

Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial

*The European Mode of Delivery Collaboration**

Summary

Background Results from observational studies suggest that caesarean-section delivery may reduce the risk of mother-to-child transmission of HIV-1 infection in comparison with vaginal delivery. We carried out a randomised clinical trial to address this issue and to assess the extent of postdelivery complications.

Methods Eligible women were between 34 and 36 weeks of pregnancy, with a confirmed diagnosis of HIV-1 infection, and without an indication for caesarean-section delivery or a contraindication to this mode of delivery. Women were randomly assigned elective caesarean-section delivery at 38 weeks of pregnancy or vaginal delivery. An infant was classified as uninfected if he or she became negative for antibody to HIV-1 by age 18 months or was negative for virus by PCR or culture on at least two occasions, with no clinical, immunological, or viral evidence of infection. From 1993, to March, 1998, 436 women were randomised.

Findings We present the results of an analysis updated to November, 1998, with data on the infection status of 370 infants. Three (1.8%) of 170 infants born to women assigned caesarean-section delivery were infected, compared with 21 (10.5%) of 200 born to women assigned vaginal delivery ($p < 0.001$). Seven (3.4%) of 203 infants of women who actually gave birth by caesarean section were infected compared with 15 (10.2%) of 167 born vaginally ($p = 0.009$). There were few postpartum complications and no serious adverse events in either group.

Interpretation Our findings provide evidence that elective caesarean-section delivery significantly lowers the risk of mother-to-child transmission of HIV-1 infection without a significantly increased risk of complications for the mother.

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See *Commentary page 1030–1031*

Introduction

Mother-to-child transmission of HIV-1 infection usually occurs around the time of delivery.¹ Elective caesarean-section delivery, before rupture of membranes and labour, might therefore reduce the risk of vertical transmission by avoiding direct contact with maternal vaginal secretions and infected blood during the infant's passage through the birth canal, and reducing influx of maternal blood during uterine contractions.

In 1992, results from the European Collaborative Study suggested that infants of HIV-1 infected women delivered by elective caesarean section had a lower risk of HIV-1 infection than infants delivered vaginally, although the difference was not significant.² Similar reductions in risk were reported from the Swiss perinatal study³ and the Italian Paediatric Register.⁴ A subsequent analysis of a larger dataset from the European Collaborative Study,⁵ with allowance for other risk factors such as prematurity and maternal clinical and immunological disease progression, showed that elective caesarean-section delivery significantly reduced the risk of vertical transmission by about 50%. On the other hand, no protective effect of elective caesarean section on vertical transmission of HIV-1 was shown in the French perinatal study,⁶ or in several US studies.⁷ However, few studies distinguished elective from emergency procedures, and analyses could not always take account of other factors known to be associated with increased transmission risk.

We therefore set up a randomised clinical trial to assess the relative risks and benefits of elective caesarean-section versus vaginal delivery in the overall population of randomised women and in subgroups of zidovudine use in pregnancy and viral load. Since caesarean-section delivery carries a potential risk of postoperative complications, particularly in HIV-1-infected women who may be immunocompromised,⁸ and when carried out as an emergency procedure,⁹ a secondary objective was to assess the extent of postdelivery complications in HIV-1-infected women. This trial was initiated in Italy in 1993, and extended to other European centres in 1995.

