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THE MODE OF DELIVERY AND THE RISK OF VERTICAL TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1

A Meta-Analysis of 15 Prospective Cohort Studies

THE INTERNATIONAL PERINATAL HIV GROUP*

ABSTRACT

Background To evaluate the relation between elective cesarean section and vertical transmission of human immunodeficiency virus type 1 (HIV-1), we performed a meta-analysis using data on individual patients from 15 prospective cohort studies.

Methods North American and European studies of at least 100 mother–child pairs were included in the meta-analysis. Uniform definitions of modes of delivery were used. Elective cesarean sections were defined as those performed before onset of labor and rupture of membranes. Multivariate logistic-regression analysis was used to adjust for other factors known to be associated with vertical transmission.

Results The primary analysis included data on 8533 mother–child pairs. After adjustment for receipt of antiretroviral therapy, maternal stage of disease, and infant birth weight, the likelihood of vertical transmission of HIV-1 was decreased by approximately 50 percent with elective cesarean section, as compared with other modes of delivery (adjusted odds ratio, 0.43; 95 percent confidence interval, 0.33 to 0.56). The results were similar when the study population was limited to those with rupture of membranes shortly before delivery. The likelihood of transmission was reduced by approximately 87 percent with both elective cesarean section and receipt of antiretroviral therapy during the prenatal, intrapartum, and neonatal periods, as compared with other modes of delivery and the absence of therapy (adjusted odds ratio, 0.13; 95 percent confidence interval, 0.09 to 0.19). Among mother–child pairs receiving antiretroviral therapy during the prenatal, intrapartum, and neonatal periods, rates of vertical transmission were 2.0 percent among the 196 mothers who underwent elective cesarean section and 7.3 percent among the 1255 mothers with other modes of delivery.

Conclusions The results of this meta-analysis suggest that elective cesarean section reduces the risk of transmission of HIV-1 from mother to child independently of the effects of treatment with zidovudine. (N Engl J Med 1999;340:977-87.)

A SUBSTANTIAL proportion of the cases of mother-to-child (vertical) transmission of human immunodeficiency virus type 1 (HIV-1) occur during the intrapartum period.[1] 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.[2,3] Therefore, performing cesarean section before the onset of labor and the rupture of membranes could decrease the risk of vertical transmission.

Early findings from ongoing European cohort studies suggested an association between the mode of delivery and vertical transmission of HIV-1.[4-6] Subsequently, studies that used multivariate analyses found a decreased likelihood of transmission with cesarean section[7-10] or elective cesarean section.[11,12] An association between the mode of delivery and the risk of vertical transmission was not demonstrated in other studies, possibly owing to small sample sizes[13,14] or an inability to distinguish between elective and nonelective cesarean sections.[13,15,16] A relation between the mode of delivery and the risk of mother-to-infant transmission of HIV-1 has never been demonstrated in analyses of data from North American cohort studies or, until recently, from a large European cohort study in which elective cesarean sections were distinguished from nonelective cesarean sections.[17] Previous meta-analyses were unable to distinguish between elective and nonelective

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*The persons and studies participating in the International Perinatal HIV Group are listed in the Appendix.

cesarean section or to control for potentially confounding variables.[18,19]

In the absence of data from the European randomized clinical trial of the mode of delivery,[20] we initiated an international collaborative effort resulting in a meta-analysis of data on individual patients in prospective cohort studies to evaluate the association between the mode of delivery and the risk of vertical transmission of HIV-1. The a priori hypothesis was that the risk of vertical transmission is lower among HIV-1–infected women who undergo elective cesarean section than among those who use other modes of delivery.

METHODS

Eligible studies were prospective cohort studies that included at least 100 mother–child pairs, that had data on the mode of delivery and the children's infection status, and that were conducted in regions where HIV-1–infected women are advised not to breast-feed. Studies written in English were identified by computerized searches of the medical literature with the use of Medline and through discussions with colleagues.

The study population consisted of all mother–child pairs enrolled in the participating studies on or before January 1, 1997, except those enrolled after the first seven days of the child's life, those in which the mother was not known to be infected with HIV-1 on or before the date of the child's birth, those involving multiple births, and those in which the child was known to have been breast-fed. For ongoing studies, children who were not born before a study-specific date before January 1, 1997, were excluded to accommodate the varying lengths of time (3 to 18 months) required to ascertain a child's infection status, depending on the methods used (e.g., either virologic detection or serologic methods combined with clinical data) in the different studies.

Four categories of delivery were analyzed: elective cesarean section, which was performed before the rupture of membranes and the onset of labor; nonelective cesarean section, which was performed after the rupture of membranes or the onset of labor, or both; instrumental vaginal delivery, in which forceps, vacuum suction, or both were used; and non-instrumental vaginal delivery, in which neither forceps nor vacuum suction was used. Medical-record abstraction was performed only to obtain missing data on the mode of delivery or a child's HIV-1–infection status.

