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Review article

The impact of highly active antiretroviral therapy on obstetric conditions: A review

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ABSTRACT

HIV is the leading cause of maternal and neonatal morbidity and mortality in resource constrained countries. Highly active antiretroviral treatment (HAART) initiated in pregnancy has now almost eliminated mother to child transmission of the virus, and is beginning to show the desired effect of reducing HIV related maternal mortality. By modulating host immunological responses HAART has the potential to alter infections during pregnancy, in addition to modifying clinical conditions such as preeclampsia. There is increasing evidence of the benefits of HAART given to pregnant women, however there is paucity of data that distinguishes HIV or HAART as the cause or exacerbation of pre-existing medical conditions or conditions specific to pregnancy.

Anaemia is the commonest haematological disorder seen in HIV infected women and is more pronounced during pregnancy. The use of HAART has the potential to reduce the incidence and severity of the disease. Tuberculosis (TB) is the commonest chest infection amongst HIV infected people, being more common amongst pregnant than non-pregnant women. It is the leading cause of death from infectious diseases amongst women of reproductive age, and accounts for at least a quarter of all cases of maternal deaths associated with non-pregnancy related infections (NPRI). TB can manifest at any stage of the HIV infection, including during treatment with HAART. The latter (ie TB manifestation during HAART treatment) is thought to be the commonest manifestation of what is now known as immune reconstitution inflammatory syndrome (IRIS). In a South African report on maternal deaths, 55% of women who died of TB were on HAART, and a further 35% of women in the NPRI category died from other pneumoniae, notably pneumocystis jorevicci, which is also related to HIV infection. With regards to puerperal sepsis, studies are yet to show the impact of HAART independent of antibiotics in reducing infectious morbidity in HIV infected women.

Preeclampsia has been associated with HIV infection, where most studies point towards a reduced risk in HIV infected women. There is increasing evidence that this reduced risk is reversed in the presence of HAART, with women accessing HAART having almost the same risk as HIV uninfected women. HIV or its treatment may be associated with increased risk of obstetric haemorrhage, and an increasing trend of obstetric haemorrhage as a cause of maternal deaths has been recently reported, proportionally in line with the introduction and increasing availability of HAART for pregnant women The mechanism by which this may occur remains elusive since pregnancy is a pro-thrombotic state, however, HIV-related thrombocytopenia or vasculitis could account for the association, if found. HAART would then be expected to reverse this.

HAART especially protease inhibitor containing combinations, have been associated with preterm deliveries and low birth weight, particularly when initiated prior to the index pregnancy.

With these overall findings of the effect of HAART on obstetric conditions, this review is intended to encourage heightened surveillance of adverse events associated with HAART use in pregnant women.

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Introduction

Human Immunodeficiency Virus (HIV) is the leading cause of maternal mortality in resource poor countries accounting for approximately 40% of all deaths [1]. In addition, there are reports of considerable maternal morbidity arising from co-infections, in particular tuberculosis [2,3]. The use of highly active antiretroviral treatment (HAART) in the last decade has been hailed as one of the most effective interventions which has almost eliminated mother-to-child-transmission (MTCT) of the virus and associated with the reduction of maternal deaths [1,4]. Given the positive impact of the increased coverage of HAART on both the reduction in absolute numbers and ratio of maternal deaths, the focus is now shifting to HIV issues such as the direct and indirect effects of HAART on other pregnancy related co-morbidities. The era before the widespread use of HAART in pregnancy had a plethora of literature documenting serious morbidity and mortality due to the HIV disease and its co-infections. However, apart from the reports on perinatal outcomes, there has not been an equal enthusiasm in tracking the improvements in maternal and possibly obstetric conditions in the era of HAART particularly in countries with the highest burden of HIV disease.

There are several biologically plausible mechanisms why HAART may have unforeseen consequences on common conditions in pregnancy. Some of the antiretroviral drugs, such as zidovudine, a nucleoside reverse transcriptase inhibitor, can lead to mitochondrial toxicity and affect blood cell counts particularly reticulocytes, and thereby worsen the anaemia commonly associated with pregnancy itself. Other drugs are nephrotoxic or hepatotoxic, and can therefore affect the course of diseases such as preeclampsia and diabetes mellitus. Additionally, the immune reconstitution following the use of HAART may trigger or unmask certain inflammatory conditions, such as tuberculosis (TB), as well as preeclampsia, which is thought to involve an exaggerated inflammatory response as part of its pathogenesis Moreover, pregnancy related factors, such as changes in blood volume, body mass, elevations in hormonal level and alterations in enzyme activity may impact on the expected response to antiretroviral drugs.

The following is a narrative review of the current evidence regarding the use of HAART and its impact on obstetric conditions.

Medical conditions during pregnancy

Haematological disorders in pregnancy

In 2011, the WHO estimated the global prevalence of anaemia in pregnancy to be 38.2% [95% confidence intervals (CI): 33.5–42.6], much higher than that for all women of reproductive age, (29.4%, 95% CI: 24.5–35.0) [5]. Anaemia is said to be the most common hematological abnormality in HIV infected patients, and in pregnancy, it can be as high as 88.5% [6]. Several mechanisms have been suggested to explain the association between HIV and anaemia and these include direct infection of the bone marrow, which may inhibit growth of hematopoietic cells, with subsequent reticulopenia, or low endogenous erythropoietin concentrations, and rarely, deficiencies of iron or folic acid or Vitamin B12 [7].

The effect of HAART to possibly improve the prevalence or severity of anemia in pregnancy has also not been explicitly reported. A South African study, found no difference in the prevalence of anemia in those who were treated with HAART compared to those who received zidovudine alone (ZDV) during pregnancy [8]. The authors noted that, after adjusting for antiretroviral regimen, age and gravidity, only the CD4 count remained a significant risk factor for anaemia in pregnancy and post-delivery. However, regardless of CD4 counts, following the use of HAART and prophylactic iron supplementation during pregnancy, there was a 2.5 times less incidence of anaemia at 2 weeks postpartum compared to the time of antenatal registration. The latter implies that HAART has the potential to improve anaemia of pregnancy in HIV treated women. Even though anaemia in pregnancy is predominantly characterised as normocytic and normochromic (82.8%), possibly due to reduced erythropoietin production during states of HIV related chronic inflammation [8], this is probably a mixed picture of chronic HIV disease and micronutrient deficiencies, including iron. Hence not all women will respond to iron supplementation in pregnancy.

Thrombocytopenia (TCP) has been reported as another common haematological complication of HIV, and is said to affect at least 21% of patients with AIDS defining conditions [9]. However, in another study, there was no difference in the prevalence of TCP amongst HIV uninfected pregnant women, compared to those who were infected but untreated, (4.7% compared to 6%, $p = 0.292$) [10]. It is unlikely therefore that the effects of HAART would be easily appreciable.

Tuberculosis in pregnancy

Tuberculosis (TB) is said to be the leading cause of deaths in women aged 15–44 years globally [2,11]. It remains the single most common cause of maternal deaths from non-pregnancy related infections (NPRI). In the latest South African report on maternal deaths, 35% of which were due to NPRI, it accounted for 26% of deaths in this category [1]. In subSaharan Africa where both epidemics of TB and HIV co-exist, dual infections were found to be