# Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV-1 (Review)

**Read JS, Newell ML**


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## ABSTRACT

**Background**
Cesarean section before labor and before ruptured membranes ("elective cesarean section", or ECS) has been introduced as an intervention for the prevention of mother-to-child transmission (MTCT) of HIV-1. The role of mode of delivery in the management of HIV-1-infected women should be assessed in light of risks as well as benefits, since HIV-1-infected pregnant women must be provided with available information with which to make informed decisions regarding cesarean section and other options to prevent transmission of infection to their children.

**Objectives**
Our objectives were to assess the efficacy (for prevention of MTCT of HIV-1) and the safety of ECS among HIV-1-infected women.

**Search strategy**
Electronic searches were undertaken using MEDLINE and other databases. Hand searches of reference lists of pertinent reviews and studies, as well as abstracts from relevant conferences, were also conducted. Experts in the field were contacted to locate any other studies. The search strategy was iterative.

**Selection criteria**
Randomized clinical trials assessing the efficacy and safety of ECS for prevention of MTCT of HIV-1 were included in the analysis, as were observational studies with relevant data.

**Data collection and analysis**
Data regarding HIV-1 infection status of infants born to HIV-1-infected women according to mode of delivery were extracted from the reports of the studies. Similarly, data regarding postpartum morbidity (PPM) (including minor (e.g., febrile morbidity, urinary tract infection) and major (e.g., endometritis, thromboembolism) morbidity) of the HIV-1-infected women, and infant morbidity, according to mode of delivery were extracted.

**Main results**
One randomized clinical trial of the efficacy of ECS for prevention of MTCT of HIV-1 was identified. No data regarding infant morbidity according to the HIV-1-infected mother's mode of delivery were available. Data regarding PPM according to mode of delivery were available from this clinical trial as well as from five observational studies. Among HIV-1-infected women not taking antiretrovirals (ARVs) during pregnancy or taking only zidovudine, ECS was found to be efficacious for prevention of MTCT of HIV-1. PPM is generally higher among HIV-1-infected women who undergo cesarean as compared to vaginal delivery, with the risk with ECS being intermediate between that of vaginal delivery and NECS (including emergency procedures). Other factors associated with the risk of PPM among HIV-1-infected women include HIV-1 disease stage (more advanced disease, as manifested by lower CD4 counts and higher viral loads, being associated with a greater risk of PPM) and co-morbid conditions (e.g., diabetes).

**Authors' conclusions**
ECS is an efficacious intervention for the prevention of MTCT among HIV-1-infected women not taking ARVs or taking only zidovudine. The risk of PPM with ECS is higher than that associated with vaginal delivery, yet lower than with NECS. Among HIV-1-

infected women, more advanced maternal HIV-1 disease stage and concomitant medical conditions (e.g., diabetes) are independent risk factors for PPM. The risk of MTCT of HIV-1 according to mode of delivery among HIV-1-infected women with low viral loads (low either because the woman's HIV-1 disease is not advanced, or because her HIV-1 disease is well-controlled with ARVs) is unclear. Therefore, an important issue to be addressed in one or more large studies (individual studies or an individual patient data meta-analysis combining data from more than one study) is assessment of the effectiveness of ECS for prevention of MTCT of HIV-1 among HIV-1-infected women with undetectable viral loads (with or without receipt of highly active ARV therapy (HAART)).

## PLAIN LANGUAGE SUMMARY

Mother-to-child transmission (MTCT) of HIV is the primary way that children become infected with HIV. More than 2000 children worldwide are infected in this way every day.

Cesarean section before labor and before ruptured membranes (also called "elective cesarean section," or ECS) has been introduced as an intervention for the prevention of MTCT of HIV. The objectives of this review were to assess the efficacy (for prevention of MTCT of HIV) and the safety of ECS among HIV-infected women.

The authors found that ECS is a good intervention for the prevention of MTCT among HIV-infected women not taking antiretrovirals (ARV), or taking only zidovudine. The risk of MTCT of HIV according to mode of delivery among HIV-infected women with low HIV viral loads (low either because the woman's HIV disease is not advanced, or because her HIV disease is well-controlled with ARVs) is unclear. Therefore, an important issue to be addressed in one or more large studies is an assessment of the effectiveness of ECS for prevention of MTCT of HIV among HIV-infected women with undetectable viral loads, whether or not they are receiving highly active ARV therapy (HAART).

## BACKGROUND

An estimated 500,000 children died of AIDS in 2004 (UNAIDS 2004). Mother-to-child transmission (MTCT) of human immunodeficiency virus type 1 (HIV-1) is the most common etiology of pediatric HIV-1 infection throughout the world. A large proportion of the cases of MTCT of HIV-1 occur during the intrapartum period (Kourtis 2001). Possible mechanisms include transfusion of the mother's blood to the fetus during labor contractions, infection after the rupture of membranes, and direct contact of the fetus with infected secretions or blood from the maternal genital tract (Mofenson 1997; Kuhn 1995). Therefore, performing a cesarean section before the onset of labor and the rupture of membranes could decrease the risk of MTCT of HIV-1 (compared with vaginal delivery or cesarean section after onset of labor and/or after rupture of membranes).

It is well known that, in the absence of HIV-1 infection, cesarean section is associated with increased risks of maternal and infant morbidity (Pettiti 1985; Miller 1988; Morrison 1995). In a population of HIV-1-infected women, the procedure would be expected to be associated with the same, if not greater, deleterious effects on both mother and infant. For example, surgical delivery would be expected to increase the risk of fever, endometritis, and hemorrhage and severe anemia among women. In general, neonatal morbidity related to cesarean section would be expected to result from iatrogenic preterm delivery in situations where the gestational age is not accurately assessed prior to delivery. Even with accurate assessment of gestational age, the relative risk of neonatal respiratory morbidity with delivery by cesarean section before the onset of labor is higher if performed during the 38th week than during the 39th week of gestation (Morrison 1995). However, although the risk of neonatal respiratory morbidity is higher, the number of affected infants is small. In addition to respiratory morbidity (respiratory distress syndrome, transient tachypnea of the newborn), an increased risk of lacerations of newborn skin is also of concern with surgical delivery. In more unusual instances, the occurrence of postpartum or neonatal mortality is related to mode of delivery.