Potential covariates were selected on the basis of the results of previously published studies of risk factors for the vertical transmission of HIV-1 and on the availability and comparability of data among studies. The following covariates met these criteria: receipt or nonreceipt of antiretroviral therapy during three periods (prenatal, intrapartum, and neonatal), the presence or absence of the acquired immunodeficiency syndrome (AIDS) in the mother, and the presence or absence of substance abuse during pregnancy as categorical variables and maternal CD4+ cells as an absolute count and as a percentage of all lymphocytes, the child's birth weight, and the week of gestation as continuous variables. Since the interval between the rupture of membranes and delivery was incorporated into definitions of elective and nonelective cesarean section, this variable was not included in the primary analysis. Data were transmitted from each study to the data-coordinating center after the completion, if necessary, of medical-record abstraction.

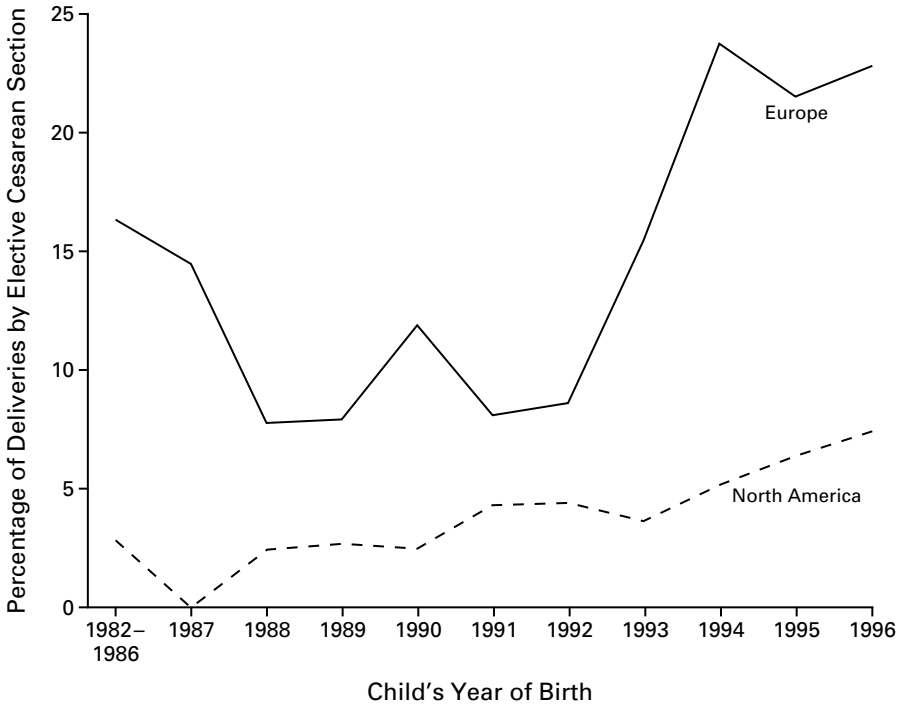
An initial meta-analysis was conducted that was stratified according to the study cohort; a Breslow–Day test[21] was used to assess the homogeneity of the odds ratios relating the mode of delivery to the infection status of the child. In unadjusted analyses we used the exact conditional method[22] and a random-effects model to estimate the common odds ratio.[23] The odds ratio, derived from logistic-regression modeling, was used to test the study's hypothesis by assessing the strength of the association between the mode of delivery and the child's infection status, after adjustment for other covariates included in the model. The likelihood ratio and Wald tests were used to select the model, such as to test the main effect of covariates or to test for interactions between the mode of delivery and the covariates. A Pearson chi-square test was used to assess the goodness of fit between the model and the data.[24] Reported P values for all statistical tests are two-sided.

RESULTS

Representatives of 15 of the 16 eligible studies agreed to participate in the meta-analysis, including all 5 European and all 10 North American studies: the Ariel Project; the Centre Maternel et Infantile sur le SIDA cohort; the European Collaborative Study, with the Italian Collaborative Group on HIV and Pregnancy; the French Perinatal Cohort Study; the Italian Register for HIV Infection in Children; the University of Miami Infants of HIV-1 Seropositive Mothers Study; the Mothers and Infants Cohort Study; the Perinatal AIDS Collaborative Transmission Studies; the Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection Study; the Swiss Neonatal HIV Study–Swiss HIV and Pregnancy Study; the UCLA–Los Angeles Maternal–Infant HIV Transmission Study; the Los Angeles County–University of Southern California Perinatal Transmission Study; the Women and Infants Transmission Study; and the Yale Prospective Longitudinal Cohort Study. Details regarding the study designs, data collection, and study populations have been reported previously.[12-14,16,25-35] Data from one eligible study in Asia that did not participate indicate that cesarean section is associated with a lower risk of vertical transmission of HIV-1.[36] Several hundred mother–child pairs who were enrolled in both the European Collaborative Study and the Italian Register for HIV Infection in Children were treated as a separate group.

Of 15,471 mother–child pairs enrolled in participating studies, 4585 met the exclusion criteria. The data included in the primary analysis were further restricted to mothers for whom the type of cesarean section (elective or nonelective) was known or who underwent vaginal delivery, to children whose HIV-1 status was known (infected or uninfected), and to the older (or oldest) child when there were younger siblings in the data set; 8533 mother–child pairs were eligible for inclusion in the primary analysis. As Figure 1 indicates, elective cesarean section was performed significantly more frequently in Europe than in North America from 1982 through 1996 ($P<0.05$).