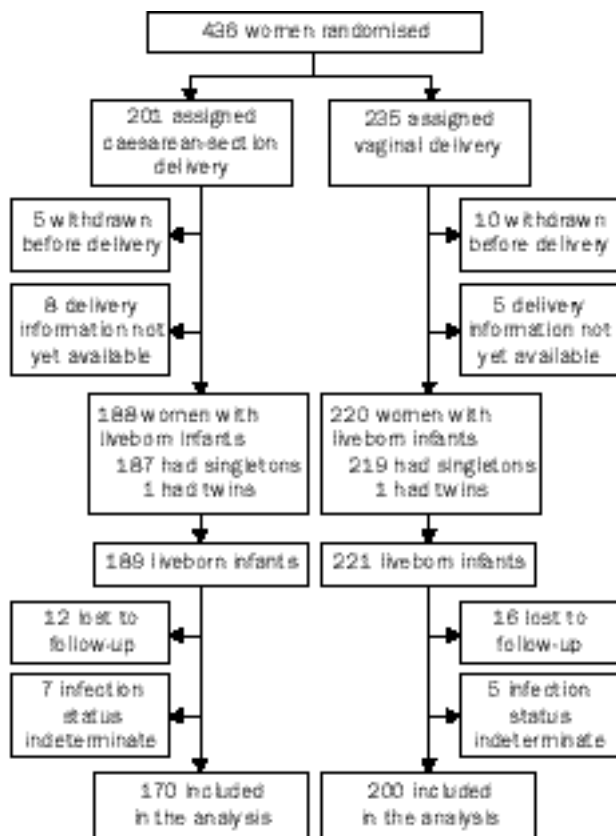
Methods

Patients

Women between 34 and 36 weeks of pregnancy with a confirmed diagnosis of HIV-1 infection were eligible for study. Those with an obstetric indication that necessitated caesarean-section delivery (such as central placenta praevia or fetal-pelvic disproportion) or with a contraindication to elective caesarean-section delivery for non-obstetric reasons (for example, women who had a contraindication to anaesthetics, or those who came from countries where caesarean delivery is not an option and who might have further pregnancies in their countries of origin) were not eligible. For women with a previous caesarean-section

*Study organisation given at end of paper

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Trial profile

delivery, twin pregnancy, breech presentation, intrauterine growth retardation, or vaginal infection (eg, active herpes infection), the decision to randomise was at the clinician's discretion.

Between 34 and 36 weeks of pregnancy, eligible women were randomly assigned individually by means of computer-generated random lists either elective caesarean-section delivery at 38 weeks of pregnancy or vaginal delivery. Group allocation was carried out by telephone at the Analytical Epidemiological Unit of the Mario Negri Institute in Milan for the Italian centres, at the INSERM HIV trial centre for French centres, and at the UK Medical Research Council HIV Trials Centre in London for the remaining centres, with separate randomisation lists.

The study protocol was approved independently by the ethics committees of individual centres, which established the procedures for obtaining informed consent. The Italian trial was also approved by a specific trial ethics committee, and the French and European groups also obtained additional ethics permission from appropriate national committees.

The study started in Italy during 1993 at ten obstetrics centres, subsequently increasing to 19. Randomisation started in other countries in 1995 (France 14 centres, UK one centre, Spain five centres, Switzerland two centres, Sweden two centres). In mid-1996, the French investigators decided to stop enrolment in France. This decision was based on results from the French perinatal transmission study,^{10,11} which showed a substantial reduction in vertical transmission in France after the almost universal use of prophylactic zidovudine to reduce transmission.¹¹ In view of this finding, the French investigators concluded that the sample size required for the mode of delivery trial would need to be increased to an even larger number than previously calculated, which was not considered feasible. They also wanted to explore other interventions to prevent vertical transmission. In March, 1998, the European Steering Committee decided to stop enrolment in other centres after the results of an interim analysis.

20 mother-child pairs were enrolled in Baragwanath Hospital, Johannesburg, South Africa, between February and November,

1995, but have been excluded from this analysis. They were the only infants who were breastfed, and the trial was prematurely ended in that centre after the introduction of another international trial.

In Italy, at the start of the trial, women were assigned to the study groups with a two to one ratio of vaginal to caesarean-section delivery, to reduce the number of women assigned caesarean-delivery section, because at that time, vaginal delivery was the standard mode of delivery in Italy for women with HIV-1 infection. Subsequently, all Italian centres adopted a one to one ratio, which was used from the beginning of the trial in other European centres.

