Is there still a role for Caesarean section in preventing vertical HIV transmission in the era of highly active antiretroviral therapy?

Sebitloane HM, MBChB, FCOG, MMed, Chief Specialist; Senior Lecturer
Department of Obstetrics and Gynaecology, University of KwaZulu-Natal, Durban, KwaZulu-Natal
Correspondence to: Hannah Sebitloane, e-mail: sebitloanem@ukzn.ac.za
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Abstract

Human immunodeficiency virus (HIV) may be transmitted from an infected mother to her child during pregnancy, delivery or breastfeeding. Without any intervention, transmission rates may range from 15-45%. However, this can be reduced to < 5% with effective drug therapy. A scheduled Caesarean section that is performed before the onset of labour or the rupture of membranes has been shown to reduce the intrapartum risk in a meta-analysis of earlier studies. The review further concluded that the benefit of performing an elective Caesarean section outweighed the risk of postpartum morbidity in HIV-infected women. However, balancing the risk to benefit ratio is influenced by the underlying rate of mother-to-child transmission (MTCT) in an individual patient.

Caesarean section, while initially shown to reduce the MTCT risk, is itself associated with significant morbidity to the mother. Pregnancy-related sepsis is among the leading causes of maternal deaths, particularly in women who deliver by Caesarean section.

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Introduction

Human immunodeficiency virus (HIV) may be transmitted from an infected mother to her child during pregnancy, delivery or breastfeeding. Without any intervention, transmission rates may range from 15-45%. However, this can be reduced to < 5% with effective drug therapy.[1] A scheduled Caesarean section that is performed before the onset of labour or the rupture of membranes has been shown to reduce the intrapartum risk in a meta-analysis of earlier studies.[2]

The most recent Cochrane review (2005) of the efficacy and the safety of Caesarean section in preventing the vertical transmission of HIV-1 concluded that Caesarean section that is performed before labour or the rupture of membranes was shown to be effective in earlier studies that were conducted among women who received zidovudine [(ZDV), formerly azidothymidine (AZT)] or no antiretroviral (ARV) therapy.[3] The review further concluded that the benefit of performing an elective Caesarean section outweighed the risk of postpartum morbidity in HIV-infected women. However, balancing the risk to benefit ratio is influenced by the underlying rate of mother-to-child transmission (MTCT) in an individual patient.

Caesarean section, while initially shown to reduce the MTCT risk, is itself associated with significant morbidity to the mother. This is the inherent risk of any surgical procedure, compounded by the HIV-related immunosuppression which predisposes the woman to postpartum infectious morbidity. The latter occurs despite the routine use of prophylactic antibiotics that are given during the procedure. Pregnancy-related sepsis is among the leading causes of maternal deaths,[4] particularly in women who deliver by Caesarean section.[5] Several authors have reported an increase in the risk of postpartum endometritis and other infectious morbidity in HIV-infected women undergoing Caesarean section, compared to those who are uninfected.[6-8]

The conclusions of Read and Newell in the Cochrane review (2005) are worth noting, namely that the risk of vertical transmission among women with less advanced or well controlled disease is very low, and hence the benefit of a Caesarean section is unclear. It may well be that the primary objective of preventing MTCT by performing an elective Caesarean section is outweighed by the morbidity that may be experienced by the mother, particularly because less invasive interventions are not only very effective, but also more feasible to implement in resource-poor countries.