The crude odds ratio for the relation between elective cesarean section and the infection status of the child was calculated for each study cohort (Fig. 2). There was no evidence that the relation between the mode of delivery and risk of vertical transmission



No. of Mother–Child Pairs											
Europe	435	408	439	507	565	583	596	591	565	373	189
North America	71	92	124	150	284	398	481	554	548	444	136

Figure 1. Unadjusted Proportions of Elective Cesarean Sections among 8533 HIV-1–Infected Women in Europe and North America, According to the Child's Year of Birth.

For each year, a significantly larger proportion of deliveries was performed by elective cesarean section in Europe than in North America ($P<0.05$).

varied significantly among the studies (chi-square = 9.8 with 14 df by the Breslow–Day test of homogeneity; $P=0.78$). The individual odds ratios for studies were pooled to create a summary estimate of the overall odds ratio. According to the exact conditional method, the summary odds ratio was 0.45 (95 percent confidence interval, 0.35 to 0.58; $P<0.001$ for a test of the null hypothesis that the odds ratio is equal to 1.0). A similar summary odds ratio was obtained with use of the random-effects model.

The use of antiretroviral therapy during the prenatal, intrapartum, and neonatal periods increased dramatically in 1994 after the report from the AIDS Clinical Trials Group Protocol 076 that a three-part regimen of zidovudine given to the mother before and during labor and delivery and to the infant after birth significantly reduced the risk of perinatal transmission of HIV-1[37] (Fig. 3). Of the 4675 mother–child pairs who did not receive prenatal or neonatal antiretroviral therapy, over 99 percent also did not receive intrapartum antiretroviral therapy. Therefore, 1294 mother–child pairs who did not receive prenatal or neonatal antiretroviral therapy but whose status with respect to intrapartum therapy was unknown were considered not to have received intrapartum antiretroviral therapy.

A composite variable representing advanced maternal disease was created because data on the absolute CD4+ lymphocyte count and the percentage of CD4+ lymphocytes were missing for over 30 percent of the mothers and because of the close relation between these data and the presence of AIDS. A woman was considered to have advanced disease only if she had been given a diagnosis of AIDS or, in the absence of such a diagnosis, if she had a CD4+ cell count of less than 200 cells per cubic millimeter or if less than 14 percent of all lymphocytes were CD4+ cells.

Since the birth-weight and gestational-age variables were correlated, only birth weight was incorporated into the multivariate analyses. Birth weight was selected because of the greater variability in the methods of ascertaining gestational age among the studies. Birth weight was dichotomized as low (<2500 g) or not low (≥ 2500 g). Substance abuse during pregnancy was not included in the primary analysis be-