Study design

Women assigned to the elective caesarean-section group were scheduled for surgery at 38 weeks of pregnancy. If signs of obstetric disorders were detected before this time, routine clinical procedures were followed and the respective clinicians decided whether to induce delivery before the 38th week of pregnancy and the appropriate mode of delivery. If a woman who had been assigned elective caesarean section went into labour before 38 weeks of gestation. Caesarean section was undertaken if labour was diagnosed before the start of the second stage. Prophylactic antibiotic therapy was given for caesarean sections, but the choice of antibiotics was left to the clinician. Women assigned vaginal delivery waited for spontaneous labour unless there was a clinical decision for caesarean section.

We collected demographic and clinical data prospectively throughout pregnancy. No women breastfed. Maternal clinical information was collected at postpartum discharge, and at the 6-week follow-up visit. Postpartum fever was diagnosed when the temperature was more than 38°C at two measurements, 1 day apart. Newborn infants were assessed shortly after delivery. Children were followed up to the age of 18 months according to a standard protocol. HIV-1 infection status in the child was diagnosed by detection of virus (culture or PCR) on two separate specimens (at least one of which was obtained at 3 months of age or later), the development of AIDS or death from an HIV-1-related cause, or persistence of antibody to HIV-1 beyond 18 months of age. A child was classified as uninfected if he or she

	Mode of delivery allocation	
	Caesarean section (n=188)	Vaginal delivery (n=220)
Mean (range) age (years)	28.5 (18-40)	28.1 (16-43)
Country		
Italy	137 (72.9%)	175 (79.5%)
France	27 (14.4%)	27 (12.3%)
Spain/other	24 (12.8%)	18 (8.2%)
Acquisition of HIV-1 infection		
Injection-drug user	65 (34.6%)	96 (43.6%)
Heterosexual	91 (48.4%)	100 (45.4%)
Other	9 (4.8%)	8 (3.6%)
Unknown	23 (12.2%)	16 (7.3%)
Parity		
None	121 (64.4%)	144 (65.4%)
One	45 (23.9%)	49 (22.3%)
Two or more	22 (11.7%)	24 (10.9%)
Unknown	0	3 (1.4%)
CD4 cell count (per mL)		
<200	17 (9.0%)	17 (7.7%)
200-499	88 (46.8%)	100 (45.4%)
≥500	76 (40.4%)	92 (41.8%)
Unknown	7 (3.7%)	11 (5.0%)
Antiretroviral therapy before pregnancy		
No	147 (78.2%)	165 (75.0%)
Yes	40 (21.3%)	52 (23.6%)
Unknown	1 (0.5%)	3 (1.4%)
Antiretroviral therapy during pregnancy		
Yes	131 (69.7%)	128 (58.2%)
No	56 (29.8%)	91 (41.4%)
Unknown	1 (0.5%)	1 (0.4%)

Table 1: Baseline characteristics of women at randomisation

	Infection status		Odds ratio (95% CI)
	Negative	Positive	
Allocated mode			
Vaginal delivery	179 (89.5%)	21 (10.5%)	1.0†
Caesarean section	167 (98.2%)	3 (1.8%)	0.2 (0.1-0.6)
Actual mode			
Vaginal delivery	150 (89.8%)	17 (10.2%)	1.0†
Caesarean section	196 (96.5%)	7 (3.5%)	0.4 (0.2-0.9)
Elective	165 (97.6%)	4 (2.4%)	0.3 (0.1-0.8)
Emergency	31 (91.2%)	3 (8.8%)	1.0 (0.3-3.7)

*Multivariate estimate including terms for calendar period at delivery and zidovudine use in pregnancy. †Reference category.

Table 2: HIV-1 infection status of children according to allocated and actual mode of delivery

was antibody negative on at least two occasions, with no clinical, immunological, or viral evidence of infection. Children were classified as having indeterminate infection status if they were younger than 18 months and born in Italian centres where viral culture or PCR was not part of routine follow-up.

