

# Higher rates of post-partum complications in HIV-infected than in uninfected women irrespective of mode of delivery

European HIV in Obstetrics Group\*

**Objective:** To inform the debate on the use of elective caesarean section (CS) delivery in HIV-infected women, we investigated the occurrence of clinical events in the immediate post-partum period in women delivering in 13 European centres.

**Design:** Two separate matched case-control studies (vaginal and elective CS deliveries) among infected women (cases) and uninfected controls delivering between 1992 and 2002.

**Methods** The prevalence of minor and major post-partum complications was assessed overall for infected and uninfected women; within mode of delivery group (vaginal/CS) the complication rates of infected cases were compared with uninfected controls in a matched analysis.

**Results:** Overall complication rates were 29.2% (119 of 408) for HIV-infected women, 19.4% (79 of 408) for uninfected women, 42.7% (135 of 316) for CS deliveries and 12.6% (63 of 500) for vaginal deliveries. There were no major complications in women delivering vaginally; but, compared with controls, HIV-infected cases were at increased risk of puerperal fever [odds ratio (OR), 4.5; 95% confidence interval (CI), 1.55–13.07], especially after medio-lateral episiotomy. In the CS group, there were six major complications (five among cases, one control) (OR, 5.1; 95% CI, 0.58–45) and cases had an increased risk of minor complications (OR, 1.51; 95% CI, 1.22–2.41) compared with controls, mainly anaemia not requiring blood transfusion.

**Conclusion:** HIV-infected pregnant women are at increased risk of post-partum complications regardless of mode of delivery, but modification of clinical practice, particularly use of prophylactic antibiotics, would reduce this risk. Infected women should be informed about risks of vertical transmission and post-partum complications, and be involved in mode of delivery decisions. © 2004 Lippincott Williams & Wilkins

*AIDS* 2004, **18**:933–938

**Keywords:** mode of delivery, postpartum complications, Europe

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Received: 2 September 2003; revised: 12 November 2003; accepted: 8 December 2003.

DOI: 10.1097/01.aids.0000125910.42055.c1

## Introduction

A caesarean section (CS) performed before labour and before rupture of membranes in HIV-infected women substantially reduces the risk of mother-to-child transmission (MTCT) [1–3]. The independent effect of elective CS has been confirmed even in women with low viral load, and those treated with combination antiretroviral therapy (ART) [4,5]. However, it has recently been suggested that in women successfully treated with highly active antiretroviral therapy (HAART) with a low (< 1000 copies/ml) or undetectable viral load close to delivery, the potential side effects of CS delivery may outweigh the benefits of reduced MTCT risk [6].

Major complications following a normal delivery, vaginal or abdominal, are nowadays rare. However, HIV-infected women may have an increased risk of serious post-partum complications than uninfected women, especially after CS [7–9], although this was not seen in the European mode of delivery trial [2]. Maternal morbidity after CS is 5–25 times higher than after a vaginal delivery in general populations, with greatest risk associated with emergency procedures [10,11]. Various maternal and obstetric factors are associated with increased risk of post-operative complications [12–15], while antibiotic prophylaxis reduces infective complications [16,17].

To inform the debate on the use of CS delivery in HIV-infected women, we quantified major and minor adverse events in the immediate post-partum period in women delivering in centres across Europe [18,19] in two separate case–control studies comparing HIV-infected and uninfected women, delivering vaginally or by elective CS, and taking the HIV-infected women together describe the characteristics and overall prevalence of post-partum complications.

## Methods

Prospective data were collected on HIV-infected women delivering between 1992 and 2002 in 14 HIV reference centres in Italy, Spain, Sweden, Poland and Ukraine, most of which were participating in the European Collaborative Study [18,19]. Local ethics permission was obtained. In two case–control studies, one for vaginal delivery and one for CS, HIV-infected women (cases) were matched with HIV-uninfected controls that were selected as the first uninfected woman delivering after the infected index case. Cases and controls were matched by age, ethnicity and parity, for being admitted to the delivery unit with active labour in the vaginal delivery arm, and for having received antibiotics during labour or during CS in the

other arm. Women admitted for medical induction of labour or for emergency CS were not included.

