

Prevalence Miliary Tuberculosis During Pregnancy- A Cross Sectional Study in a Tertiary Hospital

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Abstract

Background: The incidence of Tuberculosis during Pregnancy has increased markedly in the present-day consultations of a Pulmonologist. The clinical features of Miliary tuberculosis in pregnant patients were analyzed in this study.

Aim of the study: To observe, analyze the clinical presentation and laboratory diagnosis of Miliary tuberculosis in pregnancy as per guidelines of WHO to recommend better practices of treatment in the Hospital.

Methods: A Prospective study to analyze the clinical presentations and laboratory diagnosis of Miliary tuberculosis occurring in various semesters of pregnancy was conducted. Demography, epidemiology, investigative procedures adopted, treatment executed, and prognosis were studied.

Results: There were 37 pregnant women with Miliary tuberculosis registered for the study. 23 (62.16%) were primi-Para, 14 (37.83%) women were multi-Para. The mean age of gestation was 28.54±2.65 weeks. The mean duration of clinical presentation was 39.50±4.32 days. Symptoms were cough, loss of appetite, fever, pain in the abdomen and pain in the chest. Acute respiratory failure was observed in 08 (21.62%) women and ARDS was observed in 06 (16.21%) women. X-Ray chest showing diffuse, small, multiple nodules in all patients. 08 patients treated with ventilator support; 02 patients underwent extracorporeal membrane oxygenation.

Conclusions: Tuberculosis of Miliary type could occur in pregnant patients; Symptoms appeared in all the trimesters of pregnancy. The common clinical symptoms were fever, breathlessness and cough. Sputum for AFB, TBNAT test, sputum for culture of TB bacilli, Montoux test, arterial blood gas analysis, pulmonary function tests, complete blood picture were significant statistically to help the diagnosis.

Keywords: Pregnancy, Tuberculosis, Miliary Tuberculosis and Mycobacterium Tuberculosis.

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Introduction

Tuberculosis still remains a major infectious and communicable disease in the developing countries especially in India following the rise of Immunodeficiency, retroviral infections in the general populations[1]. Worldwide prevalence of tuberculosis was also found on the higher side as reported in the WHO epidemiological study reports from all countries[2]. It remains as one of the top ten causes of death all over the world among the infectious agents[2]. According to WHO in 2019, new cases of Tuberculosis registered were 10 million and it was the cause of death in 1.9 million among the non-HIV populations[3]. The gender incidence of Tuberculosis was reported as 32% in women, even though it affected all the age groups and both the genders[4]. WHO reports state that nearly 700,000 women succumb to Tuberculosis and more than 3 million new cases are registered all over the world[5]. Tuberculosis was found to be the third common factor contributing to death among child bearing women (15 to 44 years)[6]. The diagnosis of Tuberculosis was described as difficult as the symptoms of physiological pregnancy and Tuberculosis mimic each other; the symptoms being fatigue, breathlessness, sweating, tiredness, cough, and mild fever[7]. Pulmonary Tuberculosis in pregnant women if treated appropriately in time does not land in maternal and fetal complications[8]. The incidence of Miliary tuberculosis per se is less than 02% of the total Tuberculosis cases all over the World. It occurs as a result of widespread dissemination of Mycobacterium tuberculosis, predisposed by risk factors such as female gender, extremes of age, immune-suppressed states, pregnancy, poor socioeconomic status and alcoholism[9]. Progressive symptoms like fatigue and weakness in more than 90%, Weight loss in 80%, Headache in 10% were experienced by the patients over a period of several months[10]. Signs such

as low-grade fever in 20%, Fever in 80%, Cough in 60%, generalized lymphadenopathy in 40%, Hepatomegaly in 40%, splenomegaly in 15%, Pancreatitis in less than 05%, Multiorgan dysfunction, adrenal insufficiency were present during the antenatal period[11]. Review of the literature showed little number of scientific papers addressing the Tuberculosis in pregnant women. In addition, controversial issues like assessing reliability, safety and feasibility of Tuberculosis screening methods, to be used during the antenatal period require further research[12]. Management of Latent Tuberculosis Infection (LTBI) by delaying anti tuberculosis treatment till post-partum period, drug therapy Multidrug resistant pregnant women also need further consideration[13]. The present study was aimed to observe, analyze the clinical presentation of Miliary tuberculosis in pregnant women and as per guidelines of WHO to recommend better practices of treatment in the Hospital.

