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HIV and Pregnancy

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Abstract
South Africa has a high burden of HIV disease. Approximately 29% of antenatal clinic attendees are infected with HIV. A compromised immune system in pregnancy was thought to render the HIV positive woman more susceptible to complications. Recent data suggests that HIV causes few adverse effects on pregnancy. Similarly, pregnancy is not associated with HIV disease progression. Appropriate use of antiretroviral therapy is a major determinant in the fall of HIV/AIDS related morbidity and mortality as well as perinatal transmission. Maternal mortality due to non-pregnancy related infection, of which HIV is the major contributor, is declining. This is a reflection of improved prevention of mother-to-child transmission of HIV guidelines in South Africa. All pregnant women are now initiated on lifelong anti-retroviral therapy. It is hoped that this will improve maternal health and thus directly impact of infant well-being.

Introduction

South Africa has a high burden of HIV disease. An estimated 5.6 million South Africans over the age of 2 years are living with HIV. Twenty three per cent of females of child-bearing age (i.e. 15-40years) are infected with HIV. Approximately 29% of antenatal clinic attendees are HIV positive.[1,2,3] This has a significant impact on the risk of vertical transmission, and maternal and neonatal morbidity and mortality.

It has been postulated that HIV positive women experience a higher level of adverse pregnancy outcomes than the general population. A possible mechanism is an imbalance between pro- and anti-angiogenic factors needed for optimal placental function. Anti-angiogenic states have been associated with low birth weight babies, preterm births and pre-eclampsia.[4]

Given the high level of HIV positive pregnant women in South Africa, it is prudent to consider any effects that HIV may have on pregnancy outcomes.

Effects of HIV on Pregnancy

Maternal Effects

HIV has been reported to be associated with an increased incidence of direct obstetric complications. Adverse events have been more commonly reported in Africa, but the evidence is poor. In the developed world, HIV infection seems to have little or no effect on pregnancy outcomes and complications.[3]

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Several biological pathways have been proposed for the adverse obstetric outcomes associated with HIV infection[5]:

- A compromised immune system and general poor health renders the woman more vulnerable to infection, including puerperal sepsis
- HIV-related thrombocytopaenia and anaemia increases the risk of obstetric haemorrhage and complications associated with caesarean section[6]
- Social factors, such as poor access to healthcare, increase the risk of complications. This may be exacerbated by stigmatization and discrimination associated with HIV.

HIV in early pregnancy is associated with an increase in spontaneous abortions, ectopic pregnancies, syphilis (which is 33% more common in HIV positive women in South Africa), systemic infections such as respiratory and urinary tract infections and co-infection with tuberculosis.[3,6] Co-infection with TB and HIV is synergistic and confers a three-fold increased risk of mortality. Furthermore, the diagnosis and management of Pneumocystis jirovecii (PCP/PJP) in pregnancy is difficult and may be delayed.[7]

The evidence for an association between HIV and pre-eclampsia, labour dystocia and haemorrhage is inconsistent. It was previously believed that HIV positive women had a lower incidence of pre-eclampsia.[8,9] Newer data concludes that HIV is in fact associated with a higher incidence of hypertension, but not pre-eclampsia or eclampsia.[5]

HIV has also been associated with an increased risk of obstetric haemorrhage. No increase in the incidence of placenta praevia, abruption placenta, post-partum

haemorrhage or retained placenta has been demonstrated. Gestational thrombocytopaenia is more common in HIV positive women – 10% in HIV positive women; 30% in women living with AIDS. Gestational thrombocytopaenia is rarely a contributor to severe obstetric haemorrhage. There is an association with HIV and uterine rupture, but the mechanism is poorly understood.[5]

People with HIV have depressed immunity and are more susceptible to infection, including infections in pregnancy, labour and the pueperium. It is uncertain whether the increased risk of endometritis or puerperal sepsis is attributable to the pregnancy alone or to the HIV/AIDS infection.[5]