Maternal post-partum complications were recorded following the US NIH Taskforce on caesarean child-birth criteria [20,21]. Major complications were post-partum haemorrhage requiring blood transfusion or surgery, pneumonia or pleural effusion, peritonitis, sepsis, diffuse intravascular coagulation and thromboembolism. Minor complications were anaemia not requiring transfusion (less than 10g%), fever in excess of 38°C beyond 24 h postpartum, wound infection, curettage of the uterine cavity, endometritis and urinary tract infection. Clinical parameters for HIV infection included CD4 cell count in late pregnancy, ART use and clinical symptoms.

Sample sizes were sufficient to provide a more than 95% power at the 5% significance level. Analysis of post-partum complications and HIV infection used conditional logistic regression analysis for the matched case–control studies. Analyses were carried out using STATA (version 6; College Station, Texas, USA).

## Results

A total of 250 matched pairs were delivered vaginally and 158 by elective CS (Table 1). The overall complication rate was 29.2% (119 of 408) among HIV-infected and 19.3% (79 of 408) among uninfected women [odds ratio (OR), 1.7; 95% confidence interval (CI), 1.22–2.40;  $P < 0.001$ ]. Of the 316 women delivered by CS, 42.7% (135) experienced complications as did 12.7% (63) of the 500 women delivering vaginally (OR, 5.1; 95% CI, 3.6–7.42;  $P = 0.001$ ).

Comparison within mode of delivery group showed no difference by infection status in age, height, birth weight and neonatal outcome. Hospital stay was longer for mothers delivered by CS, regardless of infection status (Table 1). Maternal weight at delivery for uninfected women was higher in the CS than in the vaginal delivery group. Severe immunosuppression (CD4 cell count < 200 × 10<sup>6</sup> cells/l) among infected women was rare: 7.2% (18 of 250) in the vaginal and 13.3% (21 of 158) in the caesarean arm ( $P = 0.1$ ). Among infected women, those delivered by CS were more likely to be on antenatal ART [44 (27.8%) not treated, 28 (17.7%) monotherapy, 86 (54.4%) combination therapy] than those delivered vaginally [206 (82.4%) not treated, 44 (17.6%) monotherapy,  $P < 0.001$ ]. Because deliveries occurred over 10 years, with concomitant changes in management of HIV infection and pregnancy, we evaluated incidence of overall post-partum morbidity over time. The post-partum complication rate was 28.8% (17 of 59) before December

Table 1. Maternal characteristics according to HIV infection and prevalence of post-partum complications by mode of delivery.

	HIV-infected women		HIV-uninfected women		P-value
	Vaginal delivery (n = 250)	Caesarean section (n = 158)	Vaginal delivery (n = 250)	Caesarean section (n = 158)	
Number: 816					
Age (years) mean (SD)	26.71 (3.95)	29.00 (6.944)	25.89 (3.6)	29.6 (7.8)	< 0.001
Weight (kg) mean (SD)	67.85 (11.44)	65.8 (10.52)	63.23 (9.3)	72.00 (12.93)	< 0.001
Height (cm) mean (SD)	164.80 (7.19)	163.90 (7.40)	163.55 (6.8)	162.66 (7.3)	0.10
Gestational age (weeks) mean (SD)	38 (1.6)	37.88 (1.39)	39 (1.2)	38.54 (1.5)	< 0.001
Blood loss > 500 ml n (%)	6 (2.43)	44 (28.35)	8 (3.2)	36 (23.0)	OR = 8.93 (3.8–21)
Minor complications n (%)					
Yes	42 (16.8)	77 (48.7)	21 (8.4)	58 (36.7)	OR = 0.239 (0.14–0.36)
No	208 (83.2)	81 (51.3)	229 (91.6)	100 (63.3)	
Major complications n (%)					
Yes	0	5 (3.2)	0	1 (1)	
No	250 (100)	153 (96.1)	250 (100)	157 (99)	NA
Mean hospital stay (days) (SD)	5.4 (3.3)	7.4 (3.7)	5.3 (3.2)	8.7 (5.9)	< 0.001

OR, odds ratio.

1995, 26.5% (45 of 170) in 1996 to 1999 and 29.6% (53 of 179) thereafter ( $P = 0.26$ ). Although numbers in subcategories become small, there was no evidence of either an increase or a decrease in morbidity over the study period.