Materials:

A Prospective study on 37 pregnant women with miliary Tuberculosis attending the tertiary referral Hospital in Kozhikode, Kerala between January 2018 and January 2020 were included in the study. They were observed for clinical features and laboratory test results. An Institute Ethics committee approval was taken and approved consent proforma was used.

Data analysis: The data was collected in a preformed proforma regarding epidemiological factors; social factors, clinical findings, values of laboratory investigations; management methods and its prognosis were analyzed by all the authors. Any difference in interpretation between the two authors was reviewed by the other authors.

Laboratory tests: All the 37 women were subjected to sputum for microscopy for

Tuberculous bacilli, sputum for TBNAT, sputum for culture of tuberculous bacilli. Non-Tuberculosis lab diagnostic tests like ECG, Pulmonary function tests, complete blood count (CBC) tests, coagulation function tests, liver and kidney function tests, C-reactive protein (CRP) tests, erythrocyte sedimentation rate (ESR), arterial blood gas analysis, Montoux tests were undertaken.

Pregnancy Definition: Early Pregnancy/ first trimester week 1 to 13), Middle pregnancy/ second trimester (14 weeks to 27 weeks); late pregnancy/ third trimester (28th week to the delivery).

Miliary Tuberculosis: It was defined as a pathological state with formation of small 1 to 2 mm size granulomas in different organs following excessive lymphohaematogenous spread arising from a Tuberculosis focus. The diagnosis was confirmed when clinical, X-Ray/ CT scan signs, positive pathological diagnostic values and therapeutic response[14]. ARDS was diagnosed by using the Berlin definition[15].

Statistical methods: Data was analyzed using standard statistical methods. The data was expressed in terms of percentage, mean, standard deviation. A chi square test was used to find the test reliability in the diagnosis.

Results: Among the 37 naturally Pregnant women included in the study, 23 (62.16%) were primi-Para, 14 (37.83%) women were multi-Para. The mean age of gestation was 28.54 ± 2.65 weeks. The mean duration of clinical presentation was 39.50 ± 4.32 days. Among the 37 naturally pregnant women with Miliary tuberculosis, 18 (48.64%) were aged between 18 and 27 years, 12 (32.43%) aged between 28 and 37 years, 07 (18.91%) were aged between 18 and 27 years. 16 (43.24%) women were in their first trimester, 12 (32.43%) were in their second trimester and 09 (24.32%) were in their third trimester (**Table 1**). The mean age was 21.45 ± 16 years. 22 (59.45%) pregnant women were from low socio-economic status, 08 (21.62%) from middle group and 04 (10.81%) were from high income group. The onset of symptoms was reported as less than 3 months in 16 (43.24%), 3 to 6 months in 10 (27.02%) and above 6 months in 11 (29.72%) of the subjects. The diagnosis of Tuberculosis was made in primary health centers in 09 (24.32%) patients, diagnosed by the private medical practitioners in 09 (24.32%), at the district hospitals in 13 (35.13%) women and at tertiary referral hospitals in 06 (16.21%) pregnant women (**Table 1**).

Table 1: Shows the demographic data in the study (n-37)

Observation	First trimester 16 (43.24%)	Second trimester 12 (32.43%)	Third trimester 09 (24.32%)	Total 37
Age interval				
18 to 27 years	08	06	04	18
28 to 37 years	05	04	03	12
38 to 47 years	03	02	02	07
Socio-economic status				
Low	10	07	05	22
Middle	03	02	03	08
High	03	03	01	07
Educational status				
Below Degree	04	07	04	15
Degree	11	04	03	18
Post graduation	01	01	02	04
Onset of symptoms				

Less than 3 months	09	03	04	16
3 to 6 months	04	05	03	10
Above 6 months	06	07	08	11
Primary diagnosis				
Primary Health Center	04	03	02	09
Private Practitioner	04	02	03	09
District Hospital	06	05	02	13
Tertiary Hospital	02	02	02	06

Out of 37 pregnant women 19 (51.35%) presented with Primary pulmonary tuberculosis, 07 (18.691%) presented with secondary pulmonary tuberculosis, 06

(16.21%) women presented with extra-pulmonary tuberculosis and 05 (13.51%) women presented with nodal tuberculosis (**Table 2**).