Antiretroviral use renders Caesarean section a less attractive intervention in reducing mother-to-child transmission

Significant strides have been made with regard to pursuing interventions that reduce antepartum and postpartum HIV transmission. In the antenatal period, the use of ARVs of different combinations has been found to be effective.[9-11] Whereas single-dose nevirapine (NVP), administered during labour, was considered to be the minimum that resource-poor countries could offer to many women,[12] there is now

sufficient evidence of the efficacy of longer courses of ARVs dispensed during pregnancy in resource-poor countries.[13] ZDV, administered twice daily from as early as 14 weeks, is now recommended by the World Health Organization (WHO) in resource-poor countries and has been shown to be more effective than starting the same prophylaxis at 36 weeks.[14] The addition of single-dose NVP has further enhanced this efficacy.[15]

Implementation of this recommended combination has resulted in the transmission rates in the South African prevention of mother-to-child transmission (PMTCT) programme being reduced to < 4%.[13] To cover for possible resistant mutations that may arise from the use of single-dose NVP, a "tail cover", consisting of either Truvada® (emticitrabine plus tenofivir), or alternatively ZDV plus lamuvidine (3TC), is added to the mother's therapy in the immediate peripartum period.[16,17]

Furthermore, progress has also been made with efforts to reduce postnatal transmission through breastfeeding. Unlike the case in resource-rich countries, where the risk of breastfeeding can be avoided by alternative feeding methods, e.g. infant formula, this practice has shown to have deleterious results in resource-poor countries. A study in Botswana demonstrated that infant survival was compromised in those who were formula-fed (while trying to avoid transmission from breast milk).[18] The use of either ARVs, administered to the mother [as highly active antiretroviral therapy (HAART)], or infants, has been shown to significantly reduce the risk of postnatal transmission[19] and to improve infant survival. In the postpartum period, infants should receive at least six weeks of ARV post-exposure prophylaxis, or for the duration of breastfeeding, until a week postcessation.[18,20,21] Studies have shown that this is as effective as maternal HAART if the mother is breastfeeding.[18] This practice is now recommended for up to12 months.[22]

Based on strong evidence that has emerged from different settings in resource-poor countries, the place of an elective Caesarean section performed for the sole purpose of reducing MTCT is now being questioned. This has necessitated a reappraisal of the issue of scheduled Caesarean section to prevent MTCT.

Is there any evidence that scheduled Caesarean section reduces mother-to-child transmission in patients receiving highly active antiretroviral therapy?

Since the Cochrane review, the efficacy of scheduled Caesarean section in the presence of undetectable viral load (VL), either consequent to HAART use, or long-term use of ARV prophylaxis started early in pregnancy, has been re-examined.[23,24] The findings of some key studies that have attempted to address this question are summarised.

The authors of the European Collaborative Study[23] examined MTCT rates in the HAART era. They also investigated the effects of elective Caesarean section, the duration of ruptured membranes and prematurity. Of the 4 525 mother-infant pairs who were enrolled in the study between 1998 and 2004, 44% of these were in the HAART era (1 983 pairs). In the majority of cases (57.8% or 1 147), HAART was initiated during pregnancy. In this study, in which 61% of the cohort delivered by elective Caesarean section, the mode of delivery was associated with vertical transmission. Infection occurred in 6.5% of infants who were delivered vaginally and in 1.65% of those who delivered by elective Caesarean section. This benefit of reduced vertical transmission was noticed, even after controlling for VL. The latter was found to be "the pre-eminent independent risk factor". VL > 1 000 copies/ml was associated with a 12-fold increase in the risk of MTCT. However, even after controlling for VL, elective Caesarean section remained significantly associated with a reduced risk of MTCT, a benefit that persisted even in a group of women with undetectable VL who had been receiving antenatal HAART. The study found that elective Caesarean section delivery was associated with an approximate 40% reduction in the risk of vertical HIV transmission, compared with vaginal delivery. However, the difference was not statistically significant. In the same study, the authors found that prematurity and duration of rupture of membranes were also associated with an increased risk of MTCT.

In summary, the study showed that elective Caesarean section significantly reduced MTCT in the whole group, i.e. pre-HAART and during the HAART era, even in those with undetectable VL using HAART. However, the study was not powered to further adjust for the use of HAART. The authors concluded that a large study was needed to resolve this issue, one that would require approximately 6 345 and 7 217 mother-child pairs from vaginal and Caesarean section deliveries, respectively, with 90% power.[23,25] Evidence seems to suggest that a large number of Caesarean section need to be performed to prevent a single case of MTCT.

