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Tuberculosis and pregnancy

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"The lord shall smite thee with a consumption, and with a fever, and with an inflammation... and they shall pursue thee until though perish". (Deuteronomy 28: 22)

Tuberculosis is a disease of antiquities and it has been there since medieval times though according to literature, It is no older than the first conception of Adam's wife. Despite the extensive studies on tuberculosis and it being declared a global emergency, very little literature from the developing world is available on the interaction of this disease and pregnancy. There is a serious lack of information form those countries that bear the greatest burden of the disease particularly southern Africa where the duo epidemic of tuberculosis and HIV threaten the post independence gains in education, health, economic and other sectors of the economy. The scanty information on the impact of tuberculosis- a disease with effective chemotherapy- on pregnancy raises serious ethical and moral issues, which this paper will attempt to address.

Tuberculosis is currently the most prevalent infectious cause of human suffering and death. The incidence and prevalence of the disease continues to rise in the developing countries while many developed countries have witnessed a reversal of the downward trend that had occurred since the beginning of the 20th century. There are, in fact, more cases of tuberculosis in the world today than at any previous time in human history.

In most parts of the world, tuberculosis affects young adults and, therefore, women of childbearing age are at risk. The disease is closely related to poverty and thus 95% of cases of tuberculosis, and 98% of deaths due to it, occur in the developing world. Furthermore, up to 70% of deaths due to tuberculosis occur during the childbearing years; i.e. 15-40 (Connolly and Nunn, 1996). Thus about one third of deaths due to tuberculosis, around 1 million annually, occur among women of childbearing age. The relative importance of tuberculosis is highlighted by the fact that, in the developing world, it kills more women than all causes of maternal mortality combined (Ahrned et al 1999). The specific impact of HIV on tuberculosis and pregnancy has equally not been studied.

Despite this alarming fact, and, despite the fact that, in developing countries, women often have multiple pregnancies and the interaction of pregnancy and tuberculosis must therefore be a very common event, this subject that has not received much attention.

One of the likely contributing factors to the neglect of tuberculosis in pregnancy in both the developing and developed world would be that prior to the HIV epidemic, it tended to affect older people and very young children and rarely young adults of the child bearing age. However, the problem of tuberculosis in the younger, HIV positive person has now emerged in the last twenty years. The occurrence of tuberculosis in pregnant women raises several questions and these have to be looked at from a maternal, child and the course of the disease point of view. The important questions to be addressed include:

a) Do pregnancy and/or childbirth have adverse or beneficial effects on the clinical course of tuberculosis by leading to more severe forms of the disease or less severe forms?

b) Does tuberculosis pose special risks to the pregnant woman than in the general population or does pregnancy infact confer benefits?

c) What are the particular risks and complications posed by tuberculosis and its therapy on the neonate?

d) The impact and interaction of tuberculosis in pregnancy and HIV should also be looked into. This should also spell out the role of counselling women who are pregnant and have tuberculosis for HIV. The role of chemotherapy, chemoprophylaxis and the effect on the mother and neonate should be studied.

Effect of pregnancy and childbirth on the clinical course of tuberculosis

The question as to whether pregnancy and childbirth have adverse, beneficial or no significant effects on the clinical course of tuberculosis has been controversial for quite sometime now. The early views were that pregnancy had beneficial effects on tuberculosis (Millar and Miller 1996) and only when they were advancements in the field of molecular biology and immunology did the world witness the emergence of opposing views.

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Around 1835, however, reports of an adverse effect of pregnancy on tuberculosis began to appear and led to a considerable change in medical opinion. Indeed, many advocated therapeutic abortions.

A century later, around 1930, medical opinion changed yet again with the emergence of the general view that pregnancy had no effect on mild tuberculosis and that the deterioration seen in cases of severe tuberculosis would have occurred in any case (Hedvall, 1953). There is little doubt that this is the case if effective chemotherapy is given (de March, 1975) but the effect of pregnancy on untreated or inadequately treated tuberculosis is, however, still open to question. This is an area where research will have to be conducted to have a convincing answer.

What Cytokines are at play?

