Sexually Transmitted Infections

Editorials

Preventing mother to child transmission of HIV: the role of caesarean section

Mother to child transmission of human immunodeficiency virus type 1 (HIV) is the most common aetiology of paediatric HIV infection throughout the world. Research has yielded important information regarding the timing and mechanisms of, as well as interventions to interrupt, mother to child transmission of HIV.

The biological plausibility of a lower risk of transmission with caesarean section prompted investigations of mode of delivery as a risk factor for mother to child transmission of HIV. The cumulative evidence from epidemiological studies performed over the past two decades, culminating in the publication of an individual patient data meta-analysis of prospective cohort studies from North America and Europe[1] and a randomised clinical trial from Europe,[2] demonstrates a lower risk of mother to child transmission of HIV with caesarean section before labour and ruptured membranes (hereafter referred to as scheduled caesarean section, or SCS). The individual patient data meta-analysis[1] compared the risk of mother to child transmission among approximately 8000 HIV infected women who underwent SCS with that of women with any other mode of delivery. The risk of transmission was 50% lower among women who delivered by SCS in analyses allowing for adjustment for other factors (adjusted odds ratio (OR) = 0.43 (95% confidence interval (95% CI): 0.33, 0.56)). Further analyses revealed an 87% lower likelihood of transmission among women who underwent SCS and who received antiretroviral therapy during the antepartum, intrapartum, and postnatal periods (likely zidovudine prophylaxis) compared with those with other modes of delivery and no antiretroviral therapy (adjusted OR = 0.13 (95% CI 0.09, 0.19)). In the randomised clinical trial of mode of delivery,[2] SCS resulted in a lower risk of transmission than vaginal delivery in analyses of both allocated (OR = 0.2 (95% CI 0.1, 0.6)) as well as actual modes of delivery (OR = 0.4 (95% CI 0.2, 0.9)). Similar, although not statistically significant, results were obtained for women who received zidovudine prophylaxis. Both of these studies evaluated the relation between mode of delivery and vertical transmission among HIV infected women receiving either no antiretroviral therapy or known, or likely, zidovudine prophylaxis. HIV infected women receiving potent antiretroviral therapy would be expected to have significantly lower quantities of peripheral blood HIV RNA (viral load), and a lower maternal viral load is associated with a lower risk of mother to child transmission.[3] Although analyses in each study incorporated data regarding maternal HIV disease stage (clinical (AIDS) or immunological (CD4+ lymphocyte count)), neither collected maternal viral load data. Therefore, neither study could evaluate the relation between mode of delivery and mother to child transmission according to maternal viral load. Limited, but not definitive, data suggest SCS could be associated with a lower risk of mother to child transmission across a range of maternal viral loads.[4 5]

The role of SCS, and other interventions, in the management of HIV infected women must be assessed in light of risks as well as benefits. HIV infected pregnant women must be provided with available information with which to make informed decisions regarding SCS and other options to prevent transmission of infection to their children. Firstly, the milieu of current recommendations for the prevention of mother to child transmission in those areas of the world where SCS as an intervention might reasonably be considered an option must be understood. Existing prevention programmes have three primary foci[6]: routine HIV counselling and voluntary testing for all pregnant women, as well as zidovudine prophylaxis and avoidance of breast feeding for HIV infected women. More recently, the management of HIV infected pregnant women has evolved to include highly active antiretroviral therapy.[7 8] Of note, only minimal safety data exist for antiretroviral drugs during pregnancy other than zidovudine. However, an estimated 70% of HIV infected women in the United States receive combination antiretroviral therapy during the third trimester of pregnancy, and 35% receive multiagent therapy including a protease inhibitor.[9] As expected, point estimates of mother to child transmission rates in any given study generally are lower with more intensive, combination antiretroviral therapy compared with monotherapy; however, the confidence intervals of such estimates overlap significantly.[10] It is essential to acknowledge that prescription of antiretroviral therapy during pregnancy is not synonymous with undetectable viral load at the time of delivery.[9] Potential reasons for this discordance are many, including lack of adherence to multidrug antiretroviral therapy regimens (possibly related to intolerance to one or more drugs) and viral resistance. Other issues to consider when evaluating the role of caesarean section are the risks associated with the procedure—maternal and neonatal morbidity, occupational exposure to HIV by obstetricians and others—as well as cost effectiveness.

