearing age, and HIV infection in women is intimately related to HIV infection in children. Vertical transmission of HIV from mother to infant accounts for more than 80% of AIDS cases in children in the United States (2). With the current safeguards for the blood supply, vertical transmission should become nearly the sole route of acquisition of HIV infection by children in the near future.

The annual incidence of AIDS among children and women of childbearing age in the United States has been increasing every year (3). It is inevitable that HIV-infected pregnant women will increasingly be seen in obstetric practices across the United States. Obstetricians need to be aware of the incidence of HIV infection in pregnant women and its potential effects on pregnancy and the infant. They must be capable of providing appropriate counseling and medical care for these patients.

HIV/AIDS in the United States and Women of Reproductive Age

As of July 1991, there were 20,121 cases of AIDS in females of all ages reported to the Centers for Disease Control in Atlanta. Of these patients, 15,730 (79%) were aged 13 to 44 years (2). If one examines the mode of acquisition of infection in all female adolescents and women reported to the CDC with AIDS, it becomes clear that the illicit injection of drugs is intimately related to HIV disease in females in this country. More than half (51%) of the currently reported female AIDS infections were acquired through intravenous drug use. Another 33% resulted from heterosexual contact with an infected partner. However, in this latter category, sex with an intravenous drug user accounted for more than half of the heterosexually acquired cases.

In mid-1990, the CDC reported their findings with regard to the impact of HIV/AIDS on females of reproductive age (15–44 years) in the United States (4). Using national mortality statistics, the CDC documented that HIV/AIDS is one the ten leading causes of death in women in this age group. Further, HIV/AIDS caused 18 deaths among these women in 1980 compared to 1,430 deaths in 1988, with the death rate attributable to HIV/AIDS quadrupling over the years from 1985 to 1988. The impact of this disease has fallen somewhat disproportionately on certain subgroups of the population. For example, in Caucasian women of reproductive age, in 1988 the death rate attributable to HIV/AIDS was 1.2/100,000. For black women in the same year, the rate was 10.3/100,000. In the states of New York and New Jersey, by 1987 HIV/AIDS was the leading cause of death in black women between 15 and 44 years of age. Based on AIDS case reporting of women for the years subsequent to those included in this analysis (1980–1988), the CDC predicted a continued increase in the number of deaths attributable to HIV/AIDS in women of reproductive age. They noted that, "if current mortality trends continue, AIDS can be expected to become one of the five leading causes of death by 1991."

Prevalence of HIV in Childbearing Women in the United States

The CDC and the National Institute of Child Health and Human Development of the National Institutes of Health co-sponsored a seroprevalence survey designed to quantitate the prevalence of HIV infection in women bearing children in the United States. Although the data reported above can be extrapolated to predict the potential impact of HIV infection and disease on the children in the United States, the data from this survey allow a more direct estimate of two noteworthy statistics: the prevalence of HIV infection in one important segment of the heterosexual population in the United States (i.e., childbearing women), and a projection of the number of children born annually who will go on to acquire HIV infection.

The survey was conducted using routinely collected samples of newborn blood. All jurisdictions in the United States require by statute that all newborns be screened for certain metabolic (and, in the case of some states, certain infectious) diseases. The samples of blood to be tested are collected by heelstick and absorbed and dried on special paper. The blood is eluted from each individual paper and tested according to the individual laws of each state. Hoff and colleagues at the State Laboratory in Massachusetts reasoned that these same samples of collected, dried blood could be used to test for maternal HIV antibody, which is transferred from the mother to the fetus during gestation (5). A positive sample would indicate an infected mother and a fetus/child at risk for infection. After demonstration by Hoff and colleagues of the reliability, validity, and feasibility of this methodology, the CDC adopted this technology. A recently reported survey gives the results of such testing of more than 1.8 million specimens from 38 states and the District of Columbia (6). From this serosurvey, it was estimated that in 1989, 1.5 women per

1,000 giving birth to liveborn infants, or 6,000 women, were themselves HIV infected. If one accepts the estimate that 1 of every 3 infected pregnant women will give birth to a child who is also infected (mother to child transmission rate of 30%), then 1,800 children were born in that year who are HIV infected and may die of AIDS.

