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Neonatal Outcome of Children Born to Women with Tuberculosis

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Background. As the incidence of tuberculosis (TB) has increased worldwide, it is expected that pregnant women will acquire this infection more frequently. *Mycobacterium tuberculosis* infection during pregnancy may represent a risk for maternal and neonatal complications.

Methods. We studied the perinatal events of 35 consecutive pregnancies complicated by TB from March 1990 to June 1998; 105 apparently healthy pregnant women were included as controls, matched in age, gestational age upon arrival at the Institute, and socioeconomic status. Frequency and type of neonatal complications were recorded. Relative risk (RR) with 95% confidence interval (CI) was calculated. To control potentially confounding variables, a stratified analysis was performed.

Results. Seventeen (48.5%) tuberculous mothers had a pulmonary infection and 18 (51.5%), an extrapulmonar localization of the TB. The neonatal morbidity rate in children born to women with TB was 23% against 3.8% of the children of the control cohort ($p < 0.05$). Average weight of newborn infants of tuberculous mothers was 2,859 ± 78.5 g, while average weight at birth of control neonates was 3,099 ± 484 g ($p = 0.03$). Newborns of women with TB had a higher risk of prematurity (RR 2.1; 95% CI 1–4.3), perinatal death (RR 3.1; 95% CI 1.6–6), and weight at birth less than 2,500 g (RR 2.2; 95% CI 1.1–4.9). Pulmonary localization of the TB and late start of the treatment in the mothers increase the risk of perinatal death and neonatal morbidity.

Conclusions. Children born to women with TB have an increased risk of morbidity and mortality in the neonatal period.

Key Words: Tuberculosis, Pregnancy, Newborn, *Mycobacterium tuberculosis*, Neonatal death.

Introduction

Tuberculosis (TB) is a public health problem in developing countries (1). Over the last decade, worldwide increase in the incidence of TB has been reported not only in developing countries but also in the nations of the so-called First World (2). Multiple factors have influenced this increase, including human immunodeficiency virus (HIV) infection, deterioration of public health, increased transmission in congregate settings, recent migratory population movements, and the emergence of multidrug-resistant strains of *Mycobacterium tuberculosis* (3).

As the incidence of TB increases, pregnant women are expected to acquire this infection more frequently. In hospitals in New York City located in areas where TB is endemic, the incidence of TB in pregnant women between 1985 and 1990 was 12.4 per 100,000 deliveries, increasing to 94.8 from 1991 through 1992 (4). Although the incidence of TB in Mexican pregnant women is not accurately known, Figueroa et al. (5) reported treating approximately 10 cases per year in a reference hospital for high-risk obstetric patients. *Mycobacterium tuberculosis* infection during pregnancy may represent a risk for maternal and neonatal complications (6,7).

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The aim of this article is to report the results of an evaluation of a group of newborn infants born to pregnant women with tuberculosis.

Patients and Methods

This was a retrospective cohort study that included the perinatal events of 35 consecutive pregnancies complicated by TB that were treated at the National Institute of Perinatology (INPer), a postgraduate institute of medical education and research in Mexico City, Mexico from March 1990 to June 1998. Health personnel at the INPer assist at a mean of 6,000 births per year; it has a neonatal intensive care unit of 20 beds and a neonatal intermediate-care unit of 40 beds. Healthy neonates are seen at joint shelters with their mothers.

At TB diagnosis, all pregnant women in the study had clinical manifestations of active infection (Table 1). The diagnosis of maternal TB was corroborated with acid-fast bacilli (AFB) stains, cultures for *Mycobacterium tuberculosis*, or histologic studies (Table 2). For each pregnant woman with TB, three apparently healthy pregnant women were included as controls, matched in age, gestational age on arrival at the Institute, and socioeconomic status. The control group was made up of 105 pregnant women chosen among prenatal control out-patients of the Institute. The tuberculous and control pregnant women were followed through delivery. Frequency and type of obstetric and neonatal complications were recorded, as well as anthropometric measurements of the newborns. Congenital tuberculosis was investigated by means of clinical evaluation during the first week of life, and the following tests were conducted: tuberculin skin test; AFB smear, and culture of gastric and tracheal aspirates. In neonates with clinical manifestations of sepsis liver, biopsy was performed.

Neonatal morbidity was defined as the presence of any complication in the newborn attributed directly or indirectly to the mother's infectious disease. Pregnancies ending between 27 and 36 weeks of gestation were considered premature. Perinatal death was defined as any death occurring up to 7 days after delivery or stillbirth.