Are there any immunological reasons for postulating an effect, one way or the other, of pregnancy on the course of tuberculosis? It is generally accepted that there is an increased incidence, or clinical worsening, of a variety of other infectious diseases, including Malaria, varicella, to mention but a few during pregnancy. It is also generally accepted that T lymphocytes mature along different pathways, resulting in two subsets, Th1 and Th2, which by secreting different cytokines have distinct and, in some cases, opposing activities. The aforementioned infections involve intracellular parasitism, against which an effective immune response is based on Th1 activity. A Th2 component may trigger inappropriate immune responses capable, in some cases, to induce tissue destruction and progression of disease. Tuberculosis is similar. A predominantly Th1 response is associated with protection but a significant Th2 component leads to the gross tissue destruction that occurs in progressive disease.

Studies in the mouse model showed that pregnancy induced Th2 activity (Wegmann et al., 1993) and that in experimental models in which there was a high incidence of foetal loss, the placentas contained reduced levels of Th2 cytokines but raised levels of Thl cytokines (Chaouat et al., 1995). Furthermore foetal loss could be reduced by administration of an antibody that blocked the Thl cytokine interferon gamma IFN and increased by strategies that enhance Th1 responses (Krishnan et al., 1996).

A similar situation appears to occur in humans. Some women prone to repeated miscarriages have exaggerated Th1 responses to trophoblast antigens and a generalised diminution in Th2 responses (Shaarawy and Nagui, 1997). In addition, decreased Th2 responses have also been observed in pregnancies that result in babies small for their gestational age (Marzi et al., 1996).

An additional reason for postulating a Th1 to Th2 drift in pregnancy is that cell mediated, Th1 associated, autoimmune diseases such as rheumatoid arthritis and multiple sclerosis often show improvement during pregnancy while those mediated by antibody, such as systemic lupus erythematosus, tend to worsen.

These considerations lead to the possibility that the T cell maturation patterns accompanying pregnancy are detrimental to the course of tuberculosis but as already outlined, the available clinical evidence does not support this. Neither, however, does it clearly refute it and further detailed studies are indicated. Some studies suggest that tuberculosis may worsen after childbirth although, again, this is controversial. Such worsening, if indeed it occurs, could indicate an adverse immunological switch occurring at or around childbirth, possibly mediated by hormonal changes, or it could merely indicate that the signs and symptoms of the disease are, somehow, suppressed during pregnancy. Other factors that have been thought to adversely affect the postpartum course of tuberculosis include descent of the diaphragm causing expansion of the lung, the nutritional effect of lactation and sleep deprivation (Connolly and Nunn, 1996).

Tuberculosis, pregnancy and HIV infection.

The impact of the HIV/AIDS pandemic has added a new twist to the relationship between tuberculosis and pregnancy. Of all the 40 million people infected with HIV around the world, 6 in every 10 adult men, 8 in every 10 adult women, 9 in every 10 children live in sub-Saharan Africa but yet very few studies have been done in this part of the world to look at the impact of tuberculosis on pregnancy in an HIV setting. In Zambia, for example, at least 1 in 4 pregnant women are HIV positive. Despite this, there are no data on the number of these women co-infected with M. tuberculosis, nor on the number with overt tuberculosis. Given that M. infects around 50 per cent of people in the childbearing age range living in sub-Saharan Africa and that 25 percent are infected with HIV; then one in eight pregnant women would be co-infected. As a co-infected person has an 8 per cent or more chance of developing overt tuberculosis each year, it is possible that around one 1 in 100 pregnancies would be complicated by HIV-related tuberculosis. The actual percentage urgently needs to be determined by epidemiological studies.

Not only does HIV infection have a deleterious effect on the course of tuberculosis, there is evidence that tuberculosis has a deleterious effect on the course of HIV infection and may lead to a considerable increases in the viral load levels. Several explanations have been advanced for this synergism but no single definite cause has been established. There is some evidence that progression of HIV infection to AIDS is associated with a Th1 to Th2 drift but it is not clear whether this is the predisposing factor to opportunist infections or an effect. As outlined above, pregnancy could cause such a drift but in practice there does not appear to be an accelerated decline in immune function in HIV- infected pregnant women.

While HIV infection predisposes to the development of active tuberculosis in those infected by M. tuberculosis, it is not clear whether pregnancy increases the risk. Although a study in Kenya indicated that recent pregnancy in HIV-positive women predisposed to the development of active tuberculosis (Cilks et al., 1990), other studies reveal no such association (Margano et al., 1994; Mofenson et al., 1995; Espinal et al., 1996).

Diagnosis of tuberculosis in the pregnant woman.

