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BERCULOSIS AND PREGNANCY

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INTRODUCTION

Tuberculosis (TB) and pregnancy are two different types of stresses experienced by women. Their simultaneous presence affects them both physically and mentally. To the concerned physicians, genital tuberculosis presents a diagnostic challenge and management of the underlying disease in a pregnant woman requires great care. Management of such cases in the context of the Revised National Tuberculosis Programme and the adoption of the Directly Observed Treatment-Short Course (DOTS) needs a strategy.

Magnitude of problem in India

India accounts for 30% of the burden of all TB cases in the world¹. More than 80% of the patients are in the economically productive age-group of 15—54 years.² The disease is responsible for killing more women of reproductive age than all the combined causes of maternal mortality³ and gives rise to nearly one-third of the female infertility in the country⁴. Exact data in respect of the proportion of pregnant women harbouring TB are unavailable in the Indian context because of the variance in the observed maternal outcomes in pregnancies complicated by TB. However, an increased obstetric morbidity has been reported in such women⁵. The weight gain as well as the height of uterus vs the period of gestation in tuberculous pregnant women has been found to be significantly less in comparison with healthy pregnant women⁶. An adverse pregnancy outcome was also observed in 20% cases (abortion in 6, premature delivery in 2 and intra-uterine death in 2 cases). Studies have also suggested no unusual

increase in pre-term labour or other adverse pregnancy outcomes in treated cases of TB^{7,8}.

How Does TB Effect Pregnancy?

The effects of TB on pregnancy depend upon various factors such as type, site and extent of the disease, stage of pregnancy when management gets instituted, nutritional status of mother, presence of concomitant disease, immune status and co-existence of HIV infection, availability of facilities for early diagnosis and treatment, and so on. The pulmonary and extra-pulmonary forms of TB effect pregnant women in the same way as the non-pregnant ones. A study of 27 pregnancies with culture positive TB detected abnormal radiographs in all the patients⁹. If anti-tuberculosis treatment (ATT) is started early in pregnancy, the outcome is same as that in non-pregnant patients, whereas late diagnosis and care is associated with 4-fold increase in obstetric morbidity and 9-fold increase in pre-term labour⁵. Poor nutritional states, hypo-proteinaemia, anaemia and associated medical conditions add to maternal morbidity and mortality. Co-existing HIV infection is known to augment progression of TB and worsens the immunosuppression. The two most common opportunistic diseases encountered in HIV-related lung complications during pregnancy are infection with *Pneumocystis carinii* and *Mycobacterium tuberculosis*¹⁰. Besides, the availability of appropriate diagnostic/therapeutic facilities and/or affordability of their use tend to result in poor management and outcome of pregnancy. The stage of pregnancy at which ATT is begun is the factor of paramount importance that chiefly determines the maternal outcomes in pregnancies associated with TB.

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How Does Pregnancy Effect TB?

The belief that the raised diaphragm due to pregnancy helped collapse of pulmonary cavities situated mostly in the lower lung regions, just as artificial pneumo-peritoneum does, was held until 19th century⁷. By early 20th century, induced abortion became the recommendation for pregnant tuberculous women¹².

Now, TB is believed to get flared up by the stress of pregnancy, especially in association with a poor nutritional status, **immune-deficient** state, or co-existent diseases. The loss of protective antibodies in mother during lactation too favours the development of post-partal TB. However, more studies are needed to substantiate the hypothesis.

How Does Maternal TB Affect Foetus and Neonate?

A foetus can get TB infection either by haematogenous spread through umbilical vein to foetal liver or by ingestion or aspiration of infected amniotic fluid.¹³ True congenital TB is believed to be rare. The risk to neonate of getting TB infection shortly after the birth is greater¹⁴. Cantwell et al criteria for confirming foetal/neonatal TB comprise demonstration of either primary hepatic complex/caseating hepatic granulomas or per cutaneous liver biopsy at birth or presence of maternal genital tract/placenta TB or the presence of lesions during first week of life by excluding postnatal transmission by a thorough investigation of all the contacts (including the attendants).¹⁵ A neonate having congenital TB may present with respiratory distress, fever, poor feeding, lethargy, irritability, abdominal distention, lymphadenopathy and hepato-splenomegaly. A failure to obtain favourable response with broad spectrum antibiotics along with negative results for other congenital infections should lead to the suspicion of congenital TB. An abnormal chest radiograph is found in all such cases, half of whom have a miliary pattern.¹⁶ The overall mortality for congenital TB is 38% in the untreated and 22% in the treated¹⁵.

An Indian study found a 2-fold increased occurrence of pre-maturity, smaller than expected size and low-birth weight babies in women treated with ATT for 6-9 months during pregnancy¹⁷. However, late pre-natal diagnosis of disease, late institution of ATT, incomplete / irregular adherence to therapy, advanced lung lesions and maternal nutrition due to poverty, ignorance, etc. contribute to poor foetal health.