Table 2: Shows the types of tuberculosis in the study (n-37)

Type of Tuberculosis	Number	Percentage
Primary Pulmonary	19	51.35
Secondary pulmonary	07	18.91
Extra-pulmonary	06	16.21
Nodal	05	13.51

Risk factors were observed in the pregnant women with Miliary tuberculosis and found that 21/37 (56.75%) showed risk factors such as malnutrition in 04 (10.81%) women, previous genital tuberculosis in 11 (29.72%), Diabetes Mellitus in 06 (16.21%), HIV infection in

03 (8.10%) women, end stage renal disease was found in 05 (13.51%) women, malignancy was observed in 02 (05.40%) women and 01 (02.70%) had history of prolonged intake of steroids (**Table 3**). There were no risk factors in the remaining 16/37 (43.24%) pregnant women.

Table 3: Shows the Risk Factors (n-37)

Risk Factors	Number	Percentage
Malnutrition	04	10.81
Previous genital tuberculosis	11	29.72
Diabetes Mellitus	06	16.21
Retroviral infections	03	08.10
End stage renal disease	05	13.51
Malignancy	02	05.40
Prolonged steroid therapy	01	02.70
Total	32	86.48

The presentation of symptoms in relation to the gestational age was observed and found the mean value was 18.76 weeks (range: 02–34 weeks). The duration of time before the final diagnosis was ranging from 11 to 67 days with a mean of 26.89 days. The commonest symptom was fever in 83.78% women, breathlessness in 81.08%, cough in 56.75%, headache in 37.83%, pain in the chest in 13.51%,

abdominal pain in 13.51% pregnant women. Among the signs pleurisy was observed in 08.10%, Pneumothorax in 05.40%, abdominal; Tuberculosis in 05.40%, Tuberculous encephalopathy in 02.70% and ARDS in 16.21% women and Acute respiratory failure in 21.62% pregnant women with Miliary Tuberculosis (**Table 4**).

Table 4: Shows the symptoms and signs observed in the subjects (n-37)

Symptoms and signs	Number	Percentage
Fever	31	83.78
Breathlessness	30	81.08
Cough	21	56.75
Headache	14	37.83
Pain in the chest	10	13.51
Abdominal pain	05	13.51
Pleurisy	03	08.10
Pneumothorax	02	05.40
Abdominal Tuberculosis	02	05.40
Tuberculous encephalopathy	01	02.70
ARDS	06	16.21
Acute respiratory failure	08	21.62

The laboratory investigations data was analyzed based on the significant values which helped in the diagnosis of Miliary Tuberculosis and found that the tests of sputum for AFB, TBNAT test, sputum for culture of TB bacilli, Montoux test, pulmonary function tests, arterial blood

gas analysis, complete blood picture were significant statistically with p value less than 0.05, (P was taken as significant at <0.05). Test like coagulation function tests, Liver and Kidney function tests, CRP levels, ESR were not significant with p value more than 0.05 (**Table 5**).

Table 5: Shows the various laboratory tests and their significance in the case study (n-37)

Laboratory tests	Number	Percentage	P value
<u>Sputum for TB bacilli</u>			
Positive	32	86.48	0.001
Negative	05	13.51	
<u>TB-DNA detection (TBNAT)</u>			
Positive	33	89.18	0.001
Negative	02	05.40	
<u>(PPD) skin test (Montoux test)</u>			
Positive	30	81.08	0.001
Negative	07	18.91	
<u>Culture TB organism</u>			
Positive	21	56.75	0.031
Negative	16	43.24	
<u>Pulmonary function tests</u>			
Abnormal	37	100	0.001
Normal	0	0	
<u>Arterial blood gas analysis</u>			
Abnormal	29	78.37	0.028
Normal	08	21.62	
<u>Complete blood count (CBC)</u>			
Abnormal	30	81.08	0.025
Normal	07	18.91	

<u>Coagulation function tests</u>			
Abnormal	12	32.43	0.568
Normal	25	67.56	
<u>Liver function tests</u>			
Normal	14	37.83	0.124
Abnormal	23	62.16	
<u>Kidney function tests</u>			
Normal	16	43.24	0.241
Abnormal	21	56.75	
<u>C-reactive protein (CRP)</u>			
Abnormal	18	48.64	0.251
Normal	19	51.35	
<u>ESR</u>			
Abnormal	22	59.45	0.220
Normal	15	40.54	
<u>ECG</u>			
Abnormal	11	29.72	0.124
Normal	26	70.27	