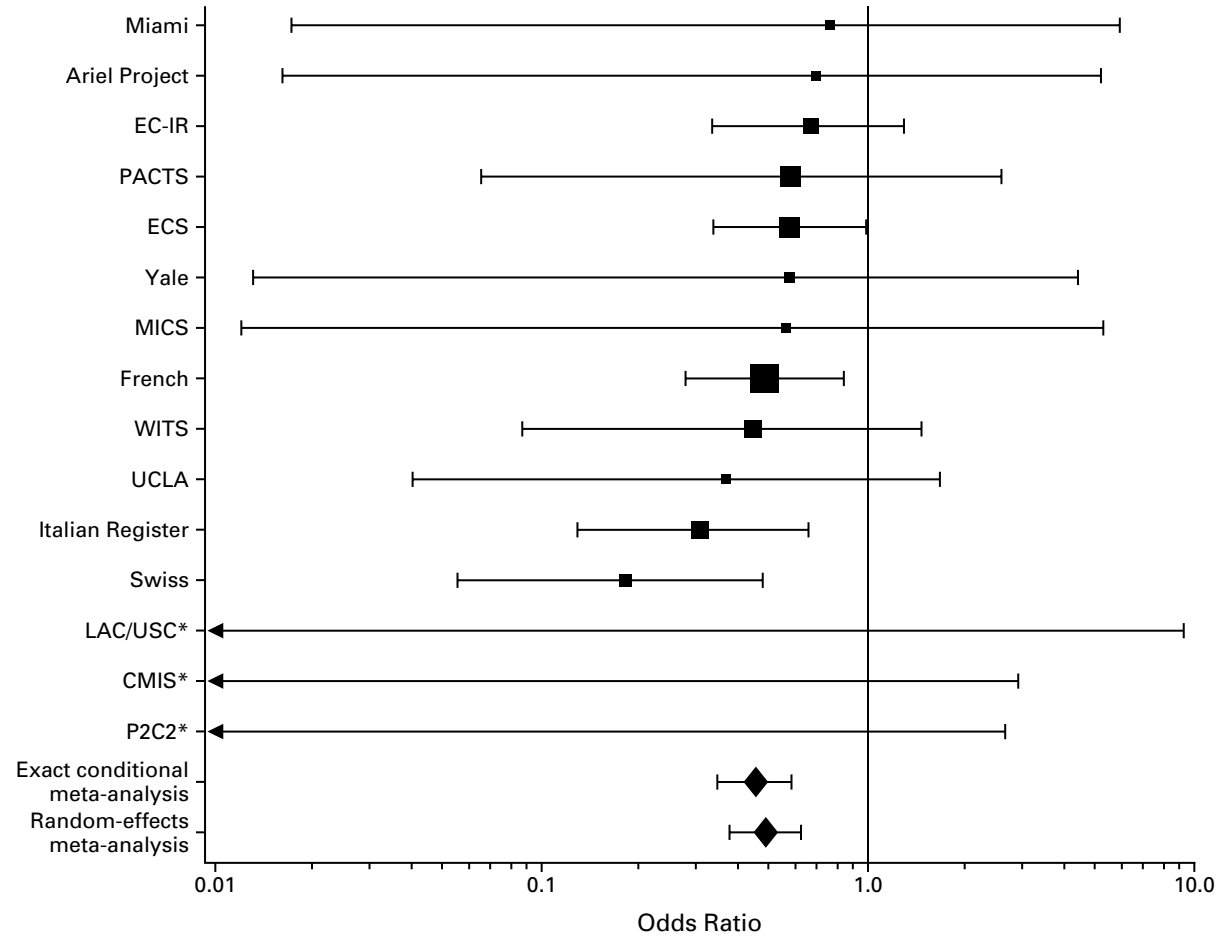


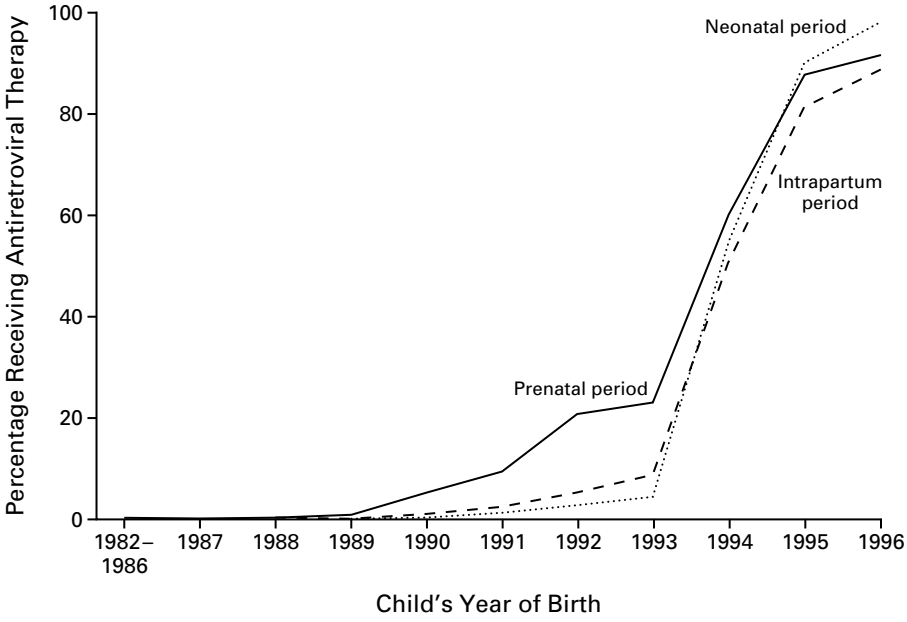
Figure 2. Crude Odds Ratios for the Association of Elective Cesarean Section with the Risk of Vertical Transmission of HIV-1 among 8533 Mother–Child Pairs in 15 Studies and in Meta-Analyses Based on the Exact Conditional Method and the DerSimonian–Laird Random-Effects Model.

Studies are listed in decreasing order of the odds ratios. Bars indicate 95 percent confidence intervals. The size of each square is proportional to the sample size of the corresponding study. Asterisks indicate that the lower limit of the confidence interval is less than 0.01; in these studies there were no cases of vertical transmission of HIV after elective cesarean section. Miami denotes University of Miami Infants of HIV-1 Seropositive Mothers Study; EC-IR, mother–child pairs enrolled in both the European Collaborative Study and the Italian Register for HIV Infection in Children; PACTS, Perinatal AIDS Collaborative Transmission Studies; ECS, European Collaborative Study, with the Italian Collaborative Group on HIV and Pregnancy; Yale, Yale Prospective Longitudinal Cohort Study; MICS, Mothers and Infants Cohort Study; French, French Perinatal Cohort Study; WITS, Women and Infants Transmission Study; UCLA, UCLA–Los Angeles Maternal–Infant HIV Transmission Study; Italian Register, Italian Register for HIV Infection in Children; Swiss, Swiss Neonatal HIV Study–Swiss HIV and Pregnancy Study; LAC/USC, Los Angeles County–University of Southern California Perinatal Transmission Study; CMIS, Centre Maternel et Infantile sur le SIDA cohort; and P2C2, Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection Study.

cause of the high proportion (over 30 percent) of mothers with missing data for this variable and because of the variability in the methods used to identify substance abuse in the different studies. The distribution of covariates included in multivariate regression modeling is shown in Table 1.

A logistic-regression model (Table 2) was fitted to the data for 7840 mother–child pairs for whom data were complete, including the mode of delivery and the following three covariates: receipt of antiretroviral therapy, advanced maternal disease, and low birth weight of infants. After adjustment for these three covariates, elective cesarean delivery remained strongly associated with a lower risk of vertical transmission of HIV-1 (odds ratio, 0.43; 95 percent confidence interval, 0.33 to 0.56). The overall fit of the model was excellent (Pearson's chi-square=12.8 with 18 df, P=0.80) (Table 3).