Table 1. Clinical manifestations of pulmonary and extrapulmonary tuberculosis in pregnant women

Localization of TB	Clinical manifestation	*n*
Pulmonary	Cough and fever	8
($n = 17$)	Chronic cough	6
	Cough, fever, hemoptysis	2
	Cough, fever, hemoptysis, weight loss	1
Renal	Dysuria and fever	5
($n = 11$)	Dysuria, fever, hematuria	4
	Dysuria, fever, back pain	2
Lymph node	Enlargement of cervical lymph node	6
($n = 6$)		
Cutaneous	Cutaneous nodular lesions	1
($n = 1$)		

Table 2. Diagnostic methods for tuberculosis infection in 35 pregnant women

Localization of TB	Test	*n*
Pulmonary	AFB[a] stain	9
($n = 17$)	AFB[a] stain + culture of sputum	7
	Culture of sputum	1
Renal	Urine culture	9
($n = 11$)	Urine AFB[a] stain	2[b]
Lymph node	Lymph node biopsy	6
($n = 6$)		
Cutaneous	Cutaneous biopsy	1
($n = 1$)		

[a]AFB: acid-fast-bacilli; [b]Both patients had fever, dysuria, and hematuria.

Results were analyzed by Student *t* test for continuous variables; chi-square test or Fisher two-tailed test was used for categorical data. Relative risk (RR) with 95% confidence interval (CI) was calculated. Stratified analysis was performed by Mantel-Haenszel chi-square procedure; the results of the study were adjusted for localization of the infection and initiation of antituberculous treatment in the mother. In this analysis, the variable localization of the infection was dicotomized into pulmonary TB and extrapulmonary TB; the variable of initiation of the antituberculous treatment in the mother was determined as early when commencement of treatment was either before or at the beginning of pregnancy, and late when treatment was begun during or after the second trimester of gestation.

Results

The mean age of pregnant women with TB in the study was 27.1–7.7 years, with a median of 24 years and a range from 14–44. Seventeen patients (48.5%) had pulmonary TB and 18 (51.5%) suffered from extrapulmonary infection. Of these cases, 11 had renal localization of TB, six showed lymph node infection, and one patient had cutaneous TB. Diagnostic methods are shown in Table 2. Median gestational age upon arrival at the Institute was 30 weeks (range 12–41). Thirteen (37.1%) were primigravidae, 11 (31.4%) experienced their second gestation, and 11 (31.4%) were multigravidae. One patient was seropositive for HIV.

In nine (25.7%) patients, treatment was started at the beginning of pregnancy, and in 26 (74.2%) during the second or third trimester of gestation. In the pulmonary cases, four pregnant women initiated the treatment during the first trimester of the gestation, two with isoniazid (I), rifampin (R), and pyrazinamide (P), and two with I, R, and ethambutol (E). Seven women started antimicrobials during the second trimester, two with I-R-E, two with I-R-P, and three with I-R. Six mothers did not begin antituberculous agents until the third trimester, five with I-R-E and one with I-R-P. In the extrapulmonary cases, five pregnant women started their treatment during the first trimester, three with I-R-E and

two with I-R. Seven patients initiated the antituberculous regimen during the second trimester, four with I-R-P, two with I-R-E, and one with I-R. Finally, six mothers did not begin treatment until the third trimester, four with I-R-E and two with I-R-P.

One hundred five healthy pregnant women constituted the control group; their age, weeks of gestation, the day on which they were included in the study, and socioeconomic status were similar to the group of mothers with TB.

Eight (23%) of the pregnant women with TB had medical complications during their gestation, while only four (3.8%) pregnant women in the control cohort experienced these types of complications ($p < 0.01$). Adverse events that occurred during the pregnancies of the women with TB are shown in Table 3.

The neonatal morbidity rate in children born to women with TB was 23% as opposed to 3.8% in the control cohort ($p < 0.05$). Table 3 shows the complications observed in newborns of the maternal TB group. Average weight of newborn infants born to mothers with TB was 2,859 ± 78.5 g, while average weight at birth of control cohort neonates was 3,099 ± 484 g ($p = 0.03$). Premature births and perinatal deaths were more frequent in newborn infants to mothers with TB (Table 4). There was no statistical difference in size and median of gestational age averages at birth between both groups of compared neonates (Table 4).

Neonatal complications observed in the pulmonary TB group were the following: two neonatal deaths; one fetal death; one preterm newborn, and one preterm newborn with fetal growth retardation. The complications observed in the extrapulmonary TB group were three preterm newborns and two newborns with fetal growth retardation.

The mortality rate of newborn infants to women with TB was 14.3%, while the mortality rate of the control cohort newborns was 0.95% ($p = 0.04$). There were three perinatal deaths in the maternal TB group: one was stillborn, and the other two cases were neonatal deaths. The latter were preterm neonates: one developed hyaline membrane syndrome and the other suffered an intraventricular hemorrhage. In neonatal fatal cases, the complications that caused death were due to prematurity, not TB infection. There were no cases of congenital tuberculosis: screening exams for congenital TB were negative in all newborns.

All neonates were immunized with bacille Calmette-Guerin (BCG) vaccine, and the newborns whose mothers did not receive antituberculous medications during pregnancy were separated from their mothers until the mothers completed 3 weeks of antituberculous treatment.