The diagnosis of tuberculosis in pregnancy should follow the usual clinical practice of a detailed history, physical examination and ordering of appropriate investigations. The diagnosis is often missed and there have been several instances when it has only been made when the neonate has developed the disease (Henderson, 1995). It should be noted that, for many women in many parts of the world, pregnancy leads to an otherwise rare encounter with health services, often the first encounter, thereby providing a unique opportunity to screen for tuberculosis and other infections. This leads to the question as to whether the diagnosis of tuberculosis during pregnancy raises particular problems. In this context, it has been

noted that there is a similarity between certain symptoms of tuberculosis and physiological changes in pregnancy, i.e. fatigue and increased respiratory rate. Tuberculin testing appears to pose no problem in addition to the usual interpretational ones but there is controversy as to whether pregnancy affects the presentation of tuberculosis.

In one study (Margono, 1994) pregnancy did not appear to affect the presentation while a study in Cameroon indicated that it predisposed to lower lung field tuberculosis (Kuaban, 1996). Lower lung lesions, as well as smear-negative, asymptomatic and non-cavitary disease, were also reported in Rhode Island, USA (Carter and Mates, 1994), although some of these patients could have been HIV positive. Certainly, the presentations of tuberculosis associated with HIV infection are likely to cause diagnostic difficulties.

Tuberculosis in pregnancy and the neonate.

The effect of tuberculosis on the morbidity and mortality of the neonate needs to be studied. There are several reports of adverse outcomes for the neonate (Miller and Miller, 1996), including reports of increased spontaneous abortion rates, early onset of labour and underweight neonates. The risk of tuberculosis-related premature birth and abortion rate appears to be greater in those who are socio-econornically disadvantaged (Anderson, 1997) and can therefore not solely be attributed to tuberculosis. There is no evidence that modern short-course chemotherapy leads to foetal abnormalities although a higher risk was reported with older regimens. Despite these risks, there is general agreement that the greatest risk to the child is that of developing tuberculosis, occasionally congenital but more likely due to post-partum infection (Starke, 1997). For this reason, antenatal diagnosis and effective therapy of tuberculosis is essential.

Treating tuberculosis during pregnancy.

The drug therapy of tuberculosis in pregnancy and in the post-partum period is very similar to that of other patients and the principles of therapy are the same: Treatment is based on the use of short course chemotherapy, based on Pyrazinamide, isoniazid, rifampicin and ethambutol. These regimens are used in different combinations and the only drug that is not widely used in pregnancy is streptomycin. If rifampicin based regimens are used in the continuation phase after 2 months, the duration of therapy tends to be significantly reduced. These drugs seem to have a minimal risk of causing foetal abnormalities and side effects in the pregnant woman are no higher than in those who are not pregnant (Brost and Newman, 1997).

Mothers taking antituberculosis drugs at the time of birth can care for, and breast-feed, their infants with little risk, unless the mother's disease is drug resistant and not responding to therapy. The treatment of multidrug resistant tuberculosis during pregnancy requires careful consideration and experience is very limited. For this kind of patients, the effect of using alternative drugs on the fetus remains unknown and with the advent of HIV, no one knows what the role of preventive therapy will be and guidelines will have to be worked out at country level.

Conclusions and the future

The challenges posed by tuberculosis in pregnancy are immense and the literature on tuberculosis and pregnancy, and the effect of the added dimension of HIV infection is confusing. In almost all aspects, some studies reveal an altered effect while others do not. The majority of the developing countries, who bear the bulk of the disease don't have adequate resources to treat the many patients let alone the pregnant woman with tuberculosis. In the industrialised nations, the availability of effective short course therapy has tended to lead to a loss of concern. According to recent data from Africa (Ahmed et al 1999), indications are that tuberculosis is the major cause of morbidity and mortality in pregnant women. For most developing countries particularly in Africa, many issues remain unresolved on tuberculosis and HIV in pregnancy. The unresolved questions include the epidemiology, maternal or foetal outcomes in pregnancy, effects of pregnancy on the natural course of tuberculosis, number of pregnant women affected by the duo infection of tuberculosis and HIV, side effects of antituberculous drugs in pregnancy and issues of adherence to therapy. The role of gender issues is another area that requires further research.

In conclusion, despite tuberculosis and HIV in pregnancy being major health problems, very little literature has emerged from the developing countries on the epidemiology and clinical outcomes. There is an urgent need to quantify and design interventional strategies in women of the childbearing age group.

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