A logistic-regression model was also fitted to the data that included the three covariates as well as in-



No. of Mother–Child Pairs											
Prenatal period	500	496	556	653	837	962	1075	1138	1108	816	323
Intrapartum period	497	495	556	651	827	941	1045	1115	1097	809	322
Neonatal period	500	499	563	657	839	967	1059	1120	1104	808	323

Figure 3. Unadjusted Proportions of 8533 Mother–Child Pairs Who Received Antiretroviral Therapy, According to the Child's Year of Birth.

dicator variables representing the individual studies. The relation between the study cohort and the child's infection status was not significant ($P=0.21$), nor was there any evidence that the relation between the mode of delivery and the risk of vertical transmission varied significantly among the studies ($P=0.76$) (data not shown). The logistic-regression model that included indicator variables for individual studies yielded an odds ratio that was essentially the same as that for the first model (odds ratio, 0.44).

Logistic-regression models were also used to examine whether there were joint or individual interactions between the mode of delivery and the three covariates (data not shown). The analyses showed that the relation between the mode of delivery and the risk of vertical transmission did not vary significantly among subgroups defined by these covariates.

The odds ratio relating the mode of delivery and the risk of vertical transmission was not altered substantially by any of the following: the inclusion of pairs in which the child's HIV-1 status was unknown and was therefore imputed to be uninfected, the inclusion of pairs in which the mother's type of cesarean section was unknown and therefore imputed to be either elective or nonelective, or the inclusion of both types of pairs; coding the three covariates in different ways; the inclusion of children's years of birth in the model; and the inclusion of younger siblings in the analysis or the substitution of younger for older siblings in the analysis (range of odds ratios, 0.41 to 0.45). All the models were reanalyzed with adjustment for individual studies, and no qualitative differences in results were identified.

The likelihood of vertical transmission was lower among women who underwent elective cesarean section than among women who underwent other specific types of delivery (range of adjusted odds ratios, 0.36 to 0.47) (Table 2). This protective effect persisted when the data were stratified according to the receipt or nonreceipt of antiretroviral therapy (data not shown). When all cesarean sections were compared with all vaginal deliveries, instrumental vaginal deliveries, and non-instrumental vaginal deliveries, the likelihood of vertical transmission was decreased by the use of cesarean section, though not to the same degree as demonstrated for only elective cesarean section as compared with other modes of delivery (range of adjusted odds ratios, 0.60 to 0.69; all P values <0.001) (data not shown).

Since a prolonged interval between rupture of the membranes and delivery has been shown to be associated with an increased risk of mother-to-infant

TABLE 1. CHARACTERISTICS OF 8533 MOTHER–CHILD PAIRS IN 15 STUDIES ACCORDING TO THE MODE OF DELIVERY.*

CHARACTERISTIC	NO. OF PAIRS	ELECTIVE CESAREAN SECTION		OTHER KNOWN MODE OF DELIVERY	
		TOTAL	HIV-1–INFECTED CHILD	TOTAL	HIV-1–INFECTED CHILD
		number (percent)			
Sample size					
All studies	8533	857 (10.0)	72 (8.4)	7676 (90.0)	1280 (16.7)
European studies	5251	717 (13.7)	61 (8.5)	4534 (86.3)	750 (16.5)
ECS	1115	194 (17.4)	19 (9.8)	921 (82.6)	143 (15.5)
EC-IR	594	112 (18.9)	13 (11.6)	482 (81.1)	78 (16.2)
French	2400	197 (8.2)	16 (8.1)	2203 (91.8)	332 (15.1)
Italian Register	790	102 (12.9)	8 (7.8)	688 (87.1)	148 (21.5)
Swiss	352	112 (31.8)	5 (4.5)	240 (68.2)	49 (20.4)
North American studies	3282	140 (4.3)	11 (7.9)	3142 (95.7)	530 (16.9)
Ariel Project	194	15 (7.7)	1 (6.7)	179 (92.3)	17 (9.5)
CMIS	95	8 (8.4)	0	87 (91.6)	13 (14.9)
Miami	194	11 (5.7)	1 (9.1)	183 (94.3)	21 (11.5)
MICS	155	6 (3.9)	1 (16.7)	149 (96.1)	39 (26.2)
P2C2	196	7 (3.6)	.0	189 (96.4)	33 (17.5)
PACTS	1143	17 (1.5)	2 (11.8)	1126 (98.5)	206 (18.3)
UCLA	156	25 (16.0)	2 (8.0)	131 (84.0)	25 (19.1)
LAC/USC	120	3 (2.5)	.0	117 (97.5)	19 (16.2)
WITS	802	38 (4.7)	3 (7.9)	764 (95.3)	122 (16.0)
Yale	227	10 (4.4)	1 (10.0)	217 (95.6)	35 (16.1)
Antiretroviral therapy†					
All three periods	1451	196 (13.5)	4 (2.0)	1255 (86.5)	92 (7.3)
One or two periods	871	85 (9.8)	7 (8.2)	786 (90.2)	129 (16.4)
Zero periods	5944	559 (9.4)	58 (10.4)	5385 (90.6)	1021 (19.0)
Unknown	267	17 (6.4)	3 (17.6)	250 (93.6)	38 (15.2)
Advanced maternal disease‡					
Yes	1101	138 (12.5)	18 (13.0)	963 (87.5)	206 (21.4)
No	7052	696 (9.9)	53 (7.6).	6356 (90.1)	1013 (15.9)
Unknown	380	23 (6.1)	1 (4.3).	357 (93.9)	61 (17.1)
Low birth weight of infant (<2500 g)					
Yes	1471	199 (13.5)	26 (13.1)	1272 (86.5)	318 (25.0)
No	6951	647 (9.3)	44 (6.8)	6304 (90.7)	947 (15.0)
Unknown	111	11 (9.9)	2 (18.2)	100 (90.1)	15 (15.0)

