

REVIEW

HIV-1: MATERNAL PROGNOSIS

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EL BEITUNE P et al. - HIV-1: maternal prognosis. *Rev. Hosp. Clín. Fac. Med. S. Paulo* 59(1):25-31, 2004.

Profound modifications in the profile of patients are currently being observed within the epidemic context of AIDS, especially with respect to pauperization and feminization of the disease. The population most frequently affected is in the reproductive age, and among adults aged 18 to 24 years, the ratio is 1 man to 1 woman, a phenomenon occurring uniformly all over the world. One of the main challenges for HIV-1-infected pregnant women and their doctors is the effect of the interaction between HIV infection and pregnancy. The present article is a review of the literature; and its objective is to assess the influence of HIV-1 infection seen from the maternal perspective, with a discussion of immunologic function, maternal prognosis, and the HIV-abortion interface. At present, we cannot conclude that pregnancy has a short-term effect on the evolution of HIV infection, but the concomitance of HIV and pregnancy may adversely affect the prognosis of gestation, especially in view of its frequent association with increased abortion and puerperal morbidity rates.

DESCRIPTORS: HIV-1. Pregnancy. Abortion. Immunology. Prognosis.

Today women represent the populational segment with the greatest increase in HIV infection. Most of the infected women are in their reproductive age, a fact resulting in 2,100 new infections detected daily in children, almost all of them due to maternal-fetal transmission of HIV¹. However, advances have been made in the understanding of the pathogenesis of vertical transmission, in parallel with significant progress against maternal-fetal transmission of HIV, which has resulted in a new opportunity to renew and fulfill the wish to be a mother for a large segment of the female population. One of the major doubts to be resolved among doctors and patients is the effect of HIV infection on pregnancy and, conversely, the effect of this association on maternal health². The present article is a review of the literature dealing with the influence of HIV-1 infection from the maternal per-

spective, with a discussion of immunologic function, the maternal and gestational prognosis, and the HIV-abortion interface.

INFLUENCE OF PREGNANCY ON HIV-INFECTED WOMEN

The influence of pregnancy on immunologic function remains poorly understood. During the past 10 years, there has been concern that pregnancy itself, either because of associated hormonal changes or because of a pregnancy-related suppression of cellular immunity, leads to an acceleration in the progressive decline of immune

function associated with human immunodeficiency virus (HIV) infection³. Reports of small observational series that document clinical deterioration during or within short periods after pregnancy have raised concern about a potentiating effect of pregnancy on HIV infection progression⁴⁻⁶. From 1985 to 1988, counseling on HIV and pregnancy was influenced by these several negative reports which reflected in the recommendation of abortion in countries like Sweden.⁷

Some studies have reported no effect of pregnancy on the rate of progression of AIDS⁸⁻¹⁵, while others have suggested that an effect could exist^{5,6,16-18}.

Currently most HIV-infected women in the world who become pregnant are asymptomatic. Previous investigations of the effects of pregnancy on HIV infection have attempted to characterize the effect of pregnancy on lymphocyte subsets, with inconsistent

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Received for publication on
March 06, 2003.

results^{3,19}. The correlation between lymphocyte parameters during the antepartum period and the puerperium reflects a stability of these parameters among HIV-infected women during pregnancy, and there is no evidence of a major effect of pregnancy upon the 1 year postpartum outcome of HIV-infected women as measured by changes in lymphocyte subsets (total T-lymphocytes or in CD4+ lymphocytes)^{3,20-22}. Other investigations have suggested the occurrence of an initial decrease and then increase or “normalization” in lymphocyte subsets during pregnancy or the postpartum period^{19,23-29}. Degenne *et al.*²⁹ have suggested that a decrease in CD4+ cells occurs as early as the fourth week of gestation. The response to pregnancy of CD8+ lymphocytes is either a slight decrease or stability throughout gestation^{24,26,27}. Biggar *et al.*¹⁹ observed a more rapid loss of CD4 cells in HIV-infected compared to non-infected women, with a decrease in absolute CD4 cell count during pregnancy through 8 weeks before delivery and a less marked predelivery and postpartum increase. Miotti *et al.*²² observed no differences comparing lymphocyte subsets in HIV-infected and uninfected pregnant women. These authors observed an increase in CD4 and CD8 cells late in pregnancy and immediately postpartum, which then decreased to normal by 6 weeks postpartum. Tuomala *et al.*³ observed a discrete increase in TCD4 cell count during the antepartum period, possibly reflecting a tendency to an improvement of lymphocytic parameters^{19,22}. This elevation, however, does not result in an objective normalization of immunologic parameters or in the reduction of complications related to HIV infection, thus representing a fact of probably no clinical relevance³.