Statistical analysis

In the original Italian trial planned in 1993, the required sample size was estimated to be about 450 women. This estimate was based on the rate of vertical transmission of HIV-1 in Italy at that time (15%) and an estimated 50% reduction associated with caesarean-section delivery.¹² Similarly, the international trial aimed to show a 50% decrease in vertical transmission associated with caesarean-section delivery, but with the publication of the results of the US/French trial of zidovudine in pregnancy¹³ an additional assumption was made about the use of zidovudine, which altered the baseline vertical transmission rate to 8% in the vaginal delivery group and substantially increased the required sample size to 1200 women.¹⁰

In March, 1998, the initially planned sample size was reached. The protocol did not foresee any interim analysis. However, with increasing evidence from observational studies of a protective effect of caesarean-section delivery in reducing mother-to-child HIV-1 transmission, with a greater effect than previously suggested,^{14,15} the Trial Coordination Committees decided to do an interim analysis. This interim analysis, in March, 1998, included data on the HIV-1 infection status of 276 infants, and showed a difference in HIV-1 status between children delivered by caesarean-section and those delivered vaginally ($p < 0.05$). Information on the HIV-1 infection status of more infants is now available, and we report here all available information as of November, 1998.

We present analyses by intention to treat and by actual mode of delivery. Analysis of maternal baseline characteristics and mode of delivery includes data on all randomised women for whom information was available. Vertical transmission analysis includes children for whom information on infection status was

available by November, 1998. There were two sets of twins; both children of each pair are included separately. Odds ratios of mother-to-child HIV-1 transmission were calculated and logistic regression was used to adjust simultaneously for the potential confounding effect of calendar period at delivery, and use of prophylactic zidovudine during pregnancy.¹⁶

Results

Between 1993 and March, 1998, 436 women were randomised (figure). 15 women withdrew from the trial before delivery, and for 13 women delivery information is not yet available. 408 women delivered 410 liveborn infants (this number includes two sets of twins). 28 children were lost to follow-up, and 12 infants are currently too young to have their infection status determined. Thus, 370 infants were included in this preliminary analysis. The two groups were similar in terms of the proportions of women who withdrew from the study before delivery and children lost to follow-up.

The caesarean-section and vaginal-delivery groups were similar in terms of baseline characteristics (table 1). Prophylactic antiretroviral therapy was generally given according to the 076 US/French trial regimen.¹³ The mean duration of gestation at delivery was 37.9 weeks (SD=1.5) in the caesarean-section group and 39.2 weeks in the vaginal-delivery group.

Of the 188 women in the caesarean-section group at delivery, 22 (11.7%) gave birth vaginally and 166 (88.3%) by caesarean section, eight (4.3%) of which were emergency procedures. Of the 220 in the vaginal-delivery group, 161 (73.2%) gave birth vaginally and 59 (26.8%) by caesarean section (32 [54%] emergency procedures). The reasons why women originally assigned vaginal delivery, then delivered by caesarean section were: fetal distress (18 cases), failure to progress (ten), malpresentation (five), pre-eclampsia (four), maternal request (two), fetopelvic disproportion (two), and other unreported reasons (18 cases). Of the 22 women in the caesarean-section group who gave birth vaginally, 13 had preterm deliveries, three decided against caesarean delivery, one had a maternal indication, and for five women the reason was not reported.

