IMPACT OF MATERNAL ANTIRETROVIRAL DRUGS DURING PREGNANCY ON RISK OF PRETERM BIRTH AND LOW BIRTH WEIGHT.

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ABSTRACT

Introduction- HIV infection is a leading medical complication of pregnancy in most sub-Saharan African countries including Nigeria. Strategies involving antiretroviral medication and good obstetric practice have greatly reduced maternal deaths and vertical transmission of HIV. However, antiretroviral therapy could also have adverse effects on the pregnant woman or developing fetus e.g. preterm delivery and low birth weight. Preterm birth and low birth weight contribute significantly to perinatal morbidity and mortality. This review examined the impact of HAART on preterm birth and low birth weight.

Methodology- The authors reviewed literature using the search terms of HIV, preterm birth, low birth weight, antiretroviral. Cross-sectional, observational and randomized controlled studies obtained from the commonly used medical databases, published between 1994 and 2013 were reviewed.

Results- The results were conflicting with some studies demonstrating increased risk of prematurity with anti-retrovirals. Others demonstrated no effect on risk of prematurity while others demonstrated a protective effect of these drugs. Similarly, studies that explored the association between duration of therapy and prematurity were conflicting. While some failed to detect a significantly increased risk of prematurity with longer duration of therapy following early exposure (compared with following initiation at 13-26 weeks gestation), others noted that starting PI-based HAART before pregnancy or in the first trimester was associated with higher risk of preterm delivery. Differences in population characteristics, indication for therapy, data collection or analytical approaches have been suggested as possible reasons for these discrepant findings. A reason proffered for the association of preterm births and antiretrovirals is the Th2 to Th1 cytokine shift associated with HAART administration. Successful pregnancies are characterized by a Th1 to Th2 cytokine shift. Other associated factors were immuno-suppression, multiple pregnancies and other psychosocial factors e.g. illicit drug use.

Some studies, after standardizing for gestational age demonstrated that HAART exposed infants were significantly lighter than those exposed to mono or dual therapy. Others did not support an association between receipt of HAART during pregnancy and an increased risk of LBW. Other factors associated with low birth weight include immuno-suppression (CD4 < 200 cells/ml) and the HIV status of the HIV exposed infant.

Conclusion- With an increasing number of women on HAART at conception, it is reassuring that the strong benefits of prevention of MTCT are not outweighed by risks attributable to HAART. However, monitoring adverse pregnancy and perinatal outcomes should remain a priority and further research into the mechanisms leading to preterm birth and / or LBW in HIV positive women needed.

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INTRODUCTION

In most sub-Saharan African countries including Nigeria, HIV infection remains a major public health challenge [1]. This region accounts for over two third of the global estimate of persons living with HIV/AIDS and has mostly young adults, especially women in the reproductive age group, mainly affected [2]. The result is that HIV infection has become a leading medical complication of pregnancy and cause of maternal and neonatal morbidity and mortality [2,3] . Fortunately, strategies involving antiretroviral medication and good obstetric practice have greatly reduced both maternal deaths and the vertical transmission of HIV [4,5]. These strategies which include at the provision of HIV counseling and testing for pregnant women, aggressive viral load suppression with multi-drug regimen, elective caesarean delivery and precautions during breast feeding including antiretroviral prophylaxis for the infant has resulted in a dramatic decrease in the mother-to-child transmission rates [6,7].

While antiretroviral therapy provides clear benefits, these highly potent drugs could also have adverse effects on the pregnant woman or developing fetus [8]. For example, exposure to antiretroviral therapy in fetal life has in rare cases been associated with mitochondrial abnormalities although causality is difficult to prove. Similarly, for some other adverse pregnancy outcomes, the evidence is conflicting. For example, receipt of antiretroviral drugs during pregnancy has been associated with an increased risk of preterm birth (PTB) and low birth weight in some studies [9-11] but not others [12-14] . Preterm birth and low birth weight are particularly important because of their contribution to perinatal morbidity and mortality [8,15] . It is therefore necessary, because of the near routine use of these drugs in PMTCT programs [6,16] , to continue to examine their effects on pregnancy outcomes. The objective of this review article is to examine the impact of HAART on pregnancy outcomes, especially preterm birth and low birth weight.