*Mother–child pairs in which the mother underwent elective cesarean section delivery differed significantly with regard to each of the characteristics ($P<0.01$) from pairs in which another known mode of delivery was used. ECS denotes the European Collaborative Study, with the Italian Collaborative Group on HIV and Pregnancy; EC-IR, mother–child pairs enrolled in both the European Collaborative Study and the Italian Register for HIV Infection in Children; French, French Perinatal Cohort Study; Italian Register, Italian Register for HIV Infection in Children; Swiss, Swiss Neonatal HIV Study–Swiss HIV and Pregnancy Study; CMIS, Centre Maternel et Infantile sur le SIDA cohort; Miami, University of Miami Infants of HIV-1 Seropositive Mothers Study; MICS, Mothers and Infants Cohort Study; P2C2, Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection Study; PACTS, Perinatal AIDS Collaborative Transmission Studies; UCLA, UCLA–Los Angeles Maternal–Infant HIV Transmission Study; LAC/USC, Los Angeles County–University of Southern California Perinatal Transmission Study; WITS, Women and Infants Transmission Study; and Yale, Yale Prospective Longitudinal Cohort Study.

†The three periods were prenatal, intrapartum, and neonatal.

‡A woman was considered to have advanced disease if she had been given a diagnosis of AIDS or, in the absence of such a diagnosis, if she had a CD4+ cell count of less than 200 per cubic millimeter or if less than 14 percent of all lymphocytes were CD4+ cells.

TABLE 2. RATE OF VERTICAL TRANSMISSION OF HIV-1, WITH ADJUSTED ODDS RATIOS, AMONG 7840 MOTHER–CHILD PAIRS.

VARIABLE	TOTAL NO. OF PAIRS	RATE OF VERTICAL TRANSMISSION (%)	ADJUSTED ODDS RATIO (95% CI)*
Antiretroviral therapy†			
All three periods	1424	6.6	0.31 (0.25–0.38)
One or two periods	845	15.3	0.70 (0.57–0.86)
Zero periods	5571	18.3	1.00
Advanced maternal disease			
Yes	1033	20.6	1.71 (1.43–2.04)
No	6807	15.1	1.00
Low birth weight of infant (<2500 g)			
Yes	1352	23.6	1.79 (1.54–2.07)
No	6488	14.2	1.00
Mode of delivery			
Elective cesarean section	809	8.2	0.43 (0.33–0.56)
Any other mode	7031	16.7	1.00
Elective cesarean section			
Vs. nonelective cesarean section	895	16.2	0.45 (0.33–0.61)
Vs. vaginal delivery	6136	16.8	0.42 (0.33–0.55)
Instrumental	520	18.3	0.36 (0.25–0.51)
Non-instrumental	4971	16.4	0.43 (0.33–0.56)
Type unknown	645	18.6	0.47 (0.33–0.66)

*Values were adjusted for receipt of antiretroviral therapy, presence or absence of advanced maternal disease, and presence or absence of low birth weight of infant. An odds ratio of 1.00 indicates the reference group. CI denotes confidence interval.

†The three periods were prenatal, intrapartum, and neonatal.

transmission of HIV-1,[15,16,31] subanalyses examining the interval between the rupture of membranes and delivery in relation to the risk of vertical transmission were performed. The crude rate of vertical transmission observed with elective cesarean section (8.4 percent) was lower than that associated with vaginal delivery after a short interval between rupture of membranes and delivery, either less than one hour (transmission rate, 11.7 percent) or less than four hours (transmission rate, 13.5 percent). The primary logistic-regression model was fitted to the data for 1719 deliveries in which rupture of membranes occurred less than one hour before delivery and for 3212 deliveries in which rupture of membranes occurred less than four hours before delivery. These analyses again showed that the likelihood of vertical transmission was lower with elective cesarean section than with other modes of delivery (odds ratio, 0.55; 95 percent confidence interval, 0.40 to 0.77; $P<0.001$ among women with rupture of membranes less than one hour before delivery; odds ratio, 0.53; 95 percent confidence interval, 0.40 to 0.71; $P<0.001$ among women with rupture of membranes less than four hours before delivery).