The role of mode of delivery in the management of HIV-1-infected women must be assessed in light of risks as well as benefits, since HIV-1-infected pregnant women must be provided with available information with which to make informed decisions regarding cesarean section and other options to prevent transmission of infection to their children.

## OBJECTIVES

1) To examine the efficacy of ECS for prevention of MTCT of HIV-1.

2) To evaluate the safety (in terms of postpartum and infant morbidity) of ECS compared with other mothers of delivery among HIV-1-infected women

## CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

### Types of studies

Analytic epidemiologic studies, both observational (case control and cohort studies) and interventional (clinical trials), of HIV-1-infected women and their infants were included. Studies performed in general or specific populations and in hospitals or clinics were included. Studies performed in any country and published in any language were included. Studies with historical controls and ecological studies were excluded. Mode of delivery must have been explicitly described, such that the risk of transmission of HIV-1 could be assessed according to at least the following types of deliveries: ECS; other cesarean section (NECS); vaginal delivery.

### Types of participants

HIV-1-infected pregnant women and their children.

### Types of intervention

Mode of delivery: ECS compared to other modes of delivery (vaginal delivery, NECS).

### Types of outcome measures

The outcome measures were:

1) HIV-1 infection in children born to HIV-1-infected women;

2) morbidity among HIV-1-infected women and their children. Types of PPM evaluated included: febrile morbidity, endometritis, hemorrhage or severe anemia, pneumonia, and urinary tract infections. Types of infant morbidity evaluated included: respiratory morbidity (respiratory distress syndrome and transient tachypnea of the newborn) and skin lacerations.

## SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

Electronic searches were undertaken using the following databases: MEDLINE, Embase, AIDSLINE, CINAHL, Scisearch, the Cochrane Controlled Trials Register, Database of Abstracts of Reviews of Effectiveness (DARE), Latin American and Caribbean Health Sciences (LILACS), the Cochrane HIV/AIDS and the Cochrane STD registers of studies. Hand searches of the reference lists of all pertinent reviews and studies found also were undertaken, as well as abstracts from relevant conferences, including the International AIDS Conferences and the annual Conference on Retroviruses and Opportunistic Infections over the past 10 years. Experts in the field of HIV-1 prevention were contacted to locate any further studies or relevant conference proceedings not included in the databases to ensure that unpublished studies were included. The search strategy was iterative.

Search
1 HIV
2 HIV-1
3 HIV-2
4 HIV INFECT*
5 HIV INFECTIONS
6 HIV INFECTED
7 (ACQUIRED IMMUNODEFICIENCY SYNDROME)
8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9 DELIVERY, OBSTETRIC
10 DELIVERY AND PREGNANCY
11 CAESAREAN SECTION
12“ MODE OF DELIVERY” AND PREGNANCY
13 #9 OR #10 OR #11 OR #12
14 INFANT MORTALITY
15 INFANT MORBIDITY
16 NEONATAL MORTALITY
17 NEONATAL MORBIDITY
18 MATERNAL MORTALITY
19 MATERNAL MORBIDITY
20 POSTPARTUM MORTALITY
21 POSTPARTUM MORBIDITY
22 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
23 #8 AND #13 AND #22
24 (ANIMAL OF ANIMALS) NOT HUMAN
25 #23 NOT #24

With regard to the electronic literature search, the optimal sensitive search strategy developed by The Cochrane Collaboration and detailed in the Cochrane Reviewers' Handbook (Handbook 2005) was used, in conjunction with search terms identified above, to identify relevant studies from 1966 to 2004.

## METHODS OF THE REVIEW

The search for studies was performed with the assistance of the Cochrane HIV/AIDS Group. The authors performed the selection of potentially relevant studies. The titles, abstracts and descriptor terms of all downloaded material from the electronic searches were read and irrelevant reports discarded to create a pool of potentially eligible studies. All citations identified then were inspected independently by JSR and MLN to establish relevance of the article and whether or not the full article should be acquired. If there is uncertainty, the full article was obtained.

1. Selection of studies:

The authors independently applied the inclusion criteria. Studies were reviewed for relevance based on study design, types of participants, exposures and outcome measures. Finally, where resolution was not possible because further information was

necessary, attempts were made to contact authors to provide further clarification of data. The method of conflict of resolution was by consensus.

2. Data extraction:

Using a standardized data extraction form, the authors independently extracted data.. The following characteristics were extracted from each included study:

Administrative details: Identification; author(s); published or unpublished; year of publication; year in which study was conducted

Details of study: Study design; type, duration and completeness of follow-up in the case of cohort studies; country and location of the study; setting in which the study was performed (e.g. urban or rural; population or hospital/clinic based); method(s) of recruitment; number of participants

Characteristics of participants: Age; socio-economic status; other identified risk factors (e.g., HIV-1 disease stage)

Details of intervention: Mode of delivery based on obstetrical record

Details of outcomes: MTCT of HIV-1; PPM (overall, and specific types, e.g., endometritis), neonatal morbidity (e.g., respiratory distress syndrome)

3. Quality assessment:

Quality assessment was performed using standardized quality assessment forms.

Randomized Controlled Trial: The methodological quality of included clinical trials was evaluated independently by the authors according to a validity checklist for clinical trials (ter Reit G 1997).