METHODOLOGY

The authors reviewed literature using keywords of the thrust of this review; hence ,search terms such as HIV, preterm birth, low birth weight, antiretroviral, pregnancy outcome were used. Literature on cross-sectional, observational and randomized controlled studies published on the subject in the last twenty five years were reviewed. Fifty found to be suitable were found suitable and served as the main sources of information; these were obtained from the commonly used medical databases such as PubMed (Medline) , AJOL and Google scholar. Cochrane library was searched for systematic reviews while websites of international organizations served as sources for expert reports and updates.

Preterm birth

Every year, thirteen million babies are the products of preterm births (i.e. born before 37 completed weeks of gestation) [15]. Preterm birth (PTB) has been described as the single most important cause of neonatal deaths and disability, directly accounting for a quarter of the global neonatal deaths [8,15,17]. Countries in sub-Saharan Africa and South Central Asia are disproportionately affected by PTB and carry a greater burden of death and disabilities attributed to preterm births [18-21].

While various workers have identified HIV as a major cause of spontaneous preterm birth [22-24], preterm birth has been identified as a major risk factor for mother-to-child transmission of HIV infection [22,24-26]. Thus, identification of the factors associated with spontaneous preterm birth in HIV positive women will not only prevent mother to child transmission but will also reduce the morbidity and mortality associated with prematurity [15].

Risk of prematurity with ARV

A possible association between antiretroviral therapy and prematurity was initially identified in 1998 in a Swiss study [10]. An initial combined analysis of the Swiss and European collaborative study (ECS) data confirmed that prematurity rates were higher among women on combination therapy compared with untreated women [11]. They demonstrated that the odds (OR) of prematurity was 2.60 (95% CI, 1.43-4.75) and 1.82 (95% CI, 1.13-2.92) for infants exposed to combination therapy with and without a PI, respectively, compared to no treatment. Exposure to monotherapy was not associated with prematurity[11]. In another subsequent analysis, the ECS reported that infants exposed to anti-retroviral therapy with a Protease Inhibitor (PI) were 2.6 times more likely to be born prematurely compared with those unexposed, with a lower but significantly increased risk for those exposed to antiretroviral involving only Nucleoside Reverse Transcriptase Inhibitors (NRTIs) (PI-HAART 29%, nonPI-HAART 22%, mono HAART 17%, unexposed 16%, ρ=<0.001)[9]. Townsend et al also demonstrated that the odds of prematurity were higher in women on HAART[8]. Compared to women on mono/dual therapy, women on HAART were more likely to deliver before 37 weeks (14.1 % vs 10.1%, CI 1.19 – 1.93, ρ=0.001). They had a 1.5 fold increased risk of premature birth [8].

The association between antiretroviral therapy and prematurity has also been explored by studies in the United States, although, the reports have been conflicting. In an analysis involving 3266 HIV positive women in the 1990s, the receipt of combination antiretroviral was not associated with increased rate of preterm birth (compared to no antiretroviral or monotherapy) [13]. Similarly, the Women and infants Transmission Study (WITS), involving 2543 HIV infected women did not document an increase in adverse infant outcomes associated with maternal combination antiretroviral [14]. This is in contrast to the finding by SinaHaeri et al who demonstrated a 2-fold increase in the odds of spontaneous preterm birth at 37 weeks (adjusted odds ratio, 2.27; 95% CI, 1.22-4.25) among HIV positive women compared to controls [6]. Similarly, in an analysis of >1300 women, only receipt of a combination antiretroviral including a PI was associated with an increased risk of PTB compared with any other combination antiretroviral [27]. Finally, Read et al analyzing data from 3443 HIV positive women and their infants (PACTG 367), reported that maternal receipt of antiretroviral was actually associated with lower risk of PTB (compared with no ART receipt during pregnancy) [28]. Differences in population characteristics, indication for therapy, data collection or analytical approaches have been suggested as possible reasons for these discrepant findings [29,30].