It is well known that, in the absence of HIV infection, caesarean section is associated with increased risks of maternal morbidity. However, sparse data exist regarding a key question facing HIV infected pregnant women and their clinicians: what is the risk of postpartum morbidity among HIV infected women with SCS versus other modes of delivery? Among approximately 400 HIV infected

women in the randomised clinical trial,[2] postpartum fever was more common among those who delivered via caesarean section. More recently, analyses of approximately 1200 deliveries within the largest North American prospective cohort study of HIV infected women with postpartum morbidity data[11] revealed SCS was an independent risk factor for postpartum morbidity overall, and for fever without infection, specifically. Counselling of HIV infected pregnant women regarding SCS as a possible intervention to decrease maternal infant transmission of HIV should include discussion of these results, as well as new data as they become available.

In general, neonatal morbidity related to SCS would be expected to result from iatrogenic preterm delivery in situations where the gestational age is not accurately assessed before delivery. A SCS is generally performed at 39 completed weeks of gestation. However, the American College of Obstetricians and Gynecologists recommends that, for caesarean section undertaken to prevent vertical transmission of HIV, the delivery be performed at 38 completed weeks of gestation to decrease the chances of ruptured membranes or onset of labour before delivery.[12] Even with accurate assessment of gestational age, the relative risk of neonatal respiratory morbidity with delivery by caesarean section before the onset of labour is higher if performed during the 38th week than during the 39th week of gestation.[13]

Since caesarean sections are surgical procedures, an argument can be made that there is an inherently higher risk of HIV infection for healthcare providers performing such procedures compared with vaginal deliveries. Alternatively, one can postulate that a scheduled, relatively controlled surgical procedure has a lower risk of accidental transmission of HIV than a vaginal delivery, especially one with an episiotomy. However, although occupationally acquired HIV infection related to obstetric procedures is a rare possibility,[14] the risk related to mode of delivery is unknown.

Analyses comparing SCS with vaginal delivery to prevent mother to child transmission of HIV in the United States indicate SCS is a cost effective intervention to prevent vertical transmission among HIV infected women receiving various antiretroviral therapy regimens.[15] Based on the findings of this study, SCS is likely to remain a cost effective intervention over a wide range of possible clinical and economic scenarios. However, further research is needed, including threshold analyses, to evaluate the conditions under which SCS remains cost effective. Obviously, if vertical transmission rates with potent antiretroviral therapy during pregnancy were 0%, SCS would only increase costs and not improve outcomes.

What, then, is the role of caesarean section in the prevention of mother to child transmission? Obviously, SCS should only be considered in situations where an accurate assessment of gestational age can be performed, and where the necessary infrastructure and staffing both for the procedure itself and for subsequent maternal and neonatal care are available. In such settings, HIV infected pregnant women should be informed of the available data regarding both the efficacy of such an intervention for prevention of mother child transmission, as well as the associated risks. Virtually all of the available information regarding the risk of mother to child transmission according to mode of delivery exists for HIV infected pregnant women receiving either no antiretroviral therapy during pregnancy or only zidovudine prophylaxis. No definitive data are available regarding the risk of transmission according to mode of delivery among women receiving potent antiretroviral therapy, an imperfect proxy for low maternal viral load, or according to maternal viral load itself. Thus, evidence based decisions regarding mode of delivery among HIV infected women receiving potent antiretroviral therapy or with low viral loads will be precluded for the foreseeable future by the paucity of relevant data. In the interim, SCS can be reasonably recommended, as part of individualised counselling, to HIV infected women who receive no antiretroviral therapy, who receive monotherapy but with unknown viral loads, or who, irrespective of antiretroviral therapy, have higher (for example, $\geq$1000 copies/ml) viral loads. For these women, SCS is an intervention for prevention of mother to child transmission of HIV with efficacy that is likely to be of greater magnitude than the known, or anticipated, concomitant risks. However, among women with lower (for example, <1000 copies/ml) viral loads, the degree of procedure associated morbidity and cost could outweigh the benefit.

In summary, for many HIV infected women, SCS is an efficacious and cost effective intervention to decrease the risk of mother to child transmission, with associated risks to the mother, child, and clinician that must be anticipated. The role of SCS in the management of HIV infected women according to maternal viral load awaits further definition based upon future research.

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