Impact of Maternal HIV Infection on Pregnancy Outcome

Studies published to date have shown conflicting results concerning the impact of HIV infection on pregnancy outcome and fetal growth (Table 1). Confounding factors in these studies include the influence of maternal substance abuse and concomitant infections, e.g., sexually transmitted diseases. In particular, the use of illegal drugs, alcohol, and tobacco, all which may have high prevalence in populations of HIV-infected women, are all associated with adverse pregnancy outcomes such as prematurity and low birth weight. In addition, maternal health status, either as a result of the stage of HIV infection or secondary to the availability of medical prenatal health care, as well as maternal socioeconomic status, may further confound analyses and study comparisons.

Two early case series investigating the effect of HIV infection on the short-term outcome of pregnancy in a total of 86 pregnancies in HIV-infected women suggested that premature birth, premature rupture of membranes, intrauterine growth retardation, and infectious complications of pregnancy occurred commonly in HIV-infected pregnancies (7, 8). Although the HIV-infected women in both groups were relatively asymptomatic, a significant percentage were intravenous drug users or from a low socioeconomic group, characteristics that by themselves may be associated with an adverse pregnancy outcome.

Prospective, controlled studies from the United States and Scotland that examined the effect of HIV infection on pregnancy outcome have demonstrated no significant difference in the frequency of preterm birth, low birth weight, preterm rupture of the membranes, or Apgar scores in asymptomatic HIV-infected and uninfected intravenous drug-using women (9, 10). In a mixed drug-using and non-using population in New York City, Minkoff and colleagues found no significant differences in gestational age, birth weight or height, head circumference, or Apgar scores when comparing the offspring of 101 seropositive, asymptomatic pregnant women to the offspring of 129 comparable but seronegative women (11). The pregnancy outcomes for these women were influenced more by drug use, alcohol, and smoking than by HIV infection.

In a recent prospective study from New York City involving 72 children born to HIV-infected mothers and 82 children born to uninfected mothers that controlled for maternal drug, alcohol, and tobacco use, the observed mean birth weights were nearly equal in infected children, seroreverting children (i.e., children born to HIV-infected mothers who lose maternally transferred HIV antibody usually by 12–15 months of age and are therefore uninfected), and children born to uninfected mothers (12). When adjusted for differences in known confounders of infant weight, however, children who were ultimately shown to be HIV infected

TABLE 1.—Selected Studies Evaluating the Effect of Maternal HIV Infection on Short-Term Pregnancy Outcome

Site/ Reference	Number Women	Symptom Status of Infected Mothers	Association of Adverse Infant Outcome with by Maternal HIV Status	Association of Adverse Infant Outcome with Advanced Maternal Disease
NYC/ Minkoff[11]	HIV infected: 101 HIV uninfected: 129	3% AIDS	No effect: Birth weight Gestational age Head circumference Apgar score	Not reported
NYC/ Selwyn[10]	HIV infected: 25 HIV uninfected: 44	4% CDC IV A (candida) 42% Lymphadenopathy 54% Asymptomatic	No effect: Birth weight Gestational age Apgar score	Not reported
NYC/ Muenz[12]	HIV infected: 72 HIV uninfected: 82	Not reported	No effect: Birth weight	Not reported, but HIV-infected infants had lower birth weight
Haiti/ Halsey[103]	HIV infected: 199 HIV uninfected: 1994	Minimal symptoms	Significant effect: Prematurity Birth weight	Not reported
Edinburgh/ Johnstone[127]	HIV infected: 80 HIV uninfected (IVDU): 140 HIV uninfected (non-IVDU): 142	Not reported	Significant effect: Birth weight No effect: Stillbirths Prematurity Perinatal mortality	Not reported

Site/ Reference	Number Women		Symptom Status of Infected Mothers	Association of Adverse Infant Outcome with by Maternal HIV Status	Association of Adverse Infant Outcome with Advanced Maternal Disease
Rwanda/ Lepage[21]	HIV infected: HIV uninfected:	218 218	0% AIDS	Minimal effect: Birth weight No effect: Prematurity	Not reported
Zaire/ Ryder[17]	HIV infected: HIV uninfected:	466 606	18% AIDS	Significant effect: Preterm delivery Birth weight	Prematurity, low birth weight and AIDS
Nairobi/ Braddick[18]	HIV infected: HIV uninfected:	177 326	17% Advanced HIV 28% Lymphadenopathy 55% Asymptomatic	Significant effect: Birth weight No effect: Prematurity Malformations Stillbirths	Low birth weight and symptomatic disease
Zambia/ Hira[20]	HIV infected: HIV uninfected:	109 40	4% AIDS 28% ARC 46% Lymphadenopathy 22% Asymptomatic	Significant effect: Birth weight	Not reported
Rwanda/ Bulterys[126]	HIV infected: HIV uninfected:	120 170	Not reported	Significant effect: Birth length Head circumference Borderline effect: Birth weight No effect: Perinatal mortality	Not reported