Three (1.8%) of the 170 infants with known infection status born to women in the caesarean-section group were infected, compared with 21 (10.5%) of 200 born to women in the vaginal-delivery group ($p < 0.001$); elective caesarean-section delivery lowered the risk of vertical transmission by 80% (multivariate odds ratio 0.2 [95%

	Actual			Odds ratio (95% CI)	Allocated		
	Infection status		Odds ratio (95% CI)		Infection status		Odds ratio (95% CI)
	Negative	Positive			Negative	Positive	
Zidovudine during pregnancy							
No							
Vaginal delivery	60 (81.1%)	14 (18.9%)	1.0†	66 (80.5%)	16 (19.5%)	1.0†	
Caesarean section	55 (93.2%)	4 (6.8%)	0.3 (0.1-1.0)	49 (96.1%)	2 (3.9%)	0.2 (0-0.8)	
Yes							
Vaginal delivery	89 (96.7%)	3 (3.3%)	1.0†	112 (95.7%)	5 (4.3%)	1.0†	
Caesarean section	141 (97.9%)	3 (2.1%)	0.6 (0.1-3.2)	118 (99.2%)	1 (0.8%)	0.2 (0-1.7)	
CD4-cell count							
<200/ μ L							
Vaginal delivery	8 (80.0%)	2 (20.0%)		12 (85.7%)	2 (14.3%)		
Caesarean section	20 (100%)	0	.‡	16 (100%)	0	.‡	
≥200/ μ L							
Vaginal delivery	135 (90.0%)	15 (10.0%)	1.0	158 (89.3%)	19 (10.7%)	1.0	
Caesarean section	169 (96.0%)	7 (4.0%)	0.4 (0.2-1.2)	146 (98.0%)	3 (2.0%)	0.2 (0.06-0.70)	

*Adjusted for calendar period. †Reference category. ‡Fisher's exact test: not significant. In some cases the subgroups do not add up to the total because of some missing values.

Table 3: HIV-1 infection status of children by allocated and actual mode of delivery: analysis in strata of prophylactic zidovudine therapy and maternal CD4-cell count

CI 0.1–0.6] table 2). All four twins were HIV-1 negative; their inclusion or exclusion from the analysis did not greatly change the results.

We also analysed the effect of caesarean delivery on mother-to-child HIV transmission by actual mode of delivery (table 2). Of the 203 infants of women who actually gave birth by caesarean section, seven (3.5%) were infected compared with 17 (10.2%) of 167 children born vaginally ($p=0.009$).

To assess the effects of prophylactic zidovudine therapy and maternal CD4-cell count as risk factors for vertical transmission, we looked at the distribution of these factors by actual and allocated mode of delivery. By allocated mode of delivery, there was one (0.8%) infected child among the 119 babies delivered by caesarean section whose mothers received prophylactic zidovudine during pregnancy, and the lower rate of HIV-1 transmission associated with caesarean-section delivery was consistent in each stratum of CD4-cell count (table 3).

A secondary trial objective was to record adverse effects of delivery in HIV-1-infected women. Overall, the frequency of postpartum complications was low, and there were no serious adverse complications in either group. Postpartum fever was reported for two (1.1%) of the 183 women who gave birth vaginally and 15 (6.7%) of the 225 (6.7%) who gave birth by caesarean section (actual mode of delivery; $p=0.002$). Postpartum bleeding or intravascular coagulation disease occurred in one woman who gave birth vaginally and in one who gave birth by caesarean section. Anaemia of greater than moderate severity (haemoglobin <8 g/dL) was reported in six women (two who gave birth vaginally and four by caesarean-section). There were no further reports of adverse events at the 6-week follow-up examination.

Discussion

The results of this randomised trial confirm the results from European prospective studies^{14,15,17} that an elective caesarean-section delivery decreases the risk of vertical transmission of HIV infection by more than half compared with vaginal delivery. The data presented are based on information from more than 80% of all women randomised. Therefore, although caution is indicated when results are interim the findings can be considered closer to a definitive analysis, than a preliminary one.

During the past few years, several cohort studies have observed a decrease in the rate of mother-to-child transmission in HIV-infected women, independently of the use of prophylactic zidovudine treatment.¹⁸ Thus, since in this trial the initial ratio of caesarean-section to vaginal delivery was one to two, a decline in vertical transmission rate could have been masked by the fact that more of the higher risk cohort (earlier in the trial) gave birth vaginally. However, allowance for calendar year of delivery did not substantially change the estimated effect of elective caesarean section.