Observational Studies: The authors independently evaluated the methodological quality of the included observational studies. In all types of studies, particular emphasis was placed on the method of selection of the sample (criteria specific to the study design). In cohort studies, quality assessment included the type, length and completeness of follow-up and in case-control studies, case definition and control selection were included. According to the Newcastle-Ottawa Quality Assessment Scale (http://www.lri.ca/programs/ceu/oxford.htm), the authors independently evaluation the methodological quality of the observational studies,

Authors were not be blinded to the names of the authors, institutions, journal of publication or results of the studies. The method of conflict resolution was by consensus.

4. Data synthesis

Incomplete data: If data were incomplete, attempts were made to contact the authors for clarification of important information.

Data from randomized clinical trials were not combined with data from observational studies. Observational studies were assessed by type of study (e.g., prospective cohort studies).

Outcome measures: All outcomes included in this review are binary. Measures of association generally were expressed as crude and/or adjusted odds ratios together with their 95% confidence intervals. Odds ratios were used because they are the only valid estimator from case-control studies, and from adjusted analyses obtained from logistic regression.

## DESCRIPTION OF STUDIES

Studies included in this review: 1. Efficacy: Eur Mode Del 1999; 2. Safety: Eur HIV Ob 2004, Eur Mode Del 1999, Faucher 2001, Marcollet 2002, Read 2001, Watts 2000. Details of each study are given in the table "Characteristics of Included Studies" and are noted below:

1. Efficacy:

Eur Mode Del 1999: A randomized clinical trial of mode of delivery for prevention of MTCT of HIV-1 in Europe (Italy, France, United Kingdom, Spain, Switzerland, Sweden) was conducted. The primary objective of the trial was to assess MTCT rates according to mode of delivery. Women were recruited between 1993 and 1998. Women at 34-36 weeks gestation with a confirmed diagnosis of HIV-1 infection were eligible to enroll. Children were followed until 18 months after birth. Among those women who were followed until at least delivery and who delivered one or more liveborn infants, 188 women had been assigned to cesarean section and 220 women were assigned to vaginal delivery. Ninety-two women received zidovudine prophylaxis (40 in cesarean arm and 52 in vaginal arm), and none received HAART.

2. Safety:

Eur HIV Ob 2004: Two case control studies (vaginal and ECS) among HIV-1-infected women (cases) and uninfected, matched controls delivering between 1992 and 2002 were conducted. Cases and controls were enrolled at clinical centers in Europe (Sweden, Poland, Ukraine, Italy, Spain). Controls were matched to cases by selecting the first uninfected woman delivering after the index case. Cases and controls were matched on age, ethnicity, parity, for being admitted to the delivery unit with active labor (vaginal arm) and for having received antibiotics during labor or during the procedure (ECS arm). Women admitted for medical induction of labor or for emergency cesarean section were excluded. Morbidity occurring during the first six weeks after delivery was assessed. Morbidity was classified as major (postpartum hemorrhage requiring blood transfusion or surgery, pneumonia or pleural effusion, peritonitis, sepsis, diffuse intravascular coagulation and thromboembolism) or minor (anemia not requiring transfusion (less than 10 gram/dL), fever in excess of 38°C beyond 24 hours postpartum,

wound infection, curettage of the uterine cavity, endometritis, and urinary tract infection). In this case-control study, HIV-1-infected women were compared to HIV-1-uninfected women. For this systematic review, only information related to 408 HIV-1-infected women (250 with vaginal delivery; 158 with ECS) was assessed. Most women had CD4+ lymphocyte counts above 200 cells/mm3 (92.8% vaginal; 86.7% ECS). Women who delivered vaginally received either no ARVs during pregnancy (82.4%) or else received zidovudine alone (17.6%). In contrast, most women with ECS delivery received ARVs (17.7% zidovudine alone; 54.4% combination ARV regimens). All women who underwent cesarean section received prophylactic antibiotics. Women with anemia were more likely to have received one or more ARVs during pregnancy and to be immunosuppressed.

Eur Mode Del 1999: A randomized clinical trial of mode of delivery for prevention of MTCT of HIV-1 in Europe (Italy, France, United Kingdom, Spain, Switzerland, Sweden) was conducted. Assessment of PPM according to mode of delivery was a secondary objective of the trial. Women were recruited between 1993 and 1998. Women at 34-36 weeks gestation with a confirmed diagnosis of HIV-1 infection were eligible to enroll. Women were followed until six weeks after delivery. The following PPM events were evaluated: postpartum fever, postpartum bleeding or intravascular coagulation disease, and anemia of greater than moderate severity. Among those women who were followed until at least delivery and who delivered one or more liveborn infants, 188 women had been assigned to cesarean section and 220 women were assigned to vaginal delivery. Most women had CD4+ lymphocyte counts at or above 200 cells/mm3 (91% among those with cesarean section; 92.3% among those who delivered vaginally). According to actual mode of delivery, 225 women delivered by cesarean section and 183 delivered vaginally.

Faucher 2001: A retrospective cohort study of 202 HIV-1-infected pregnant women who received care at a French hospital (Bichat-Claude Bernard Hospital; Paris) between 1990 and 1998, irrespective of whether the infant was live born or stillborn, was conducted. Most of the information presented is descriptive in nature, including characteristics of the mothers and infants (geographic origin, mode of acquisition of HIV-1 infection, socioeconomic status, how HIV-1 infection was diagnosed, infections and cervical dysplasia, medical care during pregnancy, ARVs received during pregnancy, viral load, maternal and fetal pathology, mode of delivery, MTCT of HIV-1, risk factors for HIV-1 transmission) and PPM. Of the 202 women, 111 delivered vaginally, 69 by ECS, and 22 by NECS. Baseline viral load was only known for approximately one quarter of the cohort and, of these 55 women, 50% had a viral load < 500 copies/mL). Most women received ARVs during pregnancy [zidovudine only (83), zidovudine with lamivudine (54), and other ARV combinations (3)].