Mental health is an often neglected area of obstetric care. It is thus noteworthy that mental illness was found in up to 85% of HIV positive pregnant women. The most common disturbances were major depressive disorder and suicidal ideation.[10]

Maternal Mortality

The HIV/AIDS epidemic intersects with the epidemic of maternal mortality in many circumstances. HIV impacts on the direct obstetric causes of maternal mortality by its association with anaemia, post-partum haemorrhage and puerperal sepsis. It is also a major indirect cause of the increase in infections. The maternal mortality ratio may be increased up to ten-times in HIV positive women. Non-pregnancy related infections, of which HIV is a major contributor, remains the main cause of maternal mortality in South Africa, contributing to 53.3% of maternal deaths in the last report.[11] Appropriate use of antiretroviral therapy (ART) could reverse the toll of HIV-related maternal mortality. With improved access to ART the mortality of people living with AIDS has decreased. This is evident in the downward trend observed in maternal deaths due to non-pregnancy related infections in South Africa. The current recommendation of life-long ART initiated in all pregnant women will certainly reduce the rate of AIDS-related complications and mortality in pregnancy.[12]

Fetal Effects

More advanced maternal HIV disease is associated with adverse pregnancy outcomes. Excessive neonatal mortality in HIV infected women is not primarily explained by infant HIV infection, but is strongly associated with low birth weight infants and prematurity.[13] HIV positive women on ART are not at increased risk of preterm birth or small-for-gestational age fetuses, but are at increased risk of having a low birth weight infant.[7]

HIV is associated with an increased incidence of placental membrane inflammation.[14] Intra-uterine HIV infection contributes to infant mortality as early as seventy days of life.[13] HIV is associated with a four-fold increased risk of stillbirth, infections, growth restriction and neonatal encephalopathy.[15,16] These adverse events were more frequent in patients with lower CD_4 counts.[17] Antiretroviral therapy seemed to reduce these adverse fetal and neonatal outcomes, independent of the CD_4 count or the timing of initiation.[18,19]

Prevention of Mother-to-Child Transmission (PMTCT) in Resource Limited Settings

In 2012 there were 260 000 new paediatric HIV infections worldwide. Ninety per cent of new cases occurred in sub-Saharan Africa.[3] Without ART the risk of perinatal HIV transmission varies from 15 to 45%. The most consistent risk factor for transmission has been maternal plasma and breast milk viral load, followed by maternal immunological status and clinical staging.[20,21] By contrast the use of ART coupled with the avoidance of breastfeeding and good access to comprehensive HIV and pregnancy care services have significantly reduced perinatal transmission in resource-rich countries to 1 to 2%.

Antiretroviral intervention is the cornerstone of strategies to prevent mother-to-child transmission (MTCT) of HIV. The complete cascade involves further measures including rapid HIV screening during antenatal care, CD_4 cell count screen and disease staging, use of effective ART throughout pregnancy, delivery and breastfeeding, monitoring of drug compliance and toxicities, delivery by a skilled attendant, infant HIV prophylaxis and post-partum follow-up of mother and child.

Perinatal trials in resource-limited settings have demonstrated the strong impact of maternal ART use on reducing the risk of MTCT of HIV. In these studies the use of ART interventions has been shown to be the most important factor for reducing the risk of MTCT, overriding clinical, virological and immunological risk factors.[22,23,24] Triple combination ART use has been associated with lower rates of transmission.