were found to have lower birth weights than seroreverting, uninfected children born to HIV-infected women and children born to uninfected mothers, with persistent and widening weight differences between groups over time. Other prospective studies in the United States and Europe, however, have not shown that HIV-infected infants were more likely than seroreverting, uninfected infants to differ in birth weight or to be born prematurely (13–16), although the European Collaborative Study noted that infected infants who contracted AIDS in the first 18 months of life had a tendency to be born earlier and were lighter and smaller for dates than those who did not contract AIDS. Asymptomatic maternal HIV infection during pregnancy may not be associated with adverse consequences to the fetus. It is possible that only a portion of infants in whom in utero HIV transmission occurs experience secondary growth abnormalities resulting from a potential direct effect of HIV on the fetus.

By contrast, studies from Africa appear to demonstrate an association between adverse outcome and maternal HIV serostatus. The HIV disease status of pregnant cohorts from Africa, however, is generally more advanced than that described in the American and European cohorts. In a study by Ryder and colleagues of 466 HIV-1-infected women (18% of whom had overt AIDS) compared with 606 uninfected women from Kinshasa, Zaire, women with AIDS at the time of delivery were more likely to deliver preterm or low-birth-weight infants (33%) than infected, asymptomatic women (17%) or seronegative women (11%) (17). A possible confounding effect is that many of the women with AIDS in that study delivered at a hospital serving low socioeconomic women and therefore may have had experienced different prenatal care, which could affect pregnancy outcome.

A prospective study of 177 HIV-infected and 326 seronegative women and their newborns in Nairobi, Kenya, also demonstrated a threefold risk of low birth weight (<2,500 g) in infants born to HIV-infected women (9% vs. 3% in uninfected women) (18); no difference was noted in the occurrence of congenital malformations, stillbirths, or prematurity. Advanced HIV disease was observed in 17% of infected women in this cohort; 28% had lymphadenopathy, and 55% were asymptomatic. Low birth weight was significantly more frequent in symptomatic as compared to asymptomatic HIV-infected mothers (17% vs. 6%). A second study from Nairobi compared the HIV infection status of mothers with low-birth-weight or stillborn fetuses and controlled for the presence of sexually transmitted diseases (19). Human immunodeficiency virus infection was significantly and independently associated with prematurity, low birth weight, and intrauterine or intrapartum fetal death; fetal deaths were more common in mothers with clinical signs of HIV disease progression. In a study of 109 infected and 40 uninfected pregnant women and their newborns in Zambia, infected mothers were 2.9 times more likely to deliver low-birth-weight infants (20). Correlation with maternal symptom status was not given, but more than 50% of HIV-infected women had HIV-related symptoms. Interestingly, in a prospective, chiefly asymptomatic, cohort in Rwanda comparing 218 children born to HIV-

infected mothers, none of whom had AIDS, and 218 children born to HIV-seronegative mothers, different rates of prematurity between the two groups were not demonstrated, although infants born to infected women had a mean birth weight 130 g lower than that of infants born to noninfected women (21).

Disparities between the American/European and African reports may relate to the stage of maternal HIV disease or the availability of antenatal care. More advanced HIV-related symptoms in pregnancy could cause low birth weight, either by affecting the mother's health and ability to support a pregnancy or by increasing the risk of HIV transmission to the fetus (assuming a potential but not yet documented direct adverse effect of HIV on the fetus). Further studies are needed using standardized growth measures and better assessment of confounders such as maternal drug use, socioeconomic status, and HIV disease stage before conclusions can be drawn regarding an effect of HIV on short-term pregnancy outcome.

Impact of Pregnancy on Progression of Maternal HIV Infection

There has been considerable debate regarding the impact of pregnancy on HIV disease progression. The progressively deteriorating immune function in patients with HIV infection and the alteration in immunity associated with normal pregnancy (22–26) could theoretically accelerate the progression of HIV infection during and after pregnancy. In nonpregnant adults, immune system dysfunction as measured by the CD4+ lymphocyte count has been associated with an increased risk of progression to AIDS (27, 28).