Type of ARV and duration of therapy

The type of antiretroviral agent and duration of use associated with prematurity has also been investigated. While, some workers have demonstrated a larger association between PI-based HAART and preterm births [11,15,27,31,32], Van der Merwe et al on the other hand demonstrated a larger association between non nucleoside reverse transcriptase (efavirenz; AOR 5.6, 95% CI 2.1-15.2, ρ=0.001 and nevirapine; AOR 5.4, 95% CI 2.1-13.7, ρ<0.001) based HAART and preterm birth compared with PI-based HAART [33]. Townsend et al in their study demonstrated that HAART was associated with a 1.5 fold increased risk of premature delivery compared with mono/ dual therapy (14.1% vs 10.1%; AOR 1.51, 95% CI, 1.19-1.93, ρ=0.001) [8]. Although, the risk of premature delivery was not significantly different whether HAART included a PI or not (NNRTI 14.3%, PI 13.5%, NRTI 8.7%, ρ=0.738, 95% CI 0.78-1.19) [8].

To explore the association between duration of therapy and prematurity, Townsend et al compared pregnancies with early HAART initiation with those who initiated between 13-26 weeks [8] . They failed to detect a significantly increased risk of prematurity with longer duration of therapy. The rate of prematurity was 16.4% (150/ 914) following early exposure, compared with 14.6% (188/ 1287) following initiation at 13-26 weeks gestation (AOR = 1.11; 95% CI, 0.85-1.44; ρ=0.460). Thus, they concluded that in HAART exposed pregnancies, there was no association between timing of therapy initiation and prematurity [8]. In the ECS study, compared to zidovudine or non-PI based HAART, starting PI-based HAART before pregnancy or in the first trimester was associated with higher risk of preterm delivery[11]. The risk was greatest where the anti-retroviral therapy was initiated before and retained throughout pregnancy or started in the first trimester (40%), compared with initiation of antiretroviral therapy in the 2nd/3rd trimester (18%) (P= 0.03) [11]. Indeed in that study, logistic regression showed that women on combination therapy (with or without PI) from before pregnancy were twice as likely to deliver prematurely as those who started in the third trimester (OR 2.17; 95% CI 1.03-4.58, P value= 0.043)[11].

Van der Merwe et al also explored the relationship between duration of use and prematurity [33]. They demonstrated that early experience of any regimen was associated with preterm birth compared with HAART unexposed babies / untreated women (unexposed 5%, early HAART 21%, late HAART 5%, P=0.002). They noted that in the late HAART group, there was no association between ARV and PTB[33]. This was consistent with previous studies [9,27]. In addition, they also noted that compared to PI-containing regimens, early NVP and EFV- based regimens had the strongest associations with preterm birth (AOR 5.4, 95% CI 2.1-13.7, ρ< 0.001, and AOR 5.6, 95% CI 2.1-15.2, ρ=0.001, respectively) [33]. In their cohort, women on NNRTI were more likely to be in the group with more complicated pregnancies with increased likelihood of multiple risk factors for PTB. Indeed, women on efavirenz had more advanced HIV [33].

Various reasons have been proffered for the association of preterm births and antiretrovirals in the HIV positive woman[8,34]. One of them is the Th2 to Th1 cytokine shift associated with HAART administration. Successful pregnancies are characterised by an increase in Th2 cytokines and suppression of Th1 cytokine production, a Th1 to Th2 cytokine shift [34]. A similar shift is also observed in the disease progression of HIV infection. Fiore et al (2006) hypothesized that the increased risk of premature delivery reported in HIV-infected, HAART-treated pregnant women is mediated through changes in the cytokine environment in pregnancy [34]. They investigated the levels of interleukin IL-2 (Th1) and IL-10 (Th2) in peripheral blood mononuclear cells (PBMCs) of 49 HIV-infected women. They were able to demonstrate favourable immunomodulation induced by HAART with increased IL-2 (Th1) and decreased IL-10 (Th2). They showed that each unit increase in IL-2-PHA slope was associated with an 8% increased risk of premature delivery (AOR, 1.08; 95% CI, 1.0-1.17; p=0.005). They concluded that HAART use in pregnancy while providing significant benefits in delaying HIV disease progression and reducing the risk of mother-to-child-transmission, may however be counterproductive in terms of successful pregnancy outcome.