Burns *et al.*³⁰ demonstrated in a prospective cohort of HIV-1 seropositive pregnant women (27.5% of whom

received antiretroviral therapy) that in most women, viral load remained stable during pregnancy, but it gradually increased post partum. A significant rise in HIV-1 RNA levels was observed during the second year postpartum (mean increase 0.09 log per year; $p = 0.005$). Change in HIV-1 RNA was independent of the individual's mean HIV-1 RNA level, mean CD4 cell level, or change in CD4 level³¹. There was a steady decline in CD4 cell levels during the study period. This decline inversely correlated with the individual's mean HIV-1 RNA level. The absence of any significant overall change in HIV-1 viral load during pregnancy could be due to one or more factors. A deleterious effect of the decline of certain immune responses during pregnancy, reported for both HIV-1 seronegative and HIV-1 seropositive women³²⁻³⁴ may be offset by other immunologic changes. Pregnancy has been associated with alterations in certain cytokines (in particular, increase in interleukin-10 which has been reported to downregulate HIV-1 replication), endogenous immunomodulators that appear to be very important in modifying HIV-1 replication³⁵⁻³⁸.

Parturition is associated with increased levels of specific cytokines, including interleukin-6 which is capable of upregulating HIV-1 replication, but this alteration appears to be more transient³⁹⁻⁴⁰.

Investigations suggest that the level of viral load in the peripheral blood is established after seroconversion and remains stable until it begins to rise late in HIV-1 infection^{41,42}. This plateau level or “set point”, which varies widely, appears to represent the equilibrium reached between the infecting strain of the virus and the capacity of the individual's immune system to contain it^{42,43}. The apparent stability of HIV-1 RNA levels during gestation suggests that preg-

nancy has little immediate effect on viral load in most women⁴⁴.

Alliegro *et al.*⁴⁵ evaluated the incidence and outcome of pregnancy in HIV-infected women with estimated dates of seroconversion and compared the risk of disease progression between women who were pregnant during infection and those who were not. From October 1981 through December 1994, these authors did not observe any effect of the pregnancy up to 1 year after delivery or abortion on accelerated development of AIDS, HIV-related diseases, or severe immunosuppression during pregnancy. Again, no significant differences were observed between women who were pregnant only once when compared with those with multiple pregnancies.

From survival analysis, it is estimated that 5 years after delivery 14% of mothers will have died, 24% will have developed CDC Stage IV disease, and more than 60% will still be without serious HIV-related manifestations. Women with lower CD4 counts during pregnancy subsequently progressed to CDC Stage IV at a faster rate than women with higher CD4 counts. Thorne *et al.*⁴⁶ estimated that 66% of the women with a CD4 count of less than 200 cells/mm³ will progress to stage 4 within a period of 2 years after delivery, in contrast to only 21% of women with a CD4 count of more than 499 cells/mm³.

In a prospective study of the effect of pregnancy on the progression of human immunodeficiency virus infection, there was no difference in progression of disease between child-bearing and non-pregnant HIV-infected women at a 5-year follow-up¹⁰.