Marcollet 2002: A retrospective cohort study of 401 HIV-1-infected pregnant women who delivered at a French hospital (Cochin Hospital; Paris) from 1989 through 1999 was conducted. All cesarean deliveries among HIV-1-infected women (109 ECS, 92 NECS) were included, as were those vaginal deliveries (200) among HIV-1-infected women who delivered immediately preceding each cesarean delivery. PPM through six weeks after delivery was assessed. PPM events were postpartum fever (temperature greater than 38 degrees C every 4-6 hours for at least 24 hours at any time during the hospital stay) caused by endometritis (diagnosed clinically with a positive vaginal swab), urinary tract infection (diagnosed with greater than 1,000,000 colony-forming units per mL of a single microorganism on a urine sample obtained as a clean catch or with a catheter), pneumonia (diagnosed by chest x-ray), or wound infection (diagnosed clinically); thrombosis (deep vein or pulmonary); severe anemia requiring blood transfusion; postpartum surgical procedures; wound care after discharge; complications of anesthesia; transfer to the intensive care unit; and death. Serious complications were death, life-threatening conditions (sepsis with positive blood cultures, anemia requiring transfusion, and thrombosis), and complications that required a surgical procedure. Most ECS deliveries were performed to prevent MTCT. All women who underwent cesarean delivery received peripartum antibiotic prophylaxis. Baseline CD4+ lymphocyte counts varied by mode of delivery group ($p = 0.02$, highest median CD4+ count among women with vaginal delivery), but viral loads were similar across mode of delivery groups. During 1989-1994, no women received ARVs. During 1994-1997, zidovudine alone was received. From 1997-1999, combination ARV regimens were received.

Read 2001: An analysis of data collected as part of a prospective cohort study (Women and Infants Cohort Study, WITS) in North America between 1990 and 1998 was conducted. The objective of the analysis was to assess PPM among HIV-1-infected women according to mode of delivery, with the a priori hypothesis that ECS is associated with a higher risk of PPM. Definitions of PPM were included in the manuscript. Of 1186 deliveries, 890 were vaginal, 248 cesarean (56 ECS, 147 NECS, 17 of unknown type), and 48 unknown. Of 1076 vaginal, ECS, and NECS deliveries, diabetes was more common among women with cesarean deliveries ($p < 0.001$), and peripartum antibiotics were received in 60% of ECS deliveries and in 70% of NECS deliveries. The median gestational age at delivery ranged from 37.3 to 38.1 weeks, and did not differ significantly according to mode of delivery ($p = 0.08$).

Watts 2000: An analysis of data collected as part of a clinical trial of HIV-1 hyperimmune globulin for prevention of MTCT of HIV-1 (ACTG 185) in North America between 1993 and 1997 was conducted. Eligibility criteria for enrollment into the clinical trial were HIV-1 infection, a CD4+ lymphocyte count of 500 cells/mm3 or less, and 20-30 weeks gestation. Definitions of PPM were included in the manuscript. The study population consisted of 365 women who delivered vaginally, 37 women with ECS, and 95 women with NECS. Peripartum antibiotics were administered for 68% of ECS deliveries and 76% of NECS deliveries. The baseline

CD4+ lymphocyte count was less than 200 cells/mm3 for 20% of vaginal deliveries, 35% of ECS deliveries, and 18% of NECS deliveries. Most women received one ARV during pregnancy (78 for NECS deliveries, 84% for ECS deliveries, and 89% for vaginal deliveries).

## METHODOLOGICAL QUALITY

Only one randomized trial of mode of delivery and MTCT of HIV-1 has been conducted (Eur Mode Del 1999). This study allocated mode of delivery by randomization. Women were randomized to vaginal or cesarean delivery during pregnancy, and blinding of investigators and of subjects to allocated mode of delivery was possible initially. PPM assessments were conducted with knowledge of the mode of delivery. Efficacy results were reported according to allocated mode of delivery and according to actual mode of delivery. PPM results were reported according to actual mode of delivery.

All of the cohort studies were assessed to have study populations that were representative of HIV-1-pregnant/postpartum women, with women with ECS being drawn from the same population as women with other modes of delivery. The assessment of outcome was accomplished through record linkage (delivery records linked with postpartum records), with an adequate follow-up period for the outcome of interest (PPM). Follow-up was judged to be adequate for all of these studies. The case control study was assessed to have had an adequate case definition, representativeness of the cases, and selection of controls. The same method of ascertainment was used for cases and for controls.

## RESULTS

After screening 900 citations, we identified 26 potentially relevant studies. In terms of the efficacy of ECS for prevention of MTCT of HIV-1, one randomized controlled trial comparing MTCT of HIV-1 according to mode of delivery (cesarean delivery vs. vaginal delivery) has been performed (Eur Mode Del 1999). The trial demonstrated the efficacy of cesarean section for the prevention of MTCT of HIV-1. The rate of MTCT differed significantly according to mode of delivery group, both when assessed according to allocated mode of delivery (cesarean section: 1.8%; vaginal delivery: 10.5%) and when assessed according to actual mode of delivery (cesarean section 3.5%; vaginal: 10.2%). According to allocated mode of delivery (vaginal delivery: reference), the odds ratio and 95% confidence interval for HIV-1 infection among children was 0.2 (0-0.8) for cesarean section among those women who did not receive zidovudine and 0.2 (0-1.7) among those who did receive zidovudine.