Other factors and prematurity in the HIV positive pregnant woman

Apart from the administration of antiretroviral drugs, another factor that was associated with PTB was immuno-suppression. Maternal CD4 count was

a better predictor of prematurity than maternal viral load with severe immuno-suppression being independently associated with a doubled risk of preterm labour[11,35,36] Townsend et al showed that compared with women with CD4 ≥ 500 cells/ µl, severely immuno-compromised women with CD4 cell count <200 cells / µl were more likely to deliver before 37 weeks gestation (10.1% vs. 15.9%, AOR 1.55, 95% CI 1.11-2.18, ρ= 0.010) [8]. Similarly, in the ECS analysis, compared to women with CD4 ≥ 500 cells / µl, women with CD4 <200 were significantly more likely to have premature delivery (13% vs 22%, AOR 1.93, 95% CI 1.28-2.91, ρ=<0.02) [11]. In one study, every gain of 50cells/mm3 was associated with considerably reduced risk of PTB (AOR 0.68 per 50 cells/ mm3 increase, 95% CI 0.55-0.85, p = 0.001) [33] . This highlights the importance of early HIV diagnosis and staging during pregnancy to accelerate HAAART initiation in women who qualify.

A multitude of other factors, family and psychosocial histories inclusive, have been associated with preterm birth in the HIV positive woman. The link between illicit drug use and prematurity in both HIV infected and non-infected pregnant women is well established [8,11,37,38]. In the cohort studied by Ezechi et al, in south west Nigeria, factors associated with preterm delivery included presence of reproductive tract infection, stress at work, opportunistic infection at delivery and multiple pregnancies [15]. The most important predictor of preterm delivery in that cohort was multiple pregnancy[15], similar to the finding by Taguebue et al [24]. Ezechi et al concluded that irrespective of HIV status, multiple pregnancy remains a significant cause of preterm delivery in Nigeria [15] . They also advocated the active screening and treatment of vaginal infection in HIV positive women before 36 weeks [15] .

Low birth weight

Low birth weight is birth weight less than 2500 g irrespective of gestational age [39]. It often results from prematurity or intrauterine growth restriction [40,41] though more from the latter than the former. It occurs worldwide but by far more commonly in developing countries [41] where as much as one quarter of newborns start life with impaired growth in utero often resulting in LBW at delivery [42-44]. Complications arising from LBW include infections, hypoglycemia, hypothermia, jaundice and perinatal asphyxia often resulting in significant perinatal mortality[40]. They are also predisposed to developing neurological problems and have much higher burden of disease throughout life[43] . It is easier and better to prevent the delivery of a LBW baby than preventing the perinatal morbidity and mortality, developmental problems and other life time complications consequent on its delivery.

Risk of low birth weight with ARV; Type of ARV and duration of therapy

The study by Lorenzi et al in 1998 that suggested a relationship between maternal antiretroviral therapy during pregnancy and PTB [10], prompted a number of studies that evaluated maternal Antiretroviral regimens during pregnancy and adverse infant outcomes including low birth weight [16]. These studies have had conflicting results. For example studies from Europe such as that by Townsend et al, working in England and Ireland, after standardizing for gestational age was able to demonstrate that HAART exposed infants were significantly lighter than those exposed to mono or dual therapy (HAART 2.98kg vs mono/ dual 3.10kg, P<0.001) [8]. On the other hand, an initial analysis from the ECS group did not support an association between receipt of antiretroviral therapy during pregnancy and an increased risk of LBW. Instead they noted that overall birthweight was