Biggar and colleagues reported that CD4+ cell counts in 37 HIV-infected pregnant women fell to a nadir in the third trimester, about 8 weeks before delivery, and did not recover after delivery (29). Although a similar decline in the CD4+ cell count 8 weeks before delivery was seen among 63 HIV-seronegative women, the CD4+ cell count recovered to pre-pregnancy levels in the postpartum period. These data suggest that pregnancy may increase the risk of progression to symptomatic HIV disease by accelerating the depletion of CD4+ cells.

Infection with HIV may increase the risk of infectious complications in pregnancy. In one study, sexually transmitted diseases were diagnosed almost twice as often among seropositive than among seronegative pregnant women, although this could reflect behavioral life-style differences as well as potentially enhanced susceptibility to infection (11). Opportunistic infections were uncommon but were seen only among infected women in this study. In addition, a CD4+ cell count of less than 300/mm^3 has been associated with an increased risk of serious infections in pregnancy, including both opportunistic and serious bacterial infections. (30).

The prevalence of HIV-associated disease in pregnant women reported in several pregnant cohort studies from the United States and Europe has ranged from 1% to 6% for overt AIDS (8, 11, 14, 16), and from 5% to 44% for HIV-related symptoms or lymphadenopathy (8, 14, 16). Higher rates of AIDS and AIDS-related complex (ARC) (17% to 18%) have

been reported among cohorts of African childbearing women (17, 18). The higher percentage of reported AIDS in pregnant HIV-infected women in Africa, compared with Europe or the United States, may be related to several factors. In Africa, AIDS is diagnosed from clinical findings [World Health Organization (WHO) AIDS case definition] (31) in contrast to the more laboratory-based definition in the United States (CDC AIDS case definition) (32). The WHO AIDS case definition, although possibly more sensitive, may be less specific than the CDC AIDS case definition, thus artificially estimating a higher number of symptomatic patients with AIDS in Africa. Also, in developing countries, AIDS-defining illnesses may occur more commonly because of increased exposure to potential opportunistic pathogens and the possible lesser availability of preventive therapy (33). Alternatively, the higher frequency of AIDS in African women, when compared to women from other parts of the world, may be a result of geographic variation in the duration of infection or the virulence of circulating HIV strains.

Early, retrospective studies in the United States appeared to indicate a more rapid progression to AIDS in HIV-pregnant women, with half of women identified as HIV infected during pregnancy progressing to AIDS within 2–6 years (34, 35). However, data from these reports were limited in their ability to predict the impact of pregnancy on the progression of HIV infection because the duration of a woman's infection before pregnancy was unknown and there was no correlation of the maternal CD4+ cell count during or after pregnancy with symptomatology. More recent data from prospective studies indicate that adverse effects may be uncommon. In a prospective study, the rate of progression to AIDS was reported to be 4% per year in asymptomatic pregnant women and 16% per year in pregnant women with lymphadenopathy (36). Among asymptomatic HIV-infected homosexual men, the rate of development of AIDS is 2% to 5% per year (37).

A recent population-based study from Edinburgh, following HIV-infected and uninfected intravenous drug-using women and uninfected non–drug-using women, did not show a difference in survival time after the diagnosis of AIDS in 4 HIV-infected pregnant women and 6 HIV-infected nonpregnant women (survival time, 23 months vs. 20 months, respectively) (38). There was no excess of overall infectious complications requiring hospital admission during pregnancy in their HIV-infected pregnant cohort (comparing 119 HIV-infected, 174 uninfected drug-using, and 141 non–drug-using pregnant women), but HIV-infected pregnant women experienced more episodes of serious bacterial pneumonia and 3 infected women acquired *Pneumocystis carinii* pneumonia (PCP).

Maternal mortality related to AIDS has been reported during pregnancy in HIV-infected women (8, 39–42) and within 1 year of pregnancy in an additional 20 women (43). In 79% of cases of reported maternal deaths, PCP was the cause of mortality.

Treatment of HIV Infection in Pregnancy

The risk of opportunistic infection in pregnant women with a low CD4+ count, the risk of mortality caused by PCP in this population, and

the benefits of early treatment with zidovudine therapy (44, 45) and PCP prophylaxis (46) in asymptomatic, nonpregnant adults with CD4+ counts of less than 500/mm^3, have led to encouraging the obstetrician to become more active in the clinical management of HIV infection in pregnancy. In particular, the obstetrician should be familiar with counseling the HIV-infected woman, evaluating her clinical disease status, and discussing and offering her appropriate therapies.