The CCR5 chemokine receptor acts as a coreceptor with CD4 to permit infection by primary macrophage-tropic HIV-1 strains. The CCR5-Delta32 mutation, which is associated with resistance to infection in homozygous individuals and delayed

disease progression in heterozygous individuals, is rare in places where the HIV-1 epidemic is growing rapidly. Several polymorphisms in the promoter region of CCR5 have been identified. In this context, John *et al.*⁴⁷ evaluated the effect of CCR5 promoter mutations on systemic and mucosal HIV-1 replication, disease progression, and perinatal transmission in a cohort of 276 HIV-1-seropositive women in Nairobi, Kenya. These authors demonstrated that women with the 59356 C/T genotype had a 3.1-fold increased risk of death during the 2-year follow-up period and a significant increase in vaginal shedding of HIV-1-infected cells, compared with women with the 59356 C/C genotype.

INFLUENCE OF HIV-1 ON PREGNANCY

Whether HIV-1 infection itself may adversely affect pregnancy remains controversial. From 1985 to 1989, Minkoff *et al.*⁴⁸ studied the gestational and neonatal prognosis of 92 seropositive and 126 seronegative women who gave birth during the study period and did not observe any demonstrable effect of HIV infection on the gestational prognosis. These data agree with those reported by Selwyn *et al.*⁸, who studied American female drug users. Similar results were also reported by Johnstone *et al.*¹¹ in a study on female drug users in Edinburgh.

A higher incidence of postpartum genital infection in HIV-seropositive women than in seronegative women has been reported.⁴⁹⁻⁵¹ The power of the study by Minkoff *et al.*⁴⁸ to detect adverse effects of HIV infection on infrequent complications of pregnancy, such as endometritis or toxemia, is limited⁴⁸. Sexually transmissible diseases and medical complications were diagnosed almost twice as often among seropositive women⁵². After

controlling for factors such as sexually transmissible diseases, Leroy *et al.*⁴⁹ observed a significant increase in adverse obstetrical events, such as maternal postpartum haemorrhage and postoperative endometritis, as also confirmed by other authors⁵⁰.

Some studies have shown an association between HIV-1 infection and miscarriage^{8,11,51,53-63}, while other authors do not confirm this assertive⁶⁴⁻⁶⁹.

In a systematic review of the literature and meta-analysis, Brocklehurst & French⁶³ observed an association between the risk of spontaneous abortion and women infected with HIV-1 that varied from 1.8 to 6 times greater.

Considerable evidence shows that raised anticardiolipin antibody levels are associated not only with thromboembolism but also with preterm delivery, intrauterine growth restriction (IUGR), and fetal loss at all stages of pregnancy⁷⁰. Studies have also demonstrated that raised anticardiolipin antibody levels are uncommon in the general obstetric populations (2%) and that there is a significantly increased risk of pregnancy wastage when they do occur^{71,72}.

Johnstone *et al.*⁷⁰ in a study of largely asymptomatic, pregnant HIV-seropositive women showed that approximately 25% had abnormally raised levels of anticardiolipin antibodies, compared with none of the HIV-negative IV drug users or controls. As others have found⁷³⁻⁷⁵, there seemed to be no association between anticardiolipin antibodies and length of time since seroconversion or overt illness, and the abnormality appeared to be a direct response to HIV⁷⁰.

Viscarello *et al.*⁷⁶ observed that 53% of HIV-1 pregnant women were positive for anticardiolipin antibody. In addition, these authors did not observe association among this positivity and adverse maternal or neonatal outcome, maternal human immunodeficiency virus status, or perinatal trans-

mission of virus-seropositive human immunodeficiency.

It is possible that this higher positivity for anticardiolipin antibody is not real. It has been observed that HIV-infected patients often exhibit hypergammaglobulinemia, a potential cause of false-positive results through nonspecific binding of IgG⁷⁴. Another source of false-positive anticardiolipin levels is heat treatment of serum⁷⁷.

Adverse pregnancy outcome has frequently been reported in HIV infection⁶³. However, the hypothesis that part of this effect may result from anticardiolipin antibodies has not been proven. The hypothesis regarding placental size is interesting, since antiphospholipid antibodies may cause placental thrombosis and infarction by blocking the release of arachidonic acid from endothelial cells and hence inhibiting production of prostacyclin⁷⁰.