Radiological investigations included plain X-Ray chest PA view performed in all the 37 patients (100%) and HRCT chest (Coronal and axial cuts) performed in only 20 (54.05%) patients showed uniformly distributed nodules of 1 to 2 mm size all over both lung fields were noted. 04 (10.81%) patients showed chronic miliary Tuberculosis with unevenly distributed nodules of 2–4 mm size shown in upper and middle lung lobes. In 06 patients with ARDS grouped and partly consolidated nodules were observed bilaterally in the basal regions of lungs on HRCT chest. All the 37 pregnant women were given first-line anti-tuberculosis therapy, 11 of them were administered hormone supplementation. 05 patients were intubated to connect to ventilator and 04 were on ventilated without intubation for a mean period of 07.85 ± 1.05 days. 02 patients were on ECMO. All the 37 patients were discharged successfully after treatment. 05 patients requiring re-admission for minor complaints unrelated to miliary Tuberculosis. There were no abortions, and 28 patients had normal delivery and 09 patients the labour was induced. All the patients were for follow-up till they completed their anti-

Tuberculous medication. There were no drug interactions or drug reactions observed during their completion of medical treatment.

Discussion:

Among the 37 naturally Pregnant women included in the study, 23 (62.16%) were primi-Para, 14 (37.83%) women were multi-Para. The mean age of gestation was 28.54 ± 2.65 weeks. The mean duration of clinical presentation was 39.50 ± 4.32 days. Most probably the endocrine or immune efficiencies might be the risk factors to cause Miliary Tuberculosis occurring in pregnant women[14]. Hormonal imbalance inhibits the normal function of the immune system and lymphocytes and thereby increases the vulnerability of the pregnant mother[15]. In IVF treatment as glucocorticoids are frequently used to sensitize the ovaries to gonadotropin stimulation, it makes the pregnant women more susceptible to tuberculosis and may lead to Miliary Tuberculosis[16]. Increased micro vascular permeability in pregnant women facilitates Tuberculous bacilli to enter the bloodstream, thus causing Miliary Tuberculosis[17]. In China more than 360 million people are infected with M. tuberculosis[18], hence

Miliary tuberculosis in pregnant women is not uncommon[19]. Pregnant women are more susceptible to respiratory virus infections especially influenza[20] and COVID-19[21]. As reported by Singh et al.[22] in 2008, from his study women seeking IVF treatment were found to have tubal factor as infertility with a increased incidence of genital tuberculosis (48.5%). The incidence of genital tuberculosis in this study was 29.72%. In another study by Parikh et al.[23] the genital tuberculosis incidence was 39%. In women with adopting IVF and ET techniques for pregnancy as the fertilized eggs bypass the tuberculosis affected fallopian tubes, there is a chance of pregnancy and tuberculosis co-existing[24]. Miliary tuberculosis involves multiple organs in the body; resulting in liver, lungs and marrow involvement and its lung involvement could cause ARDS[25]. Extra Corporeal Membrane Oxygenation treatment was shown to be an effective treatment in such patients[26]. In the present study extra pulmonary organ involvement was noted in 16.21% of the subjects. Factors found to be favourable for a good recovery without complications in this study were women belonging to younger age groups, without disturbances in consciousness and immediate relevant ventilator support and anti-Tuberculosis treatment.

Conclusions: Tuberculosis of Miliary type could occur in all trimesters of pregnant women; Symptoms appeared in all the trimesters of pregnancy. The common clinical symptoms were fever, breathlessness and cough. Sputum for AFB, TBNAT test, sputum culture of TB bacilli, Montoux test, pulmonary function tests, arterial blood gas analysis, complete blood picture were significant statistically to help the diagnosis.

References:

1. Jana N, Barik S, Arora N, et al. Tuberculosis in pregnancy: the challenges for South Asian countries. *J*

Obstet Gynaecol Res. 2012;38(9):1125–1136.