The effectiveness of cesarean section before labor and before ruptured membranes was demonstrated in an individual patient data meta-analysis of European and North American data (Int Perin HIV 1999) and confirmed results from observational studies (primarily from Europe) suggesting ECS was associated with a lower risk of MTCT of HIV-1 (Kuhn 1995; Bobat 1996; Ital Coll Stud 1999; Europ Coll Stud 1999; Grosch-Worner 2000; Europ Coll Stud 2001; Ital Reg 2002). The results of the individual patient data meta-analysis suggested the effectiveness of cesarean section before labor and before ruptured membranes existed both among women who were not receiving any ARVs during pregnancy and among those women receiving zidovudine prophylaxis alone.

In terms of the safety of cesarean section for prevention of mother-to-child transmission of HIV-1, there were no data regarding infant morbidity according to mode of delivery among HIV-1-infected women. However, several studies have evaluated PPM according to mode of delivery among HIV-1-infected women. Most of these studies compared morbidity among HIV-1-infected and -uninfected women (Semprini 1995; Grubert 1999; Maiques 1999; Vimercati 2000; Rodriguez 2001; Urbani 2001; Grubert 2002; Avidan 2002; Ferrero 2003; Panburana 2003). Other studies have described PPM among HIV-1-infected women who underwent cesarean delivery to prevent MTCT (Bremerich 2003; Panburana 2004).

The only studies evaluating the risk of PPM according to mode of delivery among HIV-1-infected women are the European randomized clinical trial of mode of delivery (Eur Mode Del 1999) and five observational studies from North America and Europe (Eur HIV Ob 2004; Faucher 2001; Marcollet 2002; Read 2001; Watts 2000).

Eur HIV Ob 2004: The overall PPM rate among HIV-1-infected women was 29% (119/408), with 17% (42/250) of vaginal deliveries complicated by minor PPM and none with major PPM. Among cesarean section deliveries, 49% (77/158) were complicated by minor PPM and 3% (124/408) by major PPM. There was no significant time trend in PPM rates. Also, hospitalization after delivery was longer for mothers who delivered by cesarean section. There were no major PPM events among women who delivered vaginally, but 16.8% (42/250) experienced minor complications: fever (18), anemia not requiring transfusion (7), urinary tract infection (3), endometritis (11), hematoma (1), wound dehiscence (1), and wound infection (1). Women with fever were more likely to have had an episiotomy, especially one with a medio-lateral incision. In contrast, there were five (3.2%) major PPM events among women who delivered by cesarean section: peritonitis (3) and pneumonia (2). All received one or more ARVs during pregnancy. Almost half of women who delivered by cesarean section (77/158; 48.7%) had minor morbidity: fever (3); anemia not requiring transfusion (64), urinary tract infection (4), endometritis (2), wound dehiscence (3), and wound infection (1). All received prophylactic antibiotics. HIV-1-infected women who underwent cesarean section were more likely to have minor PPM [OR = 2.94

(95%CI: 2.13, 4.0) and major PPM [OR = 8.4 (95%CI: 0.92, 18.2)].

Eur Mode Del 1999: Postpartum fever was more common among women who delivered by cesarean section (6.7%) than with vaginal delivery (1.1%). Postpartum bleeding and intravascular coagulation disease occurred among one woman in each mode of delivery group. Anemia (hemoglobin < 8 g/dL) occurred among two women who delivered vaginally and four women who delivered by cesarean section.

Faucher 2001: The overall PPM rate was 10%. Two women (1%) had phlebitis (one who delivered vaginally and the other who delivered by cesarean section). There were three cases of endometritis (one of which was following cesarean section), two transfusions because of severe anemia, one case of placental retention, one tearing of the perineal scar necessitating reintervention, two cases of septicemia, two pneumonias, and two cerebral toxoplasmosis cases. Four women died after delivery (two pneumonias, one lymphoma, one septicemia), and all were very ill prior to delivery. One death occurred after a vaginal delivery, and the others after cesarean sections. Overall, 8/91 (8.8%) women who delivered by cesarean section experienced PPM.

Marcollet 2002: The overall PPM rate was 21.7% (serious: 6.5%). In general, NECS was associated with the highest risk of PPM, vaginal delivery the lowest, and ECS with intermediate risk. Women in the ECS group were significantly more likely to have postpartum fever, to need wound care after discharge, and to have more than one complication than those delivered vaginally. In adjusted analyses, controlling for maternal CD4+ count and antepartum hemorrhage, the relative risk of any PPM was 1.85 (95%CI: 1.00, 3.39) after ECS and 4.17 (95%CI: 2.32, 7.49) after NECS, compared with vaginal deliveries. In multivariable analysis of febrile morbidity, the risk was significantly increased only in cases of NECS and was significantly associated with low maternal CD4+ lymphocyte counts.

Read 2001: PPM complicated 178 (15%) of 1186 deliveries. PPM events observed were (all events defined according to WITS a priori definitions): fever without diagnosed infection (63), hemorrhage or severe anemia (60 deliveries), endometritis (44), urinary tract infection (39 cystitis and 1 pyelonephritis), cesarean incision infection (15) or dehiscence (27), episiotomy infection (5) or dehiscence (12), and pneumonia (9). Two women died within the first 8 weeks after delivery (1 delivered vaginally, the other delivered by cesarean section of unknown type), both due to Pneumocystis pneumonia. In general, the risk of PPM was greatest with NECS, intermediate with ECS, and lowest with vaginal delivery. In unadjusted analyses, the likelihood of overall PPM was increased (compared to vaginal delivery) among women undergoing ECS [OR = 3.19 (95%CI: 1.69, 6.00)] or NECS [OR = 4.10 (95%CI: 2.71, 6.19)]. Other factors besides mode of delivery found to be independently associated with the risk of PPM overall, or specific types of PPM, were: maternal CD4+ lymphocyte count and plasma HIV-1 RNA concentration, receipt of ARVs during pregnancy, and diabetes.

