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Low Complication Rate Associated with Cesarean Section under Spinal Anesthesia for HIV-1–Infected Women on Antiretroviral Therapy

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Background: **Elective cesarean section decreases the likelihood of vertical human immunodeficiency virus (HIV) transmission from mother to infant. This study aimed to determine whether cesarean section done with spinal anesthesia on HIV-1–infected pregnant women taking antiretroviral therapy is associated with intraoperative hemodynamic instability, postoperative complications, or changes in immune function or HIV-1 viral load.**

Methods: **A case-controlled study was conducted over a 3-year period in a London academic hospital. Forty-four women infected with HIV-1 and a control group of 45 HIV-negative women undergoing cesarean sections were included. The main outcome measures included intraoperative blood pressure, heart rate, blood loss, and ephedrine requirements, and postoperative infective complications, blood transfusion, changes in blood HIV-1 viral load and lymphocyte subsets, and time to hospital discharge.**

Results: **There were no differences in hemodynamic stability and postoperative complications between the HIV-infected group and the controls. There was an acute postoperative increase in the CD4T lymphocyte count ($P = 0.01$), but the CD4T: CD8T ratio and viral load did not change.**

Conclusions: **Elective cesarean section under spinal anesthesia for women infected with HIV-1 taking antiretroviral therapy was not associated with intraoperative or postoperative complications.**

HUMAN Immunodeficiency Virus (HIV) and the resultant Acquired Immunodeficiency Syndrome (AIDS) pandemic pose a major threat to global health.[1] It is estimated that 36 million people worldwide are infected with HIV, which is thought to have caused approximately 20 million deaths to date.[1] The infection continues to spread apace, the most rapid increases being observed in Southern and Central Africa and in South Asia.[1] The predominant mode of HIV transmission is heterosexual sex, and women represent a high proportion of new infections, including in developed countries.[2]

It has been reported that elective cesarean section independent of antiretroviral therapy decreases the risk of HIV vertical transmission from mother to baby.[3,4] Such reports have prompted the American College of Obstetricians and Gynecologists and the British HIV Association to suggest that pregnant women infected with HIV may be offered elective cesarean sections.[5–7] However, a cesarean section is a major surgical intervention that has well-reported complications. There is a higher incidence of morbidity after cesarean section compared with vaginal childbirth in healthy women. This includes more prolonged and intense pain, longer duration of bed rest, increased blood loss, and more frequent venous thrombosis and wound infection. Women infected with HIV have been reported to be more susceptible to such complications.[8–10] Findings from recent studies suggest that women infected with HIV have increased blood loss, prolonged hospital stays, and increased infective complications after cesarean sections compared with HIV-negative women. It has been suggested that the higher complication rate is related to impaired immune response.[8–10] Many practitioners today do not recommend elective cesarean section to HIV-infected women who are compliant with antiretroviral therapy and have undetectable HIV viral loads.[11]

There are few studies concerning anesthetic technique in HIV-infected individuals. An increase in postoperative morbidity and mortality after general anesthesia compared with regional anesthesia has been reported in a recent meta-analysis.[12] The stress response to surgery may be more profound after general anesthesia, which in turn may lead to impaired immune function.[12] One study reported on 30 HIV-infected parturients in labor.[13] Eighteen of these received regional anesthesia and six underwent cesarean sections, two of which were under spinal anesthesia. This study suggests that regional anesthesia was safe for HIV-infected women during labor.[13]

The aim of the current study was to determine whether elective cesarean section done with spinal an-

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esthesia on women infected with HIV-1 taking antiretroviral therapy is associated with a high incidence of intraoperative or postoperative complications.

Materials and Methods

A case-controlled study was conducted in King's College Hospital, London, United Kingdom. Ethics committee approval was granted, together with written informed consent from the HIV-1–infected study participants.

Routine HIV testing is offered to pregnant women at King's College Hospital. Pregnant women infected with HIV-1 were invited to participate in the study. Forty-five HIV-1–infected women were enrolled over 3 yr. Only women receiving antiretroviral therapy and presenting for elective cesarean section were eligible for inclusion. Women presenting in labor and those who had not previously started antiretroviral therapy were excluded. Patients on antiretroviral therapy were monitored as part of routine management. Early in the study, treatment was with zidovudine monotherapy, a nucleoside reverse transcriptase inhibitor. Subsequently, most of the women received combination therapy, with two nucleoside reverse transcriptase inhibitors and either a nonnucleoside reverse transcriptase inhibitor or a protease inhibitor. No women received prophylactic treatment for opportunistic infections during their pregnancies. Sequential samples were collected for measuring plasma HIV-1 viral load and CD4T lymphocyte cell counts over the course of the pregnancy. Alternative treatment regimens were discussed and started if there was evidence of treatment failure, side effects, or difficulties with adherence. The desired antiretroviral treatment efficacy was persistent suppression of HIV-1 viral load below 50 copies/ml.