In another study, Warszawski et al aimed to determine the rate of MTCT according to various components of prophylaxis.[26] Overall, there were 5 271 eligible mother-child pairs over a period of seven years, 19% of whom received monotherapy, 33% dual-drug therapy and 48% HAART at delivery. There were 67 infected neonates (an overall MTCT rate of 1.3%), and the risk was significantly associated with prematurity, HIV-1 RNA level, cluster of differentiation 4 cell count and duration of ART during the pregnancy. The study found that MTCT rates were not influenced by the mode of delivery. The only factor that influenced transmission was intrapartum prophylaxis, both in those with or without virological suppression. In general, for term deliveries where the mother had VL < 400 copies/ml, the only factor that was found to be associated with transmission was the duration of antenatal therapy [with the odds ratio (OR) calculated per week as 0.94, 95% confidence interval (CI): 0.90-0.99, p-value = 0.03]. In other words, each week of ARV use reduced the risk of transmission by 6%. There was a sharp reduction in MTCT

after the first 12 weeks of ARV use and the duration of ART remained significantly associated with MTCT, even after adjustments. The median duration of ART during pregnancy was significantly shorter in mothers who transmitted the virus to the infant (9.5 weeks), compared to those who did not (16 weeks, p-value < 0.001). Among term births with failure of virological suppression, defined as VL > 50 copies/ml, intrapartum prophylaxis that was given intrapartum was strongly associated with a lower risk of transmission (5.3% compared to 22.7% without intrapartum prophylaxis, p-value = 0.009). The OR for MTCT, when no intrapartum therapy was given, was calculated as 4.72 (95% CI: 1.42-15.71). In summary, the study found that the duration of ARV during pregnancy was the most important determining factor in the risk of vertical HIV transmission, and if VL was not suppressed, then intrapartum prophylaxis reduced the risk.

In the AmRo study, investigators reported on 143 HIV-infected women who received HAART, 78% of whom attempted vaginal delivery (111/143).[24] These had a median VL of < 50 copies/ml (undetectable in 85%). Vaginal delivery was successful in 62% of cases, with no cases of MTCT (95% CI: 0-2.4%). It was believed that when HAART was started before the third trimester, it was able to suppress the HIV RNA level to < 50 copies/ml, and thus allow for safe vaginal delivery. It was suggested that, in this scenario, at least 131 instances of elective Caesarean section would need to be carried out to prevent a single case of MTCT from occurring. The study, like others,[27] also found an association between the use of HAART in the first trimester and the risk of preterm delivery.

It seems that there is mounting evidence that HAART use may eliminate the need for elective Caesarean section to prevent MTCT, provided there is sufficient time before delivery. In a national surveillance study in the UK, Townsend et al found that the "MTCT rate was 1.2% overall, (61/5 151,95% CI: 0.9-1.5%) and 0.8% for women who received at least 14 days of ART (40/4 864, 95% CI:0,6 - 1,1%)".[28] In a local study in South Africa, women who became pregnant on HAART had lower MTCT rates compared to those who initiated HAART during pregnancy (0.7% vs. 5.7%, p-value = 0.01).[29] In the latter group, there was 8% reduction in the odds of transmission for each additional week of treatment (95% CI: 0.87-0.99, p-value = 0.02). Overall, the MTCT rate was 4.9% (43 of 874), and none of the different HAART regimens were superior to the others. Despite all these interventions, there is "residual transmission", as termed by Tubiana et al, in which MTCT continues to occur in the context of full-term deliveries and a maternal viral load of < 400 copies/ml, in the absence of breastfeeding.[30] In a study in which cases of vertical transmission were matched with controls in which there was no transmission, "the only factor that remained independently associated with residual transmission of HIV-1 was early control of the plasma HIV-1 RNA level". In this study, the majority of patients delivered by Caesarean section. Caesarean section was not found to influence the rates of MTCT.