In counseling an HIV-infected woman during pregnancy, the obstetrician should discuss the significance of HIV disease in pregnancy, the risks of vertical transmission of HIV to the infant, the availability of all reproductive options, and treatment options for the woman herself. A detailed review of counseling issues is beyond the scope of this article, but several excellent reviews have been published regarding HIV counseling and management in the prenatal setting (47–49).

The high risk for contracting opportunistic infections by nonpregnant individuals with CD4+ lymphocyte counts of less than 200/mm^3 or less than 20% of total lymphocytes led to the recommendation for nonpregnant individuals that the CD4+ lymphocyte count be measured at the time of diagnosis of HIV infection to assist in decisions regarding initiation of antiretroviral therapy (currently initiated when CD4+ count drops below 500/mm^3) and PCP prophylaxis (recommended when CD4+ count drops below 200/mm^3) (46, 50). In nonpregnant individuals with a CD4+ count of more than 200/mm^3, monitoring the CD4+ count at least every 6 months is recommended, with more frequent evaluation in patients with new-onset symptoms (e.g., fever or thrush), or a rapidly declining or borderline CD4+ count. A low CD4+ count should be reconfirmed before initiation of therapy.

Evaluation of the CD4+ count is also important during pregnancy because of the risk of development of life-threatening opportunistic infection in pregnant women with low CD4+ counts (30). In pregnant women with CD4+ counts of less than 200/mm^3, individualized consideration should be given regarding initiation of antiretroviral therapy and PCP prophylaxis. Although current Public Health Service guidelines have avoided recommendations for therapies during pregnancy or recommended deferring prophylaxis until after pregnancy ends to avoid potential theoretical harm to the fetus (46, 50), some obstetricians believe that obstetrical concerns about the pregnant woman's own health may be significant enough to warrant initiation of antiretroviral therapy or PCP prophylaxis during pregnancy, particularly for those whose CD4+ count is less than 200/mm^3 (51).

Considerations of therapy of HIV infection or prophylaxis for infectious complications during pregnancy have been difficult because of the lack of information concerning the maternal, fetal, and newborn safety of new or potentially toxic therapies, e.g., zidovudine, aerosolized pentamidine, and trimethoprim/sulfamethoxazole. Minkoff and Moreno have favored the position that the availability of HIV-related therapies should be disclosed to HIV-infected pregnant women who would warrant initiation of such therapies in the nonpregnant state (51). Assessment of the risks and benefits of HIV-related treatments during pregnancy is complex and

requires individualized discussion between the patient and her obstetrician. Table 2 provides an outline of general considerations that should be discussed with the patient. A detailed discussion of risks and benefits during pregnancy is beyond the scope of this article, but these have been reviewed by obstetricians in several recent publications (52–54).

HIV Transmission From Mother to Child: Timing of Vertical Transmission

Vertical transmission of HIV from a pregnant woman to her offspring was first described in 1982 (55). Vertical transmission of HIV may occur

TABLE 2.—Treatment Options in HIV-Infected Pregnant Women: General Considersations

I. Risks of HIV Infection in Pregnancy

Maternal infection complications (i.e., Pneumocystis carinii pneumonia)
- elevated risk with CD4+ count < 200/mm^3

Transmission of HIV from mother to fetus/infant

II. Treatment Options for Non-Acute Illness in Non-Pregnant HIV-Infected Adults

Immunologic monitoring (CD4+ lymphocyte counts)
- CD4+ counts at least every 6 months

Antiretroviral therapy
- Zidovudine (AZT) when CD4+ count < 500/mm^3
- current dose recommendation: 100 mg orally 5 times/day

Prophylaxis for Pneumocystis carinii pneumonia
- initiate when CD4+ count < 200/mm^3
- therapeutic options (also apropos to pregnant state)
  - Trimethoprim/sulfamethoxazole
  - Areosolized pentamidine

III. Potential Maternal, Fetal, or Newborn Risk of Each Therapy

Known vs unknown risks

Maternal
- general known risks in nonpregnant adult

Fetal
- potential effects on fetal growth & development, teratogenicity
- trimester of drug exposure

Newborn
- potential toxicities (i.e. potential kernicterus due to bilirubin displacement by sulfonamide present in infant)

IV. Potential Maternal and Fetal Benefit of Each Therapy

Known vs unknown benefits

Maternal
- prevention of significant morbidity and mortality

Fetal
- prevention of life-threatening disease in mother and consequences of such diseases to fetus

before, during, or after parturition; information regarding the relative proportion and efficiency of transmission during each of these time periods, however, is limted (Table 3). The actual timing of vertical transmission—intrauterine, intrapartum, or post partum—has great relevance for the design and implementation of therapeutic interventions aimed at prevention of fetal or neonatal infection.