Watts 2000: Endometritis occurred more frequently among those with cesarean sections vs. those with vaginal delivery. Other events more common among cesarean section subjects vs. vaginal delivery subjects were: amnionitis, wound infection, pneumonia, and platelet transfusion. Additional analyses were conducted regarding three complications which occurred relatively frequently, were serious, and were potentially modifiable: amnionitis-postpartum endometritis, wound infection, and red blood cell transfusion. Those women who delivered by cesarean section were more likely to have amnionitis-postpartum endometritis.

In summary, PPM is generally higher among HIV-1-infected women who undergo cesarean as compared to vaginal delivery, with the risk with ECS being intermediate between that of vaginal delivery and NECS (including emergency procedures). Other factors associated with the risk of PPM among HIV-1-infected women include HIV-1 disease stage (more advanced disease, as manifested by lower CD4 counts and higher viral loads, being associated with a greater risk of PPM) and co-morbid conditions (e.g., diabetes).

## DISCUSSION

One clinical trial was identified which evaluated the efficacy of cesarean section for prevention of MTCT of HIV-1. This trial, along with five observational studies (four cohort studies and one case control study), evaluated the safety of cesarean section and vaginal delivery among HIV-1-infected women. These studies indicate ECS can substantially reduce the risk of MTCT. It is important to note that the trial included only HIV-1-infected women taking no ARVs during pregnancy or taking only zidovudine. Although PPM is generally higher among HIV-1-infected women who undergo cesarean section (ECS or NECS, with NECS having the greatest risk of morbidity), much of the observed morbidity is minor. Both major and minor PPM may be largely avoidable with attention to known risk factors for PPM among HIV-1-infected women (e.g., more advanced maternal disease and comorbid conditions such as diabetes). In general, the benefit of ECS outweighs the risk of PPM among HIV-1-infected women, but the risk/benefit ratio depends upon the underlying rate of MTCT. With very low rates of MTCT, the risks associated with ECS may outweigh the benefit. Studies of ECS among HIV-1-infected women have been conducted almost exclusively in North America and Europe. In developing countries, the risks and benefits associated with ECS have been largely unexplored.

## AUTHORS' CONCLUSIONS

### Implications for practice

The benefit of cesarean section before labor and before ruptured membranes in preventing MTCT of HIV-1 was demonstrated among HIV-1-infected women during the mid-1990s who received either no ARV prophylaxis or treatment, or who received zidovudine alone. The magnitude of the effect of this intervention in decreasing transmission is larger than the risk of PPM observed in the one interventional study (randomized clinical trial in Europe) and the observational studies (in North America and Europe). In addition, PPM rates among HIV-1-infected women were observed to decline over time (Read 2001), suggesting that as the medical (ARV prophylaxis or treatment during pregnancy) and surgical (peripartum antibiotic prophylaxis) management of HIV-1-infected women improves, the risk of PPM with ECS will decrease.

Of note, however, is that the available data regarding the benefit of cesarean section as an intervention to prevent transmission are largely from studies conducted before the widespread utilization of HAART for women who require therapy for their own health, or ARV prophylaxis for HIV-1-infected pregnant women who do not meet criteria for treatment [e.g., whose plasma viral load measurements are above the recommended threshold for utilization of ARV prophylaxis for prevention of MTCT of HIV-1 (e.g., 1000 copies/mL in the U.S.)] (CDC 2005). Therefore, the benefit of cesarean section delivery among HIV-1-infected women with less advanced or well-controlled HIV-1 disease, among whom, the risk of MTCT is extremely low (e.g., 2% or less) is unclear. In such a setting, the short-term risk of the intervention (i.e., morbidity experienced by the mother within the first six weeks after delivery) may exceed the long-term benefit (prevention of HIV-1 transmission to the infant).

Individualized obstetrical management of these HIV-1-infected women with a very low risk of transmission to infants irrespective of mode of delivery is necessary, following discussions between the woman and her obstetrician. However, for those women with poorly controlled HIV-1 disease and/or no ARV prophylaxis or treatment, the benefit of ECS generally outweighs the risk of PPM.

### Implications for research

The risk of MTCT of HIV-1 according to mode of delivery among HIV-1-infected women with low viral loads (low either because the woman's HIV-1 disease is not advanced, or because her HIV-1 disease is well-controlled with ARV therapy) is unclear. Preliminary data suggest continued benefit of ECS among HIV-1-infected women with plasma viral loads < 1000 copies/mL (Ioannidis 2001) or women receiving HAART (Europ Coll Stud 2005). The benefit of ECS for prevention of MTCT of HIV-1 may persist among women with low plasma viral loads because of compartmentalization of HIV-1 reservoirs, i.e., a low plasma viral load does not necessarily indicate a low viral load among genital tract secretions. Therefore, an important issue to be addressed in one or more large studies (individual studies or an individual patient data meta-analysis combining data from more than one study) is assessment of the effectiveness of cesarean section for prevention of MTCT of HIV-1 among HIV-1-infected women with undetectable viral loads (with or without receipt of HAART).

## POTENTIAL CONFLICT OF INTEREST

Dr. Read was the author of two included studies. Prof. Newell was an author of two included studies.


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# REFERENCES

## References to studies included in this review


**Eur HIV Ob 2004** *{published data only}*

European HIV in Obstetrics Group. Higher rates of post-partum complications in HIV-infected than in uninfected women irrespective of mode of delivery. *AIDS* 2004;**18**:933–938.

**Eur Mode Del 1999** *{published data only}*

The European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical transmission: a randomised clinical trial. *Lancet* 1999;**353**:1035–1039.

**Faucher 2001** *{published data only}*

Faucher Ph, Batallan A, Bastian H, Matheron S, Morau G, Madelenat P, Benifla JL. Prenatal care of HIV-1-infected women in a French hospital between 1990 and 1998: a retrospective analysis of 202 pregnancies [Prise en charge des femmes enceintes infectees par le VIH a l'hopital Bichat entre 1990 et 1998: analyse de 202 grossesses]. *Gynecol Obstet Fertil* 2001;**29**:211–225.