Forty-five pregnant HIV-negative women were included for case-controlled analysis. The groups were matched for gestational age, antimicrobial prophylaxis, and surgical and anesthetic teams. The control patients were randomly selected from a list of HIV-negative women who had undergone elective cesarean sections under spinal anesthesia over the 3-year period with the same surgeon who had operated on the women infected with HIV-1.

Surgery, Anesthesia, and Perioperative Care

Women were admitted to the hospital at 38 weeks completed gestation for elective cesarean section,[5] unless early delivery was indicated. Spinal anesthesia was achieved by intrathecal injection of 2.4 ml hyperbaric 0.5% bupivacaine and 20 μg of fentanyl *via* a 25-gauge pencil point needle. Patients received 500 ml of lactated Ringer's solution before spinal anesthesia, and ephedrine was administered in 3 mg increments as required to support blood pressure. Antimicrobial prophylaxis was intravenous cefuroxime 1.5 g and metronidazole 500 mg after the infant was delivered. The control group had equivalent levels of consultant-led surgical and anesthetic care. Perioperative blood transfusion was restricted to patients whose hemoglobin concentration decreased below 8 g/dl.

Hematologic and Virologic Measurements

Blood samples were collected for HIV-1 viral load measurement and lymphocyte subsets before initiation of therapy, and subsequently, to monitor efficacy of treatment. Full blood counts were checked before, and on the day after, cesarean section. In the last 24 patients recruited to the study, additional HIV-1 viral load and lymphocyte subsets were measured at the time of cesarean section and 2 days after surgery to evaluate acute changes in these parameters. HIV antibody, p24 antigen (a component of the HIV virion), and HIV proviral DNA tests were carried out on samples collected from all the infants up to 18 months after birth. If all three tests were negative at 18 months, HIV-1 infection of the baby was excluded.

Lymphocyte Subsets and Viral Load Measurements

T cell subsets (CD4 T cells and CD8 T cells) were measured by a whole blood, lysed, no wash technique, using Trucount tubes (BD Biosciences®, Erembodegem, Belgium). The cytometer was a BD Biosciences® FacsCalibur. Several assays were used for HIV-1 plasma viral load quantification over the study time period including nucleic acid sequence based amplification (NASBA) (Organon Teknika Nuclisens HIV-1 QT, Belgium), bDNA Quantiplex HIV-1 RNA version 2.0 (Chiron Corporation, Emeryville, CA) and version 3.0 (Bayer Corporation, Tarrytown, NJ) and the Amplicor HIV-1 Monitor™ Test, version 1.5 RT-PCR (Roche Diagnostics, Branchburg, NJ). Discrepancies in HIV load measurements were detected using some of the above assays and the results evaluation was carried out using the Amplicor HIV-1 Monitor system.

Outcome Measures

The perioperative course and complications were documented for all study participants.

Intraoperative.

Blood pressure, Heart rate, Blood loss, and Ephedrine Requirements

Postoperative. Infective complications, blood transfusion, change in plasma HIV-1 viral load, change in CDT lymphocyte count, and time to hospital discharge. Apgar scores and birth weights were recorded. Babies were followed-up for evidence of HIV-1 infection.