Since the standard of care in North America and the European countries represented in this analysis now includes zidovudine prophylaxis to prevent mother-to-infant transmission of HIV-1, the likelihood of vertical transmission and the rates of transmission were examined in greater detail according to whether antiretroviral therapy was used. When both elective cesarean section and antiretroviral therapy during the prenatal, intrapartum, and neonatal periods were used, the likelihood of transmission was reduced by approximately 87 percent, as compared with the likelihood associated with the use of other modes of delivery and the absence of antiretroviral therapy (adjusted odds ratio, 0.13; 95 percent confidence interval, 0.09 to 0.19). The rates of transmission were lower with elective cesarean section than with other modes of delivery whether or not antiretroviral therapy was given. The transmission rate with elective cesarean section but without antiretroviral therapy was 10.4 percent (95 percent confidence interval, 7.8 to 12.9 percent), as compared with a rate of 19.0 percent (95 percent confidence interval, 17.9 to 20.0 percent) with other modes of delivery but without antiretroviral therapy; the respective rates with antiretroviral therapy during the prenatal, intrapartum, and neonatal periods were 2.0 percent (95 percent confidence interval, 0.1 to 4.0 percent) and 7.3 percent (95 percent confidence interval, 5.9 to 8.8 percent).

DISCUSSION

In this meta-analysis of data on individual patients from 15 prospective cohort studies, the risk of vertical transmission was significantly lower among HIV-1–infected women who underwent cesarean section before the onset of labor and the rupture of membranes than among those who underwent other modes of delivery. This association remained after

TABLE 3. OBSERVED AND PREDICTED PROBABILITIES OF VERTICAL TRANSMISSION FOR ALL COMBINATIONS OF COVARIATES DEFINED BY THE PRIMARY LOGISTIC-REGRESSION MODEL.*

MODE OF DELIVERY	COVARIATE			NO. OF MOTHER–CHILD PAIRS	NO. OF HIV-1–INFECTED CHILDREN	PROBABILITY OF VERTICAL TRANSMISSION	
	NO. OF PERIODS OF ANTIRETROVIRAL THERAPY	ADVANCED MATERNAL DISEASE	LOW BIRTH WEIGHT OF INFANT (<2500 g)			OBSERVED	PREDICTED
Elective cesarean	0	No	No	372	30	0.08	0.08
Other	0	No	No	3850	652	0.17	0.17
Elective cesarean	0	Yes	No	28	5	0.18	0.13
Other	0	Yes	No	303	74	0.24	0.25
Elective cesarean	0	No	Yes	110	17	0.15	0.13
Other	0	No	Yes	767	196	0.26	0.26
Elective cesarean	0	Yes	Yes	27	4	0.15	0.21
Other	0	Yes	Yes	114	40	0.35	0.38
Elective cesarean	1 or 2	No	No	41	0	0.00	0.06
Other	1 or 2	No	No	441	49	0.11	0.12
Elective cesarean	1 or 2	Yes	No	23	3	0.13	0.09
Other	1 or 2	Yes	No	186	33	0.18	0.19
Elective cesarean	1 or 2	No	Yes	7	0	0.00	0.10
Other	1 or 2	No	Yes	83	22	0.27	0.20
Elective cesarean	1 or 2	Yes	Yes	10	3	0.30	0.15
Other	1 or 2	Yes	Yes	54	19	0.35	0.30
Elective cesarean	3	No	No	124	2	0.02	0.03
Other	3	No	No	878	49	0.06	0.06
Elective cesarean	3	Yes	No	34	1	0.03	0.04
Other	3	Yes	No	208	24	0.12	0.10
Elective cesarean	3	No	Yes	25	0	0.00	0.04
Other	3	No	Yes	109	11	0.10	0.10
Elective cesarean	3	Yes	Yes	8	1	0.13	0.07
Other	3	Yes	Yes	38	6	0.16	0.16

*Pearson chi-square=12.8 with 18 df in goodness-of-fit test; P=0.80.

adjustment for covariates (receipt or nonreceipt of antiretroviral therapy, stage of disease in the women, and birth weight of the infants), each of which was independently associated with the risk of vertical transmission. Adjustment for the individual studies did not modify these conclusions. A subanalysis revealed similar results when the population was limited to women whose membranes ruptured shortly before delivery; this finding suggests that the decreased likelihood of transmission of HIV-1 observed with elective cesarean section was related to the avoidance of both microtransfusions of blood during labor[38] and direct contact of the fetus with maternal genital tract secretions or blood during parturition.

The results of this study reinforce the findings of prospective European cohort studies that elective cesarean section protects against the vertical transmission of HIV-1.[11,12] In addition, the results are consistent with those of a randomized clinical trial in Europe in which elective cesarean section was associated with a significantly decreased risk of vertical transmission of HIV-1.[39]

The likelihood of the transmission of HIV-1 was significantly lower with elective cesarean section than with each of the other types of deliveries, emphasizing the importance of carefully distinguishing among different modes of delivery. A clinically important implication of these results is that the risk of transmission is higher among women in whom labor begins, membranes rupture, or both occur before a planned cesarean section can be performed.