In Utero Transmission

Early data suggesting that HIV is transmitted during gestation came from clinical case reports of investigators who carefully studied infants born to HIV-infected mothers. In 1985, Lapointe and colleagues demon-

TABLE 3.—Timing of Vertical Transmission

Intrauterine Transmission	Intrapartum Transmission	Postpartum Transmission
Early onset symptoms (< 12 months old) ~ 30%	Later onset symptoms (> 12 months old) ~ 70%	HIV isolation from breast milk
Neonatal period viral identification (< 3 months old) ~ 30–50%	Delayed viral identification (≥ 4 months old) ~ 50–70%	Case reports of transmission via breastfeeding
? Dysmorphic syndrome	"Acute primary infection" viral/immunologic pattern	No evidence of transmission in households
HIV identified in placentas (≥ 8 weeks in gestation)	HIV isolation from vaginal/cervical secretions	
In vitro infection of placenta-derived cells	Discordant twins	
HIV identified in fetal tissue (≥ 13 weeks gestation)	Intrapartum blood exposure	

(Modified from Pizzo PA: *J Infect Dis* 161:316–325, 1990.)

strated HIV in thymic autopsy tissue from a 20-day-old infant born at 28 weeks' gestation to a mother with AIDS who died almost immediately after delivery (56). In 1986, DiMaria et al. reported a child born at 34 weeks' gestation to an HIV-infected woman in whom HIV was identified in cord blood lymphocytes and infant peripheral blood lymphocytes, but not the mother's peripheral blood lymphocytes (57). The child experienced early onset of HIV symptoms within the first month of life.

Marion and colleagues have described a dysmorphic syndrome involving craniofacial abnormalities, suggesting acquisition of HIV infection early in pregnancy, during the first or second trimester (58). However, this has not been confirmed by other investigators (59, 60). In the absence of well-controlled studies, there must be significant reservations about using the existence of this syndrome as indirect evidence of in utero infection.

As the technology to detect HIV has become more sophisticated, more direct evidence of in utero transmission of HIV has emerged in studies of placental and fetal tissue. Studies of placentas from HIV-infected women have shown inconsistent results. A number of studies have reportedly demonstrated HIV in placental tissue from HIV-infected women at as early as 8 weeks' gestation. In 1987, Hill and colleagues reported culturing HIV from the placenta of an HIV-infected pregnant woman delivering at term (61); however, maternal blood contamination could not be ruled out (62). Lewis and colleagues studied fetal and placental tissue from 8-week abortuses of 3 HIV-infected women using immunocytochemistry and in situ hybridization (63). Maternal decidual leukocytes, villous trophoblast derivatives, villous mesenchymal cells, and embryonic blood cell precursors were found to contain HIV gp41 antigen and nucleic acids. A series of 49 placentas were studied by European investigators, some from infected women who had therapeutic abortions between 10 and 22 weeks' gestation and others obtained at delivery. Retrovirus-like particles were observed in 6 of 13 placentas that underwent ultrastructural examination, in villous fibroblasts, syncytiotrophoblasts, and endothelial cells (64). In addition, an excess of chorioamnionitis was noted in placentas of infected women compared to uninfected women of similar background. Chandwani and colleagues reported the pathologic findings in term placentas from 43 HIV-infected women and 48 seronegative women (65). Similar to the European study, pathologic findings of chorionitis were more frequent in placentas of seropositive women compared to the seronegative controls (60% vs. 27%, $P < .01$). Human immunodeficiency virus core antigens and nucleic acids were identified by immunocytochemistry and in situ hybridization in the trophoblast of 10% of placentas that showed chorionitis.

In contrast, Peuchmaur and colleagues report on a prospective study of placentas from 75 HIV-infected women (30 term pregnancies, 45 induced abortions), only 3 of whom had symptomatic disease (CDC grade IV) (66). Mononuclear cells expressing CD4 were detected in the chorion and