Limited data are available on the potentially different protective effect of an elective caesarean-section delivery, carried out before the onset of labour and rupture of membranes, and one carried out as an emergency procedure. In the European Collaborative Study⁵ there were no differences in the rate of vertical transmission between children delivered by elective or emergency caesarean section, but in the Swiss perinatal study^{3,14} and the recent French perinatal study¹⁷ the beneficial effect of

caesarean-section was seen only in the elective procedure group. In our randomised trial, 34 infants with known infection status were delivered by emergency caesarean section, and the odds ratio of vertical transmission in this group was, in comparison with vaginal delivery, 1.0.

Findings from the Swiss perinatal study suggest a protective effect of elective caesarean-section delivery additional to the effect of prophylactic zidovudine therapy, although only a small number of women in that study received prophylactic zidovudine and delivered by caesarean section.¹⁴ Recent information from the French cohort study further supports the findings of a low risk of vertical transmission in such women.¹⁷ With the increasing use of zidovudine during pregnancy as a mean of reducing the risk of vertical transmission,^{13,19} assessment of the additional effect of elective caesarean section is important, especially in women given combination therapy. Zidovudine decreases viral load in maternal blood, whereas caesarean-section delivery reduces exposure to maternal blood and contaminated vaginal secretions. Our trial started in Italy before publication of the results of the US/French trial that showed a reduction in the risk of vertical transmission associated with zidovudine,¹³ and 35% of women in this randomised trial did not receive zidovudine prophylaxis during pregnancy. Although caution is needed in interpreting subgroup analyses, the rate of HIV-1 infection was lower, though not significantly so, in infants in the caesarean-section subgroup than in the vaginal-delivery subgroup of women who received zidovudine in pregnancy. Intrauterine transmission cannot be prevented by caesarean-section delivery, and zidovudine treatment may not completely prevent intrauterine transmission, therefore, a small number of infants will still become infected. Intrauterine acquisition of infection, however, is rare.¹

HIV-1-infected women, especially when severely immunocompromised, may be at increased risk of postdelivery infections, whatever the mode of delivery.^{8,9} We did not find a significant difference between the groups in rates of adverse effects, which may reflect the facts that most caesarean sections in our trial were elective, rather than emergency procedures and the most frequent quoted adverse effects of caesarean section linked to emergency procedures.⁹ Furthermore, prophylactic antibiotics were routinely given and few women were severely immunocompromised.

The proportions of women who withdrew before delivery and children lost to follow-up were low in both randomisation groups. Compliance with allocated mode of delivery was satisfactory, and the indications for change from allocation were consistent with clinical practice. For example, about 15% of women allocated vaginal delivery needed an emergency caesarean-section delivery for fetal distress during labour, a proportion consistent with reported data for routine clinical practice in Italy.²⁰

Previous findings from observational prospective studies have already resulted in changes in obstetric practice. In a European survey in 1997, a quarter of obstetric centres reported a policy of routine elective caesarean-section delivery for all HIV-1-infected women.¹⁹ In France, there has been a substantial increase in the proportion of elective caesarean sections, as well as prophylactic zidovudine use, resulting in a significant effect on the risk of vertical transmission.¹⁷ The results of the interim analysis of this randomised clinical trial

provides further evidence that elective caesarean-section delivery significantly reduces the risk of mother-to-child transmission of HIV-1 infection.

European Mode of Delivery Collaboration

*The European Mode of Delivery Collaboration includes the Italian Trial on Mode of Delivery in HIV Positive Women Study Group, the European and French Mode of Delivery Trial Study Groups. The trial was initiated and coordinated by the Italian Study Group through the Analytical Epidemiology Unit of the Mario Negri Institute (Milan, Italy) in collaboration with the European Collaborative Study and the MRC HIV Clinical Trials Centre (London, UK) and the Institut National de la Sante et de la Recherche Medical Service Common 10 (Villejuif, France).

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