Diagnosis of TB in Pregnancy

Diagnosis under programme conditions

For diagnosis of TB in pregnancy, programme workers have to keep in mind similarities of symptoms between TB and pregnancy like tachycardia, anaemia, raised ESR and low serum albumin level, as well as dissimilar parameters (like increase in weight during pregnancy and decrease due to TB, hypertension in the former and hypotension in the latter etc.) which may confuse the clinical presentation.

Under RNTCP, sputum examination done as per an algorithm is the preferred method for diagnosis of pulmonary TB¹⁸. A chest skiagram (performed after shielding the abdomen) is done if all the 3 sputum smears are negative and symptoms persist despite giving antibiotics for 1-2 weeks. The presence of suggestive radiographic abnormalities and a medical officer's decision to treat with ATT labels the patient as a "smear-negative" TB case. A pregnant woman with extra-pulmonary TB has constitutional and organ-affected symptoms. Routine haematology and Mantoux test (not commonly advocated in programme) along with investigations specific for the site are carried out for the establishment of specific diagnosis. Co-existence of HIV infection should specially lead to a thorough search for any extra-pulmonary tuberculous focus. A mediastinal or retro-peritoneal adenopathy, pleural effusion or parenchymal infiltrate may be detected in chest skiagram in late course of disease, whereas cavitory lesions could exist in early HIV co-infection.

Management

ATT should be started promptly as untreated disease presents a hazard to the mother and foetus.

The same regimens are recommended for use in pregnancy as for the non-pregnant state except for withholding of Streptomycin. Doubts about the use of Pyrazinamide in pregnancy have since been set at rest. Currently, an intermittent regimen (thrice weekly on alternate days) under the DOTS strategy of RNTCP is being increasingly used world-wide for the pregnant, women having TB .

A retrospective analysis of 12,367 TB patients put on DOTS had 16 pregnant women suffering from the either pulmonary or extra-pulmonary form of disease; 25% of them had become pregnant while receiving ATT. All the 16 were able to complete their treatment. The overall drug tolerance was good and no adverse pregnancy outcome took place²⁰ .

A question-mark exists on the safety of second line drugs in the pregnant state. Therefore, expectant mothers with MDR-TB should be advised to terminate the pregnancy. If a woman insists on its continuation, the possible consequences of the same should be discussed with her in detail. The management of pregnant tuberculous women becomes complicated in the presence of HIV infection due to the involved drug interactions. Hence, the regimens and drug dosages need appropriate adjustments.

Supportive measures during ATT administration include:

- a) An intake of Pyridoxine with Isoniazid during the entire period of therapy to prevent peripheral neuropathy (as being practised under the RNTCP).
- b) Prophylactic vitamin K administration to baby at birth for preventing haemorrhagic disease of the newborn.
- c) Segregation of the mother from neonate if she has active and infectious disease (especially

- MDR-TB) and is either not likely to receive ATT due to maternal non-compliance or has received it only for less than 2 weeks prior to delivery.
- d) Substitution of either protease inhibitors with another class of anti-retroviral drugs or Rifampicin with Rifabutin in case of their co-administration.
- e) Cautious addition of drugs in case multiple therapies need to be given during the co-existence of various diseases.
- f) Examination of the contacts of the pregnant woman's household.
- g) Necessary procedural interventions like pleural, pericardial or ascitic tapping, intercostal chest drainage tube etc.

Effects of Chemotherapy on Mother and Foetus

Maternal effects

Isoniazid may cause cutaneous hypersensitivity, hepatitis, peripheral neuropathy. The risk of INH-induced hepatitis may be 2.5 times higher in pre-natal patients than the general population⁷, although largely unconfirmed . Rifampicin may cause nausea, vomiting and hepatitis. Retrobulbar neuritis occurs in <1% of cases on a daily dose of 15 mg /kg of Ethambutol²². Pyrazinamide may produce gastrointestinal upsets, arthralgia, hyperuricemia and hepatitis. Streptomycin may commonly cause vertigo in mother apart from ototoxicity and nephrotoxicity, related to peak serum concentration and total dose of administered drug. Pregnant tuberculous women generally tolerate primary chemotherapy well. If second line drug therapy becomes necessary during pregnancy, gastrointestinal disturbances may be observed with Ethionamide or PAS; nephrotoxicity with Kanamycin; and psychoses, suicidal tendencies or increase in number of seizures following usage of Cycloserine. Pregnancy has been known to result if there was a simultaneous administration of Rifampicin and oral contraceptives. Rifampicin also accelerates the metabolism of protease inhibitors resulting in sub-therapeutic serum levels, whereas the latter increases the serum levels of Rifampicin and enhances the likelihood of drug toxicity²². The

ototoxicity and nephrotoxicity of Streptomycin (or aminoglycosides) may get enhanced when used in conjunction with other ototoxic or nephrotoxic drugs.