appropriate for gestational age. They reported that there were no significant differences between birth weights by treatment goup (no/ monotherapy versus combination therapy) for premature infants with means of 2170g ad 2233 respectively (ρ=0.446).[11]. In a similar manner, studies from the US have not consistently associated maternal receipt of ART during pregnancy with an increased risk of LBW. The Women and Infants Transmission Study (WITS), in an analysis of 2543 HIV infected women, did not demonstrate an increase in risk of low birth weight associated with maternal combination antiretroviral therapy [14]. This was similar to the finding of Tuomala et al, in an analysis of 3266 HIV positive women, who demonstrated that receipt of combination antiretroviral compared to no antiretroviral or mono therapy was not associated with increased rates of Low Birth Weight (odds ratio 1.03; 95% CI, 0.64 to 1.63) [13]. A subgroup analysis by that latter group of workers in their cohort, however, demonstrated an association between PI regimen and VLBW [13]. In contrast to the earlier studies, an analysis of 3443 HIV positive mothers and their infants (PACTG 36) [28], maternal receipt of ART was associated with lower risk of low Birth weight compared with no ART receipt during pregnancy [28].

Other workers who have evaluated the association between HAART and LBW include van der Merwe et al in South Africa, who reported that among HAART-unexposed infants, 27% (60/224) were low birth weight compared with 23% (90/388) of early HAART-exposed (exposed <28 weeks gestation) and 19% (76/407) of late HAART-exposed (exposed ≥28 weeks) infants (p = 0.05) [33]. Szyld et al working in Latin America and the Caribbeans did not demonstrate an increased risk of low birth weight among women receiving PI containing antiretroviral during pregnancy, compared with a regimen of 1-2 NRTIs (AOR 1.5; 95% CI, 0.7 – 3.2) [16]. However, Ezechi et al working in Nigeria compared HIV positive and HIV negative women. They were able to demonstrate adverse pregnancy outcomes, including low birth weight (9.4% vs 3.3%, ρ< 0.001, OR 3.01, 95% CI 2.30 – 3.95), independently associated with HIV infection after controlling for potential confounding variables [1].

Other factors that were found to be associated with low birth weight included immuno-suppression (CD4 < 200 cells/ml) [1]. In the cohort studied by van der Merwe, immuno-suppression emerged as an important risk for LBW and every gain of 50 cells / mm3 was associated with considerable reduction in risk of LBW (AOR 0.57 per 50 cells/mm3 increase, 95% CI 0.45-0.71, p < 0.001) [33]. As previously noted this finding highlights the importance of early HIV diagnosis and staging during pregnancy to accelerate HAART initiation. The HIV status of the HIV exposed infant has also been associated with low birth weight. Low Birth Weight was more common among the HIV positive than HIV negative infants (33% vs 22%, ρ= 0.04) [33].

Other outcomes

The association between HAART and other pregnancy outcomes is also unclear. Exposure to antiretroviral in fetal or early life has in rare cases been associated with mitochondrial abnormalities, but causality is difficult to prove [45]. Although, there is no evidence to date that exposure to antiretroviral in pregnancy is associated with congenital anomalies [46-48] or later development of cancer [11,49,50] one child with extra-hepatic biliary atresia, one with congenital glaucoma and one with intra cerebral hemorrhage at term were reported among 95 children exposed to HAART in the Swiss cohort [10,11]. Finally, an increased risk of fetal death has been reported in some studies [51] but not others [27,52,53].

CONCLUSION

With an increasing number of women on HAART at

conception, it is reassuring that the risks attributable to HAART appear to be outweighed by the strong benefits for prevention of MTCT as well as for maternal and infant morbidity and mortality [16,33]. However, monitoring adverse pregnancy and perinatal outcomes should remain a priority and further research into the mechanisms leading to preterm birth and / or LBW in HIV positive women is needed. [8,34].

The finding that women on combination therapy and receiving treatment when their pregnancy was confirmed had double the risk of PTB compared to those who started therapy within the last trimester may shed some light on the underlying mechanisms [11]. The fact that infants' birth weight was generally appropriate for their gestational age implies an effect on the mother rather than on utero-placental function [11] . in addition, it has been postulated that exposure to HAART, which often contains at least one PI, leads to insulin resistance and endothelial inflammation with a concomitantly increased risk of preeclampsia in the mother. Preeclampsia, in turn, is associated with LBW and PTB.

Finally, an HIV infected woman of child bearing age is in the unique position of making treatment decisions which will not only impact on her own health, but may also affect her future children [54], [55]. It is therefore important that health care providers discuss future plans with HIV positive women when deciding what kind of treatment to initiate [11] .

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