Table 1. Comparisons between HIV-1–Infected and Control Groups

	HIV-1–infected (n = 44) Median (IQR) [Range]	Control (n = 45) Median (IQR) [Range]
Age (yr)	26 (23–29) [17–43]	32* (30–36) [20–49]
Gestation (weeks)	39 (38–39) [30–42]	38 (38–39) [29–41]
Highest systolic blood pressure (mmHg)	140 (130–150) [110–200]	140 (130–150) [105–190]
Lowest systolic blood pressure (mmHg)	100 (90–110) [75–150]	105 (100–110) [40–145]
Ephedrine dosage (mg)	18 (3–30) [0–90]	12 (3–24) [0–42]
Operative blood loss (l)	0.425 (0.35–0.5) [0.1–1]	0.475 (0.4–0.6) [0.3–2]
Time to hospital discharge (days)	5 (4–6) [3–9]	4* (3–5) [2–9]
Preoperative haemoglobin (g/dl)	10.6 (10–11.3) [8.1–12.3]	11.5* (10.7–12.5) [8.5–13.9]
Postoperative haemoglobin (g/dl)	10.4 (9.7–11.5) [7.6–12.5]	10.7 (9–11.2) [7–12.8]
Birthweight (kg)	3 (2.7–3.2) [1.3–4.1]	3.1 (2.9–3.5) [1.4–4.2]
5 min APGAR	10 (9–10) [9–10]	10 (9–10) [8–10]

* $P < 0.001$.

IQR = interquartile range.

Statistical Analysis

A previous study reported a 25% incidence of prolonged fever requiring antibiotic therapy after cesarean section for HIV-infected women.[8] With the incidence of postoperative fever up to 5% in a control group, a power calculation suggested that 45 women in each group would be sufficient to detect a 15% difference in the incidence of this complication between groups with a power of 80% and a *P* value of 0.05.

Comparison between continuous variables including age, gestation, blood pressure, ephedrine, blood loss, time to discharge, hemoglobin, birth weight, and Apgar score in the HIV-infected group and control group was made with the Mann–Whitney U test. Other comparisons between the groups, including pyrexia, blood transfusion, further surgery, and impaired healing, were made with the Fisher exact test. The Wilcoxon signed-rank test was used for paired comparisons within the HIV-1 infected group of lymphocyte subsets and HIV-1 viral load. Results are expressed as median values (interquartile range), [full range], or number (percentage). A P value < 0.05 was regarded as significant for all tests. Statistical analysis was performed using Analyze-It® (Leeds, UK) for Microsoft® Excel (Microsoft Corporation, Redmond, WA.).

Results

Spinal anesthesia was successful in all patients and surgery was performed without intravenous sedation or conversion to general anesthesia. One enrolled patient was excluded from analysis because of incomplete data. Patient characteristics and results are shown in tables 1–3. There were no significant differences between the HIV-1–infected group and the control group with respect to blood loss, intraoperative hemodynamic stability, or ephedrine requirements. Birth weights and Apgar scores were similar in both groups. Postoperative complications were similar and low in both groups, apart from the median time to hospital discharge, which was 1 day longer in the HIV-1– infected group. None of the women reported neurologic complications immediately after spinal anesthesia or at follow-up visits.

In the subgroup of 24 patients there was an increase in the CD4T lymphocyte count (median increase = 101 cells/μl [95% CI = 18–193], $P = 0.01$) 2 days after surgery. There were no significant changes in the CD8T lymphocyte count ($P = 0.3$), the ratio of CD4T to CD8T lymphocytes ($P = 0.8$), or the plasma HIV-1 viral load ($P = 0.3$) after surgery.

All babies had regular follow-up visits for 18 months. Two babies contracted HIV-1 infection. The rest of the babies remained HIV-antibody negative at 18 months of age.

Discussion

This study demonstrates that spinal anesthesia and elective cesarean section are not associated with increased intraoperative or postoperative complications in

Table 2. Immunology and Virology Results from the Subgroup of 24 Women within the HIV-1–Infected Group

	At Surgery Median (IQR) [Range]	2 Days Postsurgery Median (IQR) [Range]
CD4T lymphocytes (cells/μl)	396 (266–553) [102–796]	553* (310–725) [92–1,064]
CD8T lymphocytes (cells/μl)	637 (529–802) [115–2,736]	717 (610–924) [291–2,422]
CD4T:CD8T	0.62 (0.45–0.95) [0.22–1.5]	0.73 (0.43–1.01) [0.1–1.39]
HIV-1 Viral load (copies/ml)	100 (50–500) [50–4,254]	91 (50–475) [50–10,000]

* $P = 0.01$.

IQR = interquartile range.

Table 3. Postoperative Complications in HIV-1–Infected and Control Groups

Complication	HIV-1–Infected Group (n = 44) Number (percent)	Control Group (n = 45) Number (percent)
Postoperative pyrexia > 48 hr	0	1 (2%)
Blood transfusion	3 (7%)	4 (9%)
Further surgery (for bleeding)	1 (2%)	0
Postoperative pyrexia < 48 hr	3 (7%)	4 (9%)
Mildly impaired wound healing	6 (14%)	4 (9%)
Endometritis	0	0
Urinary tract infection	0	0

There were no significant differences between groups.