**Marcollet 2002** *{published data only}*

Marcollet A, Goffinet F, Firtion G, Pannier E, Le Bret T, Brival M-L, Mandelbrot L. Differences in postpartum morbidity in women who are infected with human immunodeficiency virus after elective cesarean delivery, emergency cesarean delivery, or vaginal delivery. *Am J Obstet Gynecol* 2002;**186**(4):784–789.

**Read 2001** *{published data only}*

Read JS, Tuomala R, Kpamegan E, Zorrilla C, Landesman S, Brown G, Vajaranant M, Hammill H, Thompson B, for the Women and Infants Transmission Study Group. Mode of delivery and postpartum morbidity among HIV-infected women: The Women and Infants Transmission Study. *JAIDS* 2001;**26**:236–245.

**Watts 2000** *{published data only}*

Watts DH, Lambert JS, Stiehm ER, Bethel J, Whitehouse J, Fowler MG, Read J, for the Pediatric AIDS Clinical Tirals Group 185 Study Team. Complications according to mode of delivery among human immunodeficiency virus-infected women with CD4 lymphocyte counts of <= 500/uL. *Am J Obstet Gynecol* 2000;**185**(1):100–107.


## Additional references


**Avidan 2002**

Avidan MS, Groves P, Blott M, et al. Low complication rate associated with cesarean section under spinal anesthesia for HIV-1-infected women on antiretroviral therapy. *Anesthesiology* 2002;**97**:320–324.

**Bobat 1996**

Bobat R, Coovadia H, Coutsoudis A, Moodley D. Determinants of mother-to-child transmission of human immunodeficiency virus type 1 infection in a cohort from Durban, South Africa. *Pediatr Infect Dis J* 1996;**15**:604–610.

**Bremerich 2003**

Bremerich DH, Ahr A, Buchner S, et al. [Anasthesiologische Versorgung von HIV-positiven Schwangeren zur electiven Sectio caesarea]. *Anaesthesist* 2003;**52**:1124–1131.

**CDC 2005**

Centers for Disease Control and Prevention. U.S. Public Health Service Task Force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing perinatal HIV-1 transmission in the United States. *MMWR* 1998;**47**(RR-2):1-30 (Most recent revision of the guidelines available at www.aidsinfo.nih.gov).

**Europ Coll Stud 1999**

European Collaborative Study. Maternal viral load and vertical transmission of HIV-1: an important factor but not the only one. *AIDS* 1999;**13**:1377–1385.

**Europ Coll Stud 2001**

European Collaborative Study. HIV-infected pregnant women and vertical transmission in Europe since 1986. *AIDS* 2001;**15**:761–770.

**Europ Coll Stud 2005**

European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2005;**40**:458–465.

**Ferrero 2003**

Ferrero S, Bentivoglio G. Post-operative complications after caesarean section in HIV-infected women. *Arch Gynecol Obstet* 2003;**268**:268–273.

**Grosch-Worner 2000**

Grosch-Worner I, Schafer A, Obladen M, Maier RF, Seel K, Feiterna-Sperling C, Weigel R. An effective and safe protocol involving zidovudine and caesarean section to reduce vertical transmission of HIV-1 infection. *AIDS* 2000;**14**:2903–2911.

**Grubert 1999**

Grubert TA, Reindell D, Kastner R, Lutz-Freidrich R, Beloradsky BH, Dathe O. Complications after caesarean section in HIV-1-infected women not taking antiretroviral treatment. *Lancet* 1999;**354**:1612–1613.

**Grubert 2002**

Grubert TA, Reindell D, Kastner R, Belohradsky BH, Gurtler L, Stauber M, Dathe O. Rates of postoperative complications among human immunodeficiency virus-infected women who have undergone obstetric and gynecologic surgical procedures. *Clin Infect Dis* 2002;**34**:822–830.

**Handbook 2005**

Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions 4.2.5*. Oxford, 2005.

**Int Perin HIV 1999**

International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1: a meta-analysis of 15 prospective cohort studies. *N Engl J Med* 1999;**340**:977–987.

**Ioannidis 2001**

Ioannidis JP, Abrams EJ, Ammann A, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads < 1000 copies/mL. *J Infect Dis* 2001;**183**:539–545.

**Ital Coll Stud 1999**

Italian Collaborative Study on HIV Infection in Pregnancy. Mother-to-child transmission of human immunodeficiency virus in Italy: temporal trends and determinants of infection. *Hum Reprod* 1999;**14**:242–246.

**Ital Reg 2002**
Italian Register for human immunodeficiency virus infection in children. Determinants of mother-to-infant human immunodeficiency virus 1 transmission before and after the introduction of zidovudine prophylaxis. *Arch Pediatr Adolesc Med* 2002;**156**:915–921.

**Kourtis 2001**
Kourtis AP, Bulterys M, Nesheim SR, Lee FK. Understanding the timing of HIV transmission from mother to infant. *JAMA* 2001; **285**:709–712.

**Kuhn 1995**
Kuhn L, Stein ZA, Thomas PA, Singh T, Tsai W-Y. Maternal-infant HIV transmission and circumstances of delivery. *Am J Pub Hlth* 1995; **84**:1110–1115.

**Maiques 1999**
Maiques-Montesinos V, Cervera-Sanchez J, Bellver-Pradas J, et al. Post -cesarean section morbidity in HIV-positive women. Acta Obstet Gynecol Scand. *Acta Obstet Gynecol Scand* 1999;**78**:789–792.

**Miller 1988**
Miller JR Jr. Maternal and neonatal morbidity and mortality in cesarean section. *Obstet Gynecol Clin N Am* 1988;**15**:629–638.