Large scale implementation of ART has proven challenging in resource-limited settings. However, progress is being made. UNAIDS estimated that ART coverage for PMTCT has increased from 57% in 2011 to 63% in 2012 (3). For PMTCT of HIV to be effective interventions must achieve high uptake in all aspects of HIV care, from antenatal services to post-partum linkage of HIV care. Despite historical challenges, South African data is promising. In a 2011-2012 study the national MTCT rate at 4 to 8 weeks was 2.7%.[25]

Scheduled caesarean section is associated with reduced rates of MTCT among women who have received either no ART or zidovudine (AZT) alone. Elective caesarean section is thus recommended for women who have not achieved viral suppression (HIV viral load >1000 copies/mL) in resource-rich regions. This recommendation is not practical in resource-limited settings and may increase maternal morbidity.[26]

In resource-rich settings replacement infant feeding is recommended. In resource-limited settings replacement feeding is associated with greater infant

morbidity and mortality from diarrhoeal disease, pneumonia and other infections. The greatest risk via breast milk is in the first several months of life. The risk is lower, but constant through the entire period of breastfeeding. WHO recommends that HIV positive women and their breastfed infants continue ART throughout the period of breastfeeding or until the infant is 12 months old. This could reduce the risk of transmission by 42%.[27]

Effects of Pregnancy on HIV

Disease Progression

In pregnancy immune function is suppressed in both HIV-infected and uninfected women. There is a decrease in immunoglobulin, reduced complement levels and a significant decline in cell-mediated immunity. These normal changes of pregnancy have led to concern that the effect of pregnancy on HIV disease could be to accelerate progression of the disease. Early reports of pregnancy in HIV seemed to have supported this theory. Prospective follow-up studies to date have not confirmed this. There is no overall difference in the rate of death between HIV positive and negative women or in their rate of progression to any AIDS-defining event.[3] Multiple other factors such as nutritional status and genetics may influence the risk of faster progression during and post-pregnancy.[28]

Pregnancy has little or no effect on viral load or progress of HIV in asymptomatic HIV positive women or in those with early infection. There may be more rapid progression in pregnant women with late stage HIV disease. Repeat pregnancies do not have a significant impact on HIV disease. There is no substantial clinical, immunological or virological disadvantage conferred by pregnancy.[29]

In African women no more rapid progression of HIV disease has been observed in pregnancy, despite the added burden of multiple pregnancies, co-infections and malnutrition. The existing evidence does not support the theory of a short term synergistic effect on the immune system between pregnancy and HIV infection. The increased mortality associated with HIV is not due to pregnancy-induced acceleration of disease, but more likely due to women with more advanced disease becoming pregnant.[3]

Anti-retroviral Therapy (ART)

A major determinant of the fall in AIDS-related mortality in resource-rich settings has been the availability of ART. If the impact of HIV on maternal mortality is to be controlled, the appropriate use of ART is essential. Health care workers need to be trained to identify women in need of treatment and initiate and maintain this treatment. If this is not achieved, efforts for safer motherhood and safer pregnancy programmes will not be achieved.[30]

Increasing clinical expertise and routine use of ART has led to a dramatic and substantial decrease in maternal morbidity and mortality in HIV infection, as well as a decline in the rate of MTCT. In this scenario it is not surprising that fertile HIV-infected women may decide to become pregnant expecting an offspring free of HIV infection and no more complications during pregnancy than non-HIV infected women. It is currently recommended that HIV infected women receive similar ART regimens to their non-pregnant counterparts, except for considerations for potential adverse effects of such therapy on the fetus.

The use of ART during pregnancy has generally been found to be safe in trials to date, and the benefits of preventing MTCT outweigh the potential adverse reactions. However, the currently recommended first-line regimen of lamivudine (3TC), efavirenz (EFV) and tenofivir has not been extensively used in pregnancy as have other regimes such as those containing zidovudine (AZT) and nevirapine (NVP). Thus, continued monitoring for toxicities and birth defects in pregnant women and their infants is necessary to assure safety.

HIV positive women with low levels of education use ART sub-optimally.[31] Multi-class resistance in both mother and infant is possible if there is poor maternal adherence to ART. Thus continued counselling and adherence evaluation is critical.