HIV-1–infected pregnant women on antiretroviral therapy. Other studies have reported an increase in postoperative complications after cesarean section.[8–10] For example, a 25% incidence of fever for more than 48 h requiring antibiotic therapy was noted by Grubert *et al.*[8]; however, 16% of the women had not been on any antiretroviral therapy, only 82% received "perioperative" antibiotics and the mean CD4T:CD8T ratio was 0.49 in patients who had postoperative complications.[8] An inversed ratio of T helper lymphocytes (CD4T) to T suppressor lymphocytes (CD8T) is consistent with significant immune dysfunction. None of the women infected with HIV-1 in our study had a prolonged fever. Possible reasons for the low infection rate were that all women were on antiretroviral therapy, all received intraoperative cefuroxime and metronidazole, and the median CD4T:CD8T ratio at the time of cesarean section was 0.62. In another study, the only factor related to postoperative complications was a CD4T cell count less than 200/μl at the time of surgery.[10] Only three women in our study fell into this category, all of whom had uneventful postoperative recovery. In a third study that reported a high complication rate after cesarean section, operations were not all elective, and details are not provided about antiretroviral therapy or prophylactic antibiotics.[9]

Although the control group was older than the study group, this is unlikely to have biased the results in our study because the complication rate was low in both groups and compared favorably with control groups in other studies.[8,9] There are several reasons for the lower baseline hemoglobin concentration in the women infected with HIV-1, including antibodies to erythropoietin and chronic disease.[14,15] Anemia has been associated with shortened survival and recombinant human erythropoietin therapy should be considered in this setting.[16] The reason for the increased time to hospital discharge in the HIV-infected women is unclear, but does not appear to be attributable to postoperative complications.

The vertical transmission rate was low (2 of 45) and comparable with that reported in the literature when HIV-1–infected women are on antiretroviral therapy and undergo elective cesarean sections.[4] One of the babies may have contracted the virus after birth, as the mother had limited resources for formula feeding and may have breastfed. The other baby who contracted HIV-1 infection had Tetralogy of Fallot and DiGeorge Syndrome, of which congenital immunodeficiency is a feature. This may have increased the baby's susceptibility to HIV-1 infection.

Acute fluctuations in HIV-1 viral load and CD4T lymphocyte counts may occur with intercurrent infections, immunizations, and have been demonstrated following surgery.[17–19] No acute changes in plasma HIV-1 viral load were detected in the study group. An immediate postoperative increase in CD4T lymphocyte count was noted, but the CD4T to CD8T lymphocyte ratio was unchanged. Therefore, both immune function and viral burden were not demonstrably altered after elective cesarean with spinal anesthesia. This may contrast with general anesthesia, which is reportedly associated with impairment of immune function.[12,20]

Central nervous system (CNS) involvement occurs early during the course of HIV infection[21] and introduction of HIV virions into a previously virus-free CNS after penetration of the subarachnoid space during spinal anesthesia is not really a concern. No patient in the study group reported neurologic symptoms after surgery or at follow-up visits. HIV infection causes autonomic neuropathy,[22] which may accentuate hemodynamic instability caused by spinal anesthesia. This was not found in this study, but may be an issue in patients with advanced HIV infection.

Overall, no increase was seen in major or minor morbidity in HIV-1–infected women after elective cesarean section. Providing there are no contraindications to regional anesthesia, elective cesarean section under spinal anesthesia for HIV-1–infected women is an effective intervention in conjunction with other measures such as antiretroviral therapy, broad-spectrum antibiotic prophylaxis, and care for mother and baby by an experienced multidisciplinary team. These findings may not be applicable in countries where antiretroviral therapy is not readily available and where there are insufficient healthcare resources to offer safe elective cesarean sections.