**Post-partum complications in HIV-infected cases and uninfected controls after vaginal delivery**

The following analyses refer to the 250 matched uninfected–infected women pairs delivered vaginally. All women delivered at 37 to 41 weeks gestation. In 183 (73.2%) pairs membranes were intact on admission and in the remaining 67 (26.8%) with ruptured membranes, for 35 this had been for > 12 h. Eight (3%) pairs received antibiotic prophylaxis. Episiotomy was performed in 147 pairs [medio-lateral (92), median incision (55)]. Three uninfected patients required manual removal of the placenta.

There were no major complications after vaginal delivery in either HIV-infected or uninfected women. In matched analysis, post-partum fever was the only minor complication for which HIV-infected women were at significantly higher risk in comparison with uninfected women (OR, 4.5; 95% CI, 1.55–13.07;  $P = 0.001$ ). Duration of ruptured membranes was not associated with either HIV infection status or fever. A trend towards increased risk of endometritis in infected women did not reach statistical significance (OR, 4.4; 95% CI, 0.44–12;  $P = 0.3$ ). In multivariate analysis of risk factors for complications in infected women, only episiotomy, particularly a medio-lateral incision ( $P = 0.022$ ), was associated with a significant increase of puerperal fever ( $P = 0.001$ ).

**Post-partum complications in HIV-infected cases and uninfected controls after CS delivery**

All 158 matched pairs of women in the CS group were delivered at 37 to 39 weeks gestation, all had intact membranes when admitted and none were in labour. All women received prophylactic antibiotics. Median duration of the procedure was 45 min (range, 22–90 min) and 26 (8%) infected women were delivered by a senior surgeon. Clinical indications for CS delivery included reduction of MTCT for all infected cases and for the uninfected controls: breech presentation (73), macrosomia (19), maternal HCV infection (eight), maternal human papilloma virus (HPV) infection (five), maternal Hemolysis, Elevated Liver Enzymes and Low Platelets (HELLP) syndrome (10), uterine abnormalities (26), obesity (seven) and on demand (10). Wound drainage as treatment for infection was used once in four infected and two uninfected women for < 3 days and a bladder catheter was used for < 24 h in 201 (64%) patients: 85 (42%) cases and 116 (57%) controls. The CS method was reported as conventional for all patients; spinal anaesthesia was used for 13% (21 of 158) infected and 18% (28 of 158)

**Table 2. Post-partum complications, by mode of delivery and infection status.**

	Vaginal delivery: 250 matched pairs		Caesarean section: 158 matched pairs	
	HIV infected (n = 250)	HIV uninfected (n = 250)	HIV infected (n = 158)	HIV uninfected (n = 158)
<b>Minor complications</b>				
Fever > 38°	18		3	4
Anaemia not requiring transfusion	7	6	64	49
Urinary tract infections	3	3	4	1
Endometritis	11	5	2	4
Haematoma	1	1	0	0
Wound gapping	1	1	3	0
Wound infection	1	1	1	0
<b>Total</b>	<b>42<sup>a</sup></b>	<b>21<sup>a</sup></b>	<b>77<sup>b</sup></b>	<b>58<sup>b</sup></b>
<b>Major complications</b>				
Peritonitis	0	0	3	1
Pneumonia	0	0	2	0
Sepsis	0	0	0	0
Thrombosis	0	0	0	0
Diffuse intravascular dissemination	0	0	0	0
Subileus/ileus	0	0	0	0
Haemorrhage	0	0	0	0
<b>Total</b>	<b>0</b>	<b>0</b>	<b>5<sup>c</sup></b>	<b>1<sup>c</sup></b>

<sup>a</sup> $P = 0.001$  [95% confidence interval (CI), -1.61 to -0.38]. <sup>b</sup> $P = 0.02$  (95% CI, 0.6-1.1); <sup>c</sup> $P = 0.2$  (95% CI, 0.72-2.55).

uninfected women, with the remainder delivered under general anaesthetic.

Five major complications occurred in the HIV-infected cases and one among the controls (Table 2); all five infected cases received antenatal ART. Overall, infected women were at significantly higher risk of minor (OR, 1.51; 95% CI, 1.22-2.41;  $P = 0.001$ ) and non-significantly increased risk of major complications (OR, 5.1; 95% CI, 0.58-45.0). Anaemia not requiring blood transfusion was the most prevalent minor complication overall, but was more frequent among infected cases ( $P = 0.029$ ). With the exception of anaemia, no significant differences between cases and controls relating to minor complications existed ( $P = 0.27$ ). Among anaemic HIV-infected women excessive blood loss during surgery was associated with post-partum anaemia (OR, 2.7; 95% CI, 1.47-4.90), irrespective of the seniority of the surgeon. Anaemia was strongly associated with both antenatal ART (OR, 3.1; 95% CI, 2.7-6.9) and immunosuppression (OR, 2.9; 95% CI, 2.1-9.1).