It seems that there are 2 separate populations of phospholipid antibodies evoked by infectious and autoimmune diseases. Anticardiolipin antibodies evoked by infectious diseases have a narrow specificity for anionic phospholipids complexed to a plasma protein cofactor, and only this group is linked to a thrombotic tendency⁷⁸⁻⁸⁰.

Falcón *et al.*⁸¹ have suggested that anticardiolipin antibodies may not bind the cardiolipin antigen directly, but may instead bind a plasma protein (b₂-glycoprotein I) that has high affinity for anionic phospholipids. These authors hypothesized that women with antiphospholipid antibodies and a history of pregnancy loss would have a higher prevalence of antibodies against phospholipid-binding proteins than women with antiphospholipid antibodies and normal pregnancies. These authors observed a significant association between IgM anti-b₂-glycoprotein I and a history of miscarriages. Recurrent spontaneous abortion has been observed owing to alloimmunization⁸².

There may be a direct effect of HIV-1 on the placenta and on embryogenesis. HIV-1 has been identified in fetuses during the first weeks of pregnancy^{83,84}. The presence of HIV-1 infected monocyte/macrophages in the endometrial mucosa has also been demonstrated⁸⁵. There may be abnormalities in the fetal thymus, with consequent abnormal cytokine production secondarily resulting in an adverse intrauterine milieu for the adequate maintenance of pregnancy, possibly due to the deleterious effects of this event on the endometrium. As a consequence, there may also be a cumulative effect of the

immunosuppression caused by HIV infection, facilitating the ascension of infections from the lower genital tract and the development of viral or bacterial infection of the villi⁶⁸. Shearer *et al.*⁸⁶ propose that HIV infection in pregnant women produces an altered state of certain soluble immune factors such as cytokines, which in concert with other immune factor abnormalities such as a loss of immune selection in the fetal thymus predisposes the fetus to advanced HIV infection (possibly due to an imbalance of immune factors capable of contributing to immunological rejection) and possible spontaneous abortion.

CONCLUSION

Current data suggest that pregnancy bears no effect on accelerating the development of AIDS, HIV-related diseases, or severe immunosuppression during pregnancy for up to 1 year after delivery or abortion. On the other hand, HIV infection may adversely affect pregnancy, especially in terms of the overall risk of spontaneous abortion and maternal postpartum endometritis. It would be a useful practice to conduct long-term follow-up on all HIV-infected pregnancies.

RESUMO

EL BEITUNE P e col. - HIV-1: prognóstico materno. **Rev. Hosp. Clín. Fac. Med. S. Paulo** 59(1): 25-31, 2004.

Atualmente, dentro do contexto epidêmico da AIDS observam-se profundas modificações no perfil dos pacientes acometidos, especialmente traduzida pela pauperização e feminilização. A população mais afetada encontra-se em idade reprodutiva e entre adultos de 18 a 24 anos, a relação é de 1 homem para

1 mulher, o que ocorre indiscriminadamente como fenômeno global. Um dos maiores desafios para as gestantes portadoras do HIV-1 e seus médicos assistentes é a repercussão advinda da interação entre a infecção pelo HIV e a gestação. Esse artigo é uma revisão de literatura e tem por objetivos avaliar a influência da infecção pelo HIV-1 sob a perspectiva materna tecendo considerações sobre a função imunológica, o prognóstico materno e a interface HIV e abortamento. Até o presente, não se

pode concluir que a gestação tenha, a curto prazo, um efeito norteador da evolução da infecção pelo HIV, porém a concomitância HIV e gestação pode adversamente afetar o prognóstico gestacional, especialmente face à frequente associação com acréscimo nos índices de aborto e morbidade puerperal.

DESCRITORES: HIV-1. Gestação. Abortamento. Imunologia. Prognóstico.

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