References

1. The global HIV and AIDS epidemic, 2001. MMWR Morb Mortal Wkly Rep 2001; 50:434–439

2. Hader SL, Smith DK, Moore JS, Holmberg SD: HIV infection in women in the United States: Status at the Millennium. JAMA 2001; 285:1186–1192

3. The European Mode of Delivery Collaboration: Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: A randomised clinical trial. Lancet 1999; 27(353):1035–1039

4. The 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; 1(340):977–987

5. Committee on Obstetric Practice. American College of Obstetricians and Gynecologists: ACOG committee opinion: Scheduled cesarean delivery and the prevention of vertical transmission of HIV infection. Int J Gynaecol Obstet 1999; 66:305–306

6. Lyall EG, Blott M, de Ruiter A, Hawkins D, Mercy D, Mitchla Z, Newell ML, O'Shea S, Smith JR, Sunderland J, Webb R, Taylor GP: Guidelines for the management of HIV infection in pregnant women and the prevention of mother-to-child transmission. HIV Med 2001; 2:314–334

7. ACOG committee opinion scheduled Cesarean delivery and the prevention of vertical transmission of HIV infection. Int J Gynaecol Obstet 2001; 73:279–281

8. Grubert TA, Reindell D, Kastner R, Lutz-Friedrich R, Belohradsky BH, Dathe O: Complications after caesarean section in HIV-1–infected women not taking antiretroviral treatment. Lancet 1999; 6:354:1612–1613

9. Maiques-Montesinos V, Cervera-Sanchez J, Bellver-Pradas J, Abad-Carrascosa A, Serra-Serra V: Post-cesarean section morbidity in HIV-positive women. Acta Obstet Gynecol Scand 1999; 78:789–792

10. Semprini AE, Castagna C, Ravizza M, Fiore S, Savasi V, Muggiasca ML, Grossi E, Guerra B, Tibaldi C, Scaravelli G: The incidence of complications after caesarean section in 156 HIV-positive women. AIDS 1995; 9:913–917

11. Rowland BL, Vermillion ST, Soper DE: Scheduled cesarean delivery and the prevention of human immunodeficiency virus transmission: a survey of practicing obstetricians. Am J Obstet Gynecol 2001; 185:327–331

12. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, Sage D, Futter M, Saville G, Clark T, MacMahon S: Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: Results from overview of randomised trials. BMJ 2000; 16:321:1493

13. Hughes SC, Dailey PA, Landers D, Dattel BJ, Crombleholme WR, Johnson JL: Parturients infected with human immunodeficiency virus and regional anesthesia. Clinical and immunologic response. ANESTHESIOLOGY 1995; 82:32–37

14. Sipsas NV, Kokori SI, Ioannidis JP, Kyriaki D, Tzioufas AG, Kordossis T: Circulating autoantibodies to erythropoietin are associated with human immunodeficiency virus type 1-related anemia. J Infect Dis 1999; 180:2044–2047

15. Levine AM, Berhane K, Masri-Lavine L, Sanchez M, Young M, Augenbraun M, Cohen M, Anastos K, Newman M, Gange SJ, Watts H: Prevalence and correlates of anemia in a large cohort of HIV-infected women: Women's Interagency HIV Study. J Acquir Immune Defic Syndr 2001; 1 26:28–35

16. Volberding P: Consensus statement: anemia in HIV infection–current trends, treatment options, and practice strategies: Anemia in HIV working group. Clin Ther 2000; 22:1004–1020

17. Sulkowski MS, Chaisson RE, Karp CL, Moore RD, Margolick JB, Quinn TC: The effect of acute infectious illnesses on plasma human immunodeficiency virus (HIV) type 1 load and the expression of serologic markers of immune activation among HIV-infected adults. J Infect Dis 1998; 178:1642–1648

18. Mole L, Ripich S, Margolis D, Holodniy M: The impact of active herpes simplex virus infection on human immunodeficiency virus load. J Infect Dis 1997; 176:766–770

19. Masel J, Arnaout RA, O'Brien TR, Goedert JJ, Lloyd AL: Fluctuations in HIV-1 viral load are correlated to CD4+ T-lymphocyte count during the natural course of infection. J Acquir Immune Defic Syndr 2000; 15(23):375–379

20. Liu S, Carpenter RL, Neal JM: Epidural anesthesia and analgesia: Their role in postoperative outcome. ANESTHESIOLOGY 1995; 82:1474–506

21. An SF, Groves M, Gray F, Scaravilli F: Early entry and widespread cellular involvement of HIV-1 DNA in brains of HIV-1 positive asymptomatic individuals. J Neuropathol Exp Neurol 1999; 58:1156–1162

22. Gluck T, Degenhardt E, Scholmerich J, Lang B, Grossmann J, Straub RH: Autonomic neuropathy in patients with HIV: Course, impact of disease stage, and medication. Clin Auton Res 2000; 10:17–22