2. Sugarman J, Colvin C, Moran AC, et al. Tuberculosis in pregnancy: an estimate of the global burden of disease. *Lancet Glob Health.* 2014;2(12):e710–6.
3. Global tuberculosis report 2020. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.
4. Ye R, Wang C, Zhao L, et al. Characteristics of miliary tuberculosis in pregnant women after in vitro fertilisation and embryo transfer. *Int J Tuberc Lung Dis.* 2019;23(2):136–139.
5. World health Organization: Tuberculosis and gender. Accessed 2 September 2021., [<http://www.who.int/tb/challenges/gender/en/>]
6. TB alert: TB and women. Accessed 2 September 2014., [<http://www.tbalert.org/about-tb/global-tb-challenges/tb-women/>]
7. Nhan-Chang CL, Jones TB: Tuberculosis in pregnancy. *Clin Obstet Gynecol.* 2010, 53: 311-321.
8. Turnbull ER, Kancheya NG, Harris JB, Topp SM, Henostroza G, Reid SE: A model of tuberculosis screening for pregnant women in resource-limited settings using Xpert MTB/RIF. *J Pregnancy.* 2012, 2012: 565049-10.
9. Webster AS, Shandera WX. The extrapulmonary dissemination of tuberculosis: A meta-analysis. *Int J Mycobacteriol.* 2014;3(1):9-16.
10. [Guideline] Treatment of tuberculosis. *MMWR Recomm Rep.* 2003 Jun 20. 52:1-77.
11. Gounder CR, Wada NI, Kensler C, Violari A, McIntyre J, Chaisson RE, Martinson NA: Active tuberculosis

- case-finding among pregnant women presenting to antenatal clinics in Soweto, South Africa. *J Acquired Immune Defic Syndr.* 2011, 57: e77-e84.
12. Worjolah A, Kato-Maeda M, Osmond D, Freyre R, Aziz N, Cohan D: Interferon gamma release assay compared with the tuberculin skin test for latent tuberculosis detection in pregnancy. *Obstet Gynecol.* 2011, 118: 1363-1370.
 13. Sangala WT, Briggs P, Theobald S, Squire SB, Kemp J: Screening for pulmonary tuberculosis: an acceptable intervention for antenatal care clients and providers? *Int J Tuberc Lung Dis.* 2006, 10 (7): 789-794.
 14. Robinson DP, Klein SL. Pregnancy and pregnancy-associated hormones alter immune responses and disease pathogenesis. *Horm Behav.* 2012;62(3):263–271.
 15. Pazos M, Sperling RS, Moran TM, et al. The influence of pregnancy on systemic immunity. *Immunol Res.* 2012;54(1–3):254–261.
 16. Rubenfeld G, Caldwell E, Slutsky AS, et al. acute respiratory distress syndrome (ARDS): the Berlin definition. *Polskie Archiwum Medycyny Wewntznej.* 2012;103(5–6):319–327. [Google Scholar]
 17. Robinson DP, Klein SL. Pregnancy and pregnancy-associated hormones alter immune responses and disease pathogenesis. *Horm Behav.* 2012; 62(3):263–271.
 18. Pazos M, Sperling RS, Moran TM, et al. The influence of pregnancy on systemic immunity. *Immunol Res.* 2012;54(1–3):254–261.
 19. Shan L, Lin S, Tao W, et al. Effect of low-dose dexamethasone on patients with elevated early follicular phase progesterone level and pregnancy outcomes in IVF-ET treatment: a randomized controlled clinical trial. *Clin Endocrinol.* 2018; 89(6):771–778.
 20. Longman RE, Johnson TR. Viral respiratory disease in pregnancy. *Curr Opin Obstet Gynecol.* 2007;19(2):120–125.
 21. Liu H, Wang LL, Zhao SJ, et al. Why are pregnant women susceptible to COVID-19? An immunological viewpoint. *J Reprod Immunol.* 2020; 139:103122.
 22. Singh N, Sumana G, Mittal S. Genital tuberculosis: a leading cause for infertility in women seeking assisted conception in North India. *Arch Gynecol Obstet.* 2008;278(4):325–327.
 23. Parikh FR, Nadkarni SG, Kamat SA, et al. Genital tuberculosis-a major pelvic factor causing infertility in Indian women. *Fertil Steril.* 1997;67(3):497–500.
 24. Gull I, Peyser MR, Yaron Y, et al. The effect of an in-vitro fertilization pregnancy on a woman with genital tuberculosis. *Hum Reprod.* 1995;10(11):3052–3054.
 25. Piastra M, MD, Picconi E, MD, Morena TC, MD, on behalf of the Intrepid group, et al. Miliary tuberculosis leading to acute respiratory distress syndrome: clinical experience in pediatric intensive care. *Pediatr Pulmonol.* 2019;54(12):2003–2010.
 26. Edda V, Gunnar M, Sverrisson Kristinn O, et al. ARDS from miliary tuberculosis successfully treated with ECMO. *Respir Med Case Rep.* 2019; 26:165–167.