## Discussion

The overall prevalence of any post-partum complication here was five-fold higher in the CS than in the vaginal delivery group, irrespective of HIV infection. However, most complications were minor, relating to anaemia and fever, with serious complications limited to women delivered by CS. Consistent with previous

reports, we found an increased risk of minor complications after elective CS in infected women, albeit of a lesser magnitude [7,9], but we also show increased risk after spontaneous vaginal delivery.

In previous studies among infected women, post-partum fever was associated with elective CS delivery and immunosuppression [7,8,21]. However, in the present study the prevalence of fever was similar in infected and uninfected women delivered by elective CS; infected women were more likely to be on ART for long periods, with restored immune function, and were also exposed to routine antibiotic prophylaxis [22]. The infrequent use of antibiotic prophylaxis may partly explain our finding that fever was common among infected women delivering vaginally. The association found between fever and medio-lateral episiotomy is not surprising given the extensive muscular and vascular damage associated with this procedure. Any delivery, but particularly CS, results in blood loss, and a subsequent physiological fall in haemoglobin. In HIV-infected women, anaemia was also associated with ART use [23]. Prevention of MTCT relies on the combination of elective CS and antiretroviral prophylaxis [1], both of which are associated with anaemia.

Women should participate in decisions regarding mode of delivery and be informed of potential risks and benefits [1]. Paradoxically infected women at greater theoretical risk of complications following CS delivery, namely those with advanced disease, are also those who would benefit most regarding prevention of MTCT. Although antenatal HAART use is associated with a

substantial decline in MTCT, elective CS remains an independent intervention [2–4]. Furthermore, it has been shown that elective CS is cost-effective even when the MTCT rate among vaginal deliveries is low [1,19].

Our aim was to provide information on the comparative risks of complications associated with HIV infection and mode of delivery, to help inform decision-making by clinicians and women. We excluded emergency CS deliveries, which are, by definition, unplanned, as their inclusion would not have informed the current mode of delivery debate. However, infected women opting for vaginal delivery should be informed of the 8–10% chance of needing an emergency CS due to labour complications. This might expose the child to an increased MTCT risk [19] and the mother to complications.

We not only show that a strategy of elective CS for HIV-infected women in Europe does not appear to increase risk of serious maternal morbidity but also that vaginal delivery in infected women is not risk-free. Our results suggest the need to adopt precautions to reduce risk of infection after vaginal delivery specifically for infected women, and of anaemia after CS generally. HIV-infected women delivering vaginally requiring a medio-lateral episiotomy might benefit from antibiotic prophylaxis, which are already the standard of care during CS procedures. Reducing risk of anaemia after CS delivery can be achieved by prenatal iron supplementation and by spinal rather than general anaesthesia [24,25]. Spinal anaesthesia, increasingly used, is associated with reduced blood loss and additionally reduces risk of post-surgical pneumonia.

## Contributors

Simona Fiore, Marie-Louise Newell and Claire Thorne planned the study and were responsible for the analysis and preparation of the manuscript. A.E. Semprini, O. Coll, M. Leyes, S. Lindgren, T. Niemiec, J. Jiminez, I. Bates, M. Ravizza, V. Savasi, P. Martinelli, C. Tibaldi, B. Guerra, E. Ferrazzi, S. Alberico, R. Mayuta and G. Pardi collected the data and through their comments helped revise and improve the manuscript.

## Acknowledgements

We are grateful for the support from L. Gray and L. Pembrey (London, UK), S. Marini, G. Masuelli, C. Benedetto (Turin, Italy), A. Kadma (Huddinge Hospital, Stockholm, Sweden), I. Hoesli (Basel, Switzerland) S. Quarta, V. Ciardelli (Bologna, Italy), M. Crivelli, V.

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*Sponsorship: The work presented here evolved from previous work within the European Collaborative Study on HIV infection in women and their children, which is supported by the EU FP5 (QLK2-CT-2000-00002) and the UK Medical Research Council. Individual centres are supported from national sources.*

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## Appendix

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