Summary of evidence

Evidence from the above studies can be summarised as follows:

- Vaginal delivery seems to be safe among women on HAART with virological suppression.
- The duration of ARV use during pregnancy (preferably HAART) greatly determines virological success, and consequently the risk of MTCT.
- Each week of triple ARV therapy reduces the odds ratio of transmission by 6-8%.[25,29]
- In the absence of virological suppression, intrapartum prophylaxis significantly reduces the risk of MTCT.
- While there might still be a benefit in performing Caesarean section in women on HAART, the number that is needed to treat is large (> 100 Caesarean sections need to be performed to prevent one case of MTCT from occurring).

The multipronged strategy of early initiation of ARV therapy during pregnancy, administration of ARV during labour and delivery, as well as pre-exposure prophylaxis to the infant in the postpartum period, has proven to be very effective in reducing vertical transmission to < 4% in resource-poor countries.[13] The latest evidence suggests that the earlier that ARV drugs are started during pregnancy, the more effective the efforts to prevent in utero and intrapartum transmission. However, studies cannot determine "the optimal gestational age at which ART should be started, the optimal gestational age at which viral load should be controlled, or the threshold of viral load to be reached",[30] in order to completely eliminate the risk of MTCT.

Practice points

Scenario A: Assuming a woman attended for care early in pregnancy, and that the HIV infection has been diagnosed for the first time, in cases where resources are not a prohibiting factor:

- Carry out a baseline clinical (WHO) staging, viral load and CD 4 count.
- If the CD4 count is < 350, initiate HAART for maternal health, which will also benefit the infant. HAART will need to be continued for life.
- If the CD4 count is > 350, give HAART to prevent MTCT (similar to Scenario B).
- Where feasible, repeat VL count at > 36 weeks in order to decide on the mode of delivery.
- If VL > 1 000 cp/ml, a woman should be counselled on the risk of MTCT, which could be obviated by performing a scheduled Caesarean section.
- In this instance, intrapartum prophylaxis is imperative, whether or not the patient undergoes a scheduled Caesarean section (ZDV 300 mg given three hours before Caesarean section), and particularly if she opts for vaginal delivery.
- If the VL is undetectable, vaginal delivery is considered to be safe with intrapartum prophylaxis.

- Patients should be counselled that the absolute elimination of risk of MTCT is not guaranteed.

Scenario B: In cases where resources are constrained, it may not be possible to offer HAART for the sole purpose of preventing MTCT, performing a routine VL count close to term or scheduling a Caesarean section for PMTCT.

Therefore:

- HAART should be offered as early as possible in the second trimester to women whose CD4 count is < 350, or to those who are WHO stages III or IV clinically.
- For women with a CD4 count > 350, ZDV 300 mg should be started twice daily as early as 14 weeks. The dose should be increased to 300 mg three hourly during labour, with the addition of a single dose of NVP during labour.
- A "tail cover" consisting of either Truvada® or ZDV plus 3TC should be given to the mother.
- In all instances, the infant should receive a six-week course of ARV therapy (either ZDV or NVP). If the mother has chosen to breastfeed, this should continue for up to 12 months and should preferably be exclusive for the initial period. Maternal HAART or infant prophylaxis should be given for the duration of the breastfeeding period. The latter is preferred as it preserves treatment options for the mother (if she does not require HAART for her health).

Conclusion

In conclusion, evidence shows that in the era of highly effective ARV combinations that are used for PMTCT, including HAART for the mother, the role of a scheduled Caesarean section to prevent MTCT seems to be limited and remains questionable. However, it is concerning to note that while a scheduled Caesarean section is not always necessary, many procedures continue to be performed through fear of the unknown on the part of the practitioner and the "adequately counselled" mother (possibly what Tubiana et al termed "residual transmission").[30] While the private sector may be able to carry the increased number of Caesarean sections that are carried out for PMTCT, this practice would be difficult to implement on a wider public health scale, given the high costs of Caesarean section and the implications for infrastructure and personnel.

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