Foetal effects

First line drugs barring Streptomycin are safe. Congenital deafness has been reported in infants with the use of Streptomycin and Kanamycin during pregnancy and various birth defects with the use of Ethionamide and PAS²².

Effects on Breast feeding

Use of Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, Streptomycin, Kanamycin and Cycloserine has been considered safe for breast feeding, but safety of PAS is unproven²². The effect of these drugs gets minimized, if the mother breast feeds before taking the drugs and substitutes the next feed with formula preparation. Under RNTCP, breast-feeding of neonates is recommended regardless of the mother's TB status¹⁸.

Care of neonates

Neonates born to mothers having infectious TB should be given chemoprophylaxis with INH for 3 months or till the mother becomes non-infectious. BCG vaccination may be postponed or done with INH-resistant BCG vaccine. After 3 months, if mother has a negative sputum smear and the neonate (with a normal chest skiagram) has a negative Mantoux test, then INH chemoprophylaxis may be discontinued. In case, the Mantoux test is positive, a thorough search should be made for locating the presence of pulmonary or extrapulmonary focus and administration of ATT may be decided accordingly.

REFERENCES

- World Health Organisation; Research for Action : understanding and controlling tuberculosis in India;2000,12
- Central TB Division; TB India 2002; New Delhi, 2002. 7
- World Health Organisation; World Health Report; 1999, 12368
- Parikh. F.R.. Naik N.. Nadkarni S.G.. Soonawala S.B.. Kamat S.A., Parikh R.M.; Genital tuberculosis is a major pelvic factor causing infertility in Indian women; *Feril Steril*: 1997. 67, 497
- Figueroa-Damien R., Arredondo—Garcia J.L.: Pregnancy and tuberculosis; influence of treatment on perinatal outcome; *Am J Perinatal* ; 1998. 15. 303
- Jain N.K. (Safety of anti-tuberculosis drugs in pregnancy) and Kishan J.. Sailaja. Kaur S. (Tuberculosis and pregnancy); *Abstracts*; NAPCON; Nov 2001. Mumbai, 33
- Riley L.; Pneumonia and tuberculosis in pregnancy; *Infect Dis Clin North Am*: 1997 Mar. 11(1). 119
- Robinson C.A.. Rose N.C.; Tuberculosis : current implications and management in obstetrics; *Obstet Gynecol Surve*; 1996. 51. 115
- Good J.T., Iseman M.D., Davidson P.T.. *et cil*: Tuberculosis in association with pregnancy; *Am J Obstet Gynecol*: 1981, 140, 492
- Saade G.R.; Human immunodeficiency virus (HIV) related pulmonary complications in pregnancy; *Semin Perinatal*; 1997 Aug. 21(4). 336
- Snider D.I. Jr.; Pregnancy and tuberculosis; *Chest*: 1984. 86, 115
- Vallejo J.G., Starke J.R.; Tuberculosis and pregnancy; *Clin Chest Meet*: 1992. 13,693
- Hamadeh M.A.. Glassroth J.; Tuberculosis and pregnancy; *Chest* ; 1992,101. 1114
- Starke J.R.; Tuberculosis. An old disease but a new threat to the mother, foetus and neonate; *Clin Perinatal* ;1997 Mar. 24 (1), 107
- Cantwell M.F.. Shchab Z.M.. Costello A.M.; Brief report : Congenital tuberculosis; *N.EnglJ Med*; 1994. 330. 1051
- Ormerod P.; Tuberculosis and pregnancy and the puerperium; *Thorax* ; 2001, 56. 494
- Jana N. Vasishta K. Jindal S.K. *etal*; Perinatal outcome in pregnancies complicated by pulmonary tuberculosis; *Int J Gynecol Obstet*: 1994, 44, 119
- Central TB Division ; Managing the Revised National Tuberculosis Control Programme in your area - A training course; Modules 1-4. New Delhi; July 2001. 1
- Anderson G.D. ; Tuberculosis in pregnancy; *Semin Perinatal*: 1997 Aug, 21(4). 328
- Arora V.K.. Sarin R. ; Revised National Tuberculosis Control Programme: Indian Perspective; *Incl. J. Chest Dis. Allied Sci*; 2000.42,21.
- Snider D.E., Caras G.J.; Isoniazid - associated hepatitis deaths : a review of available information.; *Am Rev Respir Dis*: 1992, 145. 494
- Brost B.C.. Newman R.B.; The maternal and fetal effects of tuberculosis therapy; *Obstet Gynecol Clin North Am*: 1997 Sep. 24(3), 659
- Ross J.D.. Home N. W.; Chemoprophylaxis of tuberculosis; *In* : Home NW ;ed. *Modern drug treatment of tuberculosis*; 7th ed. (Indian ed.); New Delhi : Oxford University Press; 1992. 65