The use of ART is generally safe in pregnant women. Teratogenic effects associated with the use of ART during pregnancy have been monitored over the last three decades. Although there were initial concerns about the risk of central nervous system and other midline defects with in-utero exposure to EFV, prospective data to date is reassuring. Tenofivir use has not been associated with birth defects. Lamivudine may rarely cause significant neurological symptoms such as seizures.[32]

There is robust evidence demonstrating the overwhelming benefits of ART for the prevention of perinatal transmission of HIV and improving maternal health, which outweighs any potential risks.

Conclusion

Maternal health is a major health priority. HIV infection is the major cause of the large increase in maternal mortality. The national prevalence of HIV remains largely unchanged at around 30%. Non-pregnancy related infections, mostly related to HIV, still remains the single most common cause of maternal mortality.

Despite these bleak statistics there is cause for optimism. South Africa has the largest ART programme in the world. PMTCT has evolved despite many challenges. The current recommendations are in keeping with the WHO guidelines. All pregnant and breastfeeding women will be initiated on lifelong ART irrespective of CD_4 count or disease stage. Recent data on maternal mortality in South Africa demonstrates a significant decline in maternal mortality due to non-pregnancy related infections. There is also a decrease in MTCT with national perinatal transmission being below 3%.

Previously PMTCT services were directed at preventing perinatal HIV transmission. The focus seems to have shifted. It is now recognised that the well-being of the HIV-positive mother is essential for the health of her child. The realisation of integrated health services, access to ART, family planning, outreach care, couple counselling and destigmatization of HIV are all crucial to achieving our health goals and optimising outcomes for women with complicated pregnancies.