**Mofenson 1997**
Mofenson LM. Mother-child HIV-1 transmission: timing and determinants. *Obstet Gynecol Clin North Am* 1997;**24**:759–784.

**Morrison 1995**
Morrison JJ, Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesarean section. *Br J Obstet Gynaecol* 1995;**102**:101–106.

**Panburana 2003**
Panburana P, Phaupradit W, Tantisirin O, Sriintravanit N, Baumuenvai J. Maternal complications after Caesarean section in HIV-infected pregnant women. *Austr NZ J Obstet Gynaecol* 2003;**43**:160–163.

**Panburana 2004**
Panburana P, Sirinavin S, Phuapradit W, Vibhagool A, Chantratita W. Elective cesarean delivery plus short-course lamivudine and zidovudine for the prevention of mother-to-child transmission of human immunodeficiency virus type 1. *Am J Obstet Gynecol* 2004;**190**: 803–808.

**Pettiti 1985**
Pettiti DB. Maternal mortality and morbidity in cesarean section. *Clin Obstet Gynecol* 1985;**28**:763–769.

**Rodriguez 2001**
Rodriguez EJ, Spann C, Jamieson D, et al. Postoperative morbidity associated with cesarean delivery among human immunodeficiency virus-seropositive women. *Am J Obstet Gynecol* 2001;**184**: 1108–1111.

**Semprini 1995**
Semprini AE, Castagna C, Ravizza M, et al. The incidence of complications after caesarean section in 156 HIV-positive women. *AIDS* 1995;**9**:913–917.

**ter Reit G 1997**
der Reit G, Kessels AGH. Commentary on Rampes et al 'Does electroacupuncture reduce craving for alcohol? A randomized controlled study'. *Compl Therap in Med* 1997;**5**:116–118.

**UNAIDS 2004**
UNAIDS. Global summary of the HIV and AIDS epidemic, December 2004. Available at: www.unaids.org.

**Urbani 2001**
Urbani G, de Vries MMJ, Conje HS, et al. Complications associated with cesarean section in HIV-infected patients. *Internatl J Gynecol Obstet* 2001;**74**:9–15.

**Vimercati 2000**
Vimercati A, Greco P, Loverro G, Lopalco PL, Pansini V, Selvaggi L. Maternal complications after caesarean section in HIV infected women. *Eur J Obstet Gynecol Reprod Biol* 2000;**90**:73–76.

## TABLES

### Characteristics of included studies

| **Study** | **Eur HIV Ob 2004** |
|---|---|
| Methods | Two case control studies (vaginal and ECS) among HIV-1-infected women (cases) and uninfected, matched controls |
| Participants | HIV-1-infected women and uninfected women |
| Interventions | Mode of delivery |
| Outcomes | PPM according to mode of delivery |
| Notes | |
| Allocation concealment | D – Not used |

| **Study** | **Eur Mode Del 1999** |
|---|---|
| Methods | Randomized trial of cesarean section for prevention of MTCT of HIV-1 |

| | |
|---|---|
| Participants | HIV-1-infected women and their infants |
| Interventions | Cesarean section before labor and before ruptured membranes |
| Outcomes | HIV-1 infection in infants; PPM in women |
| Notes | Allocation concealment was not possible since intervention was surgery. |
| Allocation concealment | D – Not used |

| **Study** | **Faucher 2001** |
|---|---|
| Methods | Retrospective cohort study |
| Participants | HIV-1-infected women |
| Interventions | Mode of delivery |
| Outcomes | PPM according to mode of delivery |
| Notes | |
| Allocation concealment | D – Not used |

| **Study** | **Marcollet 2002** |
|---|---|
| Methods | Retrospective cohort study |
| Participants | HIV-1-infected women |
| Interventions | Mode of delivery |
| Outcomes | PPM according to mode of delivery |
| Notes | |
| Allocation concealment | D – Not used |

| **Study** | **Read 2001** |
|---|---|
| Methods | Analysis of data collected as part of a prospective cohort study of HIV-1-infected women and their children (the Women and Infants Transmission Study, or WITS) |
| Participants | HIV-1-infected women and their children |
| Interventions | Mode of delivery |
| Outcomes | PPM according to mode of delivery |
| Notes | |
| Allocation concealment | D – Not used |

| **Study** | **Watts 2000** |
|---|---|
| Methods | Analysis of data collected as part of a clinical trial (ACTG 185), a randomized, placebo-controlled trial of HIV-1 hyperimmune globulin (HIVIG) for prevention of MTCT of HIV-1 |
| Participants | HIV-1-infected women enrolled in this clinical trial |
| Interventions | Mode of delivery |
| Outcomes | PPM according to mode of delivery |
| Notes | |
| Allocation concealment | D – Not used |

For the European Mode of Delivery trial (1999), allocation concealment was adequate for the efficacy part of the trial; allocation concealment was not used for the safety aspect of the trial.

## GRAPHS AND OTHER TABLES

This review has no analyses.

## INDEX TERMS

**Medical Subject Headings (MeSH)**

*Cesarean Section; Disease Transmission, Vertical [*prevention & control]; *HIV-1; HIV Infections [*transmission]; Infant, Newborn; *Pregnancy Complications, Infectious

**MeSH check words**

Female; Humans; Pregnancy

## COVER SHEET

| | |
|---|---|
| **Title** | Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV-1 |
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| **Contact address** | Dr Jennifer Read<br>Pediatric, Adolescent, and Maternal AIDS Branch<br>Center for Research for Mothers and Children<br>National Institute of Child Health and Human Development, National Institutes of Health<br>Executive Building, Room 4B11F, 6100 Executive Boulevard MSC 7510<br>Bethesda<br>MD<br>20892-7510<br>USA<br>E-mail: jr92o@nih.gov<br>Tel: 301 435-6872<br>Fax: 301 496-8678 |

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