Analyses of data from North American studies have typically grouped all cesarean sections together because of the small numbers of elective cesarean sections. The result is a heterogeneous category that includes both deliveries with a lower risk of vertical transmission and those with a higher risk. Thus, in retrospect, it is not surprising that an association between the mode of delivery and the risk of vertical transmission of HIV-1 has been described in Euro-

pean studies,[4-6,8,10-12] whereas such an association has not been observed in analyses of data from North American cohorts. Previously, analysis of data from a large, prospective French cohort study, in which elective and nonelective cesarean section deliveries were distinguished, did not reveal a relation between the mode of delivery and the risk of vertical transmission of HIV-1.[17] However, in the most recent analysis, elective cesarean section was associated with a lower transmission rate only among mothers who received zidovudine prophylaxis.[40]

In our analysis, in contrast, the relation between the mode of delivery and the HIV-1–infection status of the child did not vary significantly according to the use of antiretroviral therapy. Although the results of the two studies differ in this way, they are consistent in suggesting that there is a lower likelihood of vertical transmission of HIV-1 among women who undergo elective cesarean section and receive zidovudine prophylaxis than among women in whom only one of these interventions is used. However, such direct comparisons of the results of the two studies should be limited, since different variables were available for inclusion in the two analyses.

Elective cesarean section and antiretroviral therapy each made a significant independent contribution to lowering the risk of vertical transmission of HIV-1. The combination of elective cesarean section and antiretroviral therapy during the prenatal, intrapartum, and neonatal periods was associated with a further decrease in the estimated likelihood of vertical transmission beyond that predicted for either "intervention" alone. These results support the findings in Europe of an additive effect of zidovudine prophylaxis and either cesarean section[41] or elective cesarean section.[12]

The identification of studies that were eligible for this meta-analysis was not based on previous publications. Thus, selection bias is unlikely, and probably most, or all, eligible studies from North America and Europe were included. Data regarding factors known to be associated with the vertical transmission of HIV-1 were available for statistical adjustment in multivariate analyses, and uniform definitions of variables were applied to all studies.

We used data from prospective cohort studies for this meta-analysis. Unlike a clinical trial, in which randomization generally results in approximately equal distributions of covariates between comparison groups, our study design required statistical adjustment for important covariates. Moreover, in this meta-analysis, unlike a clinical trial, an intention-to-treat analysis was not possible, since cesarean sections were categorized as elective or nonelective solely in terms of the timing of the procedure relative to the onset of labor and the rupture of membranes. The availability of data regarding potential covariates of interest was limited by whether specific variables were included in each study's protocol. For example, data on the viral load of women during pregnancy were collected in only a minority of studies. Finally, the degree of detail on the receipt of antiretroviral therapy was limited by the extent of data collected in each study regarding doses, routes of administration, and the duration of specific antiretroviral therapies. Thus, receipt of antiretroviral therapy during all three periods is most likely, but not definitely, synonymous with receipt of a regimen of zidovudine prophylaxis similar to that of the AIDS Clinical Trials Group Protocol 076.[37]

The benefit of elective cesarean section with regard to mother-to-infant transmission of HIV-1 must be weighed against the possible deleterious effects of surgical delivery. Among women without HIV-1 infection, cesarean section has been associated with increased neonatal morbidity[42] and maternal morbidity and mortality,[42-44] as compared with nonsurgical delivery, although such associations are probably subject to confounding according to the indication. In other words, the fetal or maternal indications for nonelective cesarean section themselves may be associated with postoperative neonatal or maternal morbidity. However, elective cesarean section is associated with a lower risk of maternal complications than is emergency cesarean section.[45]

Postpartum morbidity could not be examined in this meta-analysis, but previous reports indicate that HIV-1–infected women have an increased risk of peripartum and postpartum infectious complications that are related to the level of immunologic deficiency[46] and an increased risk of postoperative complications,[47] including death, if they live in less-developed countries.[48] In less-developed countries, the potential risks associated with elective cesarean section would appear to outweigh the potential benefit in terms of decreased vertical transmission of HIV-1.

There are other questions that this meta-analysis could not address. Is elective cesarean section potentially beneficial irrespective of the maternal viral load? Recent data indicate that cesarean section is associated with a lower risk of vertical transmission of HIV-1 even after adjustment for viral load.[36] A related question is whether the association between the mode of delivery and the risk of vertical transmission persists among women receiving combination antiretroviral therapy. A lower maternal viral load is associated with a lower risk of vertical transmission,[49] and women who receive combination antiretroviral therapy could have lower rates of vertical transmission than women who receive zidovudine alone.[50] However, only very limited data are available from populations of HIV-1–infected women who are receiving combination antiretroviral therapy, precluding definitive conclusions regarding the rates of vertical transmission. If the rates of vertical transmission among HIV-1–infected women who receive combination antiretroviral therapy are shown to be lower than those among women who receive zidovudine alone, the role of elective cesarean

section will need to be reevaluated. However, as rates of HIV-1 infection among infants receiving zidovudine prophylaxis continue to decline, the required sizes of study populations needed to address this question will need to be extremely large. Thus, it is unlikely that additional data on which to base clinical decisions regarding the mode of delivery will become available in the foreseeable future.

The results of this meta-analysis of more than 8000 mother–child pairs suggest that elective cesarean section could reduce mother-to-child transmission of HIV-1. HIV-1–infected pregnant women should be advised of the risk factors for vertical transmission of HIV-1 and of the means available to decrease that risk. In the United States and other developed countries, such interventions include zidovudine prophylaxis[51] and the avoidance of breast-feeding.[52,53] The potential benefit of elective cesarean section with regard to mother-to-child transmission of HIV-1, along with the possible risks associated with surgical delivery, should now be included in such discussions.

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APPENDIX

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