References

1. *Department of Health, South Africa (2012). 'The National Antenatal Sentinel HIV and Syphilis Prevalence Survey in South Africa, 2011'.*
2. *Statistics South Africa (2013). 'Mortality and causes of death in South Africa, 2010: Findings from death notification".*
3. *UNAIDS (2012) 'Global Report: UNAIDS report on the Global AIDs Epidemic 2012'.*
4. *Clayelen P, HIV-i-Base. Possible Mechanisms for adverse pregnancy outcomes in HIV positive women. http://i-base.info/htb-south/2419*
5. *Calvert C, Ronsmans C (2013). HIV and the risk of direct obstetric complications: A systematic review and meta-analysis. PLoS ONE 8 (10): @74848.doi.10.1371/journal.pone.0074848.*
6. *MacLeod J, Rhode R. Retrospective follow-up of maternal deaths and their associated risk factors in a rural district of Tanzania. Trop. Med. Int. Health (1998); 3: 130-7.*
7. *Boyajian T, Shah PS, Murphy KE. Risk of Pre-eclampsia in HIV-positive pregnant women receiving HAART: A Matched Cohort Study. J Obstet Gynaecol Can (2012); 34(2): 136-41.*
8. *Wimalasundera RC, Larbalesher N, Smith JH, et al. Pre-eclampsia, antiretroviral therapy and immune reconstitution. Lancet (2002); 360: 1152-4.*
9. *Suvy A, Martinez E, Coll O, et al. Increased risk of pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. AIDS (2006); 20: 59-66.*
10. *Kwalembota M. The effect of pregnancy in HIV-infected women. AIDS care (2002); 14: 431-3.*
11. *NCCEMD (2011 and 2012). 'Tenth interim report on Confidential Enquiries into Maternal Deaths in South Africa'.*
12. *Messeri P, Lee G, Abramson DM, et al. Antiretroviral therapy and declining AIDS mortality in New York City. Med Care (2003); 41: 512-21.*
13. *Kim HY, Kesonde P, Muviya M, et al. Pregnancy loss and role of infant HIV status on perinatal mortality among HIV-infected women. BMC Paediatrics (2012); 12: 138.*
14. *Kumar R, Voluman S, Khumrana A. Impact of HIV-1 infection of perinatal outcome. Int J Gynecol Obstet (1995); 49: 137-43.*
15. *Kennedy D, Fawcus S, Kroon M. The effect of maternal HIV status on perinatal outcome at Mowbray Maternity Hospital and referring midwife obstetric units, Cape Town. SAJOG (2012); 18(1).*
16. *Pattinson RC, Hulsbergen MH, Van Hoorick L. The effect of maternal HIV infection on maternal condition and perinatal death in south western Tshwane. Facts, views and visions in Obgyn (2010); 2(4): 227-231.*
17. *Cailhol J, Jourdain G, Le Couer S, et al. Association of low CD_4 cell count and intrauterine growth restriction in Thailand. J Acquir Immune Defic Syndr (2009); 50: 409-413.*
18. *Qaniji CD, Towobola OA, Hoque ME, et al. Impact of antiretroviral therapy on pregnancy outcomes. South African Journal of HIV (2013); 14(4): 176-178.*
19. *Marazzi MC, Palambi L, Nielsen-Saines K, et al. Extended antenatal use of triple antiretroviral therapy for prevention of mother-to-child transmission of HIV-1 correlated with favourable pregnancy outcomes. AIDS (2011); 25: 1611-1618.*
20. *Townsend CL, Byrne L, Cortina-Borya M, et al. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000-2011. AIDS (2014); 28: 1049.*
21. *Fowler MG, Kourtis AP, Alzine J, et al. Breastfeeding and transmission of HIV-1: epidemiology and global magnitude. Adv Exp Med Biol (2012); 743: 3.*
22. *Palambi L, Marazzi MC, Voetberg A, et al. Treatment acceleration program and the experience of the DREAM program in prevention of mother-to-child transmission of HIV. AIDS (2007); 21 Suppl 4: 565.*
23. *Kilewo C, Karisscon K, Ngarina M, et al. Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers with triple antiretroviral therapy in Dar es Salaam, Tanzania. PLoS Med 2011; 8: e1001015.*
24. *Shapiro RL< Hughes MD, Ogwu, et al. Antiretroviral regimens in pregnancy and breastfeeding in Botswana. N Engl J Med (2010); 362: 2282.*
25. *Goga AE, Dinh TH, Jackson DJ, Evaluation of the Effectiveness of the National Prevention of Mother-to-Child Transmission (PMTCT) Programme Measured at Six weeks Postpartum in South Africa, 2010. South African Medical Research Council, National Department of Health of South Africa and PEOFAR/US Centers for Disease Control and Prevention, 2012.*
26. *Panel on Treatment of HIV-infected pregnant women and Prevention of Perinatal Transmission. Recommendations for use of Antiretroviral Drugs in Pregnant HIV-1 infected women for maternal health and interventions to reduce Perinatal HIV transmission in the United States. http://0-aidsinfo.nih.gov.innopac.up.ac.za/contentfiles/lvguidelines/perinatal GL.pdf*
27. *World Health Organisation. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach, June 30,2013.http://0www.who.int.innopac.up.ac.za/hiv/pub/guidelines/arv2013/download/en/index.html*
28. *John GC, Bird T, Overbaugh J, et al. CCR5 promoter polymorphisms in a Kenyan perinatal human immunodeficiency virus type 1 cohort: association with increased 2-year maternal mortality. J Infect Dis (2001); 184: 89-92.*
29. *Minkoff H, Hershaw R, Watts DH, et al. The relationship of pregnancy to human immunodeficiency virus disease progression. Am J Obstet Gynecol (2003); 189(2): 552-9.*
30. *Rosenfield A, Yandon K. Aid treatment and maternal mortality in resource poor countries. J Am Womens Assoc (2002); 57: 167-8.*
31. *Onakewhar J, Olagbo B, Ezeonochie M. Pregnancy outcome among HIV positive women receiving antenatal HAART versus untreated maternal HIV infection. J Coll of Physicians and Surgeons of Pakistan (2011); 21(6): 356-359.*
32. *Ford N, Calmy A, Mofenson L. Safety of Efavirenz in the first trimester of pregnancy, an updated systemic review and meta-analysis. AIDS (2011); 25: 23011.*