The pregnant women with TB had an increased risk of medical complications during their gestation with a RR of 3.1 (95% CI 1.8–5.3), and their newborn infants had a higher risk of neonatal complications (RR 2.1; 95% CI 1.1–3.9), prematurity (RR 2.1; 95% CI 1–4.3), perinatal death (RR 3.1; 95% CI 1.6–6), and weight at birth of <2,500 g (RR 2.2; 95% C.I. 1.1–4.9).

Stratified analysis showed that the variable localization of the infection and initiation of maternal antituberculous treatment were confounding variables, noting that pulmonary localization of TB and late start of treatment increased the risk of maternal morbidity, perinatal death, and neonatal morbidity (Table 5).

Table 3. Adverse events in 35 pregnancies complicated by tuberculosis

Adverse events	*n*	%
Maternal		
Hypertensive disease of the pregnancy	3	8.6
Respiratory failure	2	5.8
Oligohydramnios	1	2.9
Premature labor	1	2.9
Premature rupture of membranes	1	2.9
Neonatal		
Prematurity	5	14.3
Fetal growth retardation[a]	3	8.6
Fetal death	1	2.9

[a]One premature neonate also had fetal growth retardation.

Table 4. Comparison of neonatal conditions between newborn infants of pregnant women with TB and newborn controls

Condition	Newborns to women with TB *n* = 35	Newborns to control women *n* = 105	*p*	RR (95% CI)
Mean birth weight (g)	2,859 ± 478	3,099 ± 484	0.03	—
Mean size (cm)	48.6 ± 2.4	49.1 ± 2.5	NS	—
Median gestational age at birth (range)	38 (31−42)	38.5 (30−42)	NS	—
Premature (%)	5 (14.3)	5 (4.8)	0.02	2.1 (1−43)
Perinatal death (%)[a]	3 (8.6)	1 (0.9)	0.04	3.1 (1.1− 4.9)

[a]One stillbirth and two neonatal deaths; NS = not significant.

Discussion

As reported elsewhere, maternal infection with *Mycobacterium tuberculosis* during pregnancy may represent a risk for maternal and fetal complications (6). This study focused on exploring the neonatal implications of TB by matching two cohorts of the same population.

Results from the current study show that newborn infants born to mothers with TB had an approximately twofold increase in neonatal complications such as prematurity and fetal growth retardation. Additionally, fetal mortality was higher in this group of children. Mean birth weight of products born to tuberculous women was significantly less than that of the newborns in the control group.

Similar results have been reported by other authors. Jana et al. (7) reported an increased risk for acute fetal distress, prematurity, small-for-gestation age, low birth weight

Table 5. Stratified analysis of the risk of complications in mothers and neonates due to TB

Complications	RR (95% CI) crude	RR (95% CI) adjusted by pulmonary TB	RR (95% CI) adjusted by late start of treatment
Obstetrics	3.1 (1.8–5.3)	4.8 (2.2–10.6)	3.9 (2–7.6)
Neonatals	2.1 (1.1−3.9)	2.5 (1–6.7)	2.5 (1.2–5)
Prematurity	2.1 (1–4.3)	3 (1.1–8.4)	2.6 (1.1–6.1)
Perinatal death	3.1 (1.6–6)	6 (2.9–13.3)	3.8 (1.5–9.2)
Newborns <2,500 g	2.2 (1.1−4.9)	2.5 (1.1−5.4)	2.6 (1.3−5.2)

(LBW), and perinatal death in neonate infants born to women with TB, while Ratner et al. (8) reported a high incidence of prematurity among newborns of tuberculous mothers, ranging from 23–64%, depending on the severity of the disease in the mother. However, other authors did not find adverse effects derived from TB in neonates: Schaefer et al. (9) documented good perinatal outcome in 68 mothers with active TB, and Bjerkedal et al. (10) reported no changes in the incidence of prematurity and LBW, while mean birth weight remained unaffected.

We consider that the differences among the studies mentioned previously are due to the fact that each author and colleagues studied a population of individuals with different socioeconomic status, social-medical conditions, country of origin, advanced maternal disease, late diagnosis, HIV coinfection, and incomplete or irregular treatment. In our study, there were two specific conditions that increased the adverse effects of maternal TB: late start of antituberculous treatment, and pulmonary localization of the infection.

Prior to this study, we were informed that, although antituberculous chemotherapy poses a special problem during pregnancy due to its potential teratogenic effects, early treatment of TB during gestation reverts to its negative impact on perinatal outcome (6). In addition, in the medical literature extensive experience with isoniazid, rifampin, and ethambutol has failed to document teratogenic effects on the fetus (11).

Early diagnosis of this infectious disease in pregnant women also must have beneficial effects on their neonates. At present, the recommendations of the Advisory Committee for the Elimination of Tuberculosis of the Centers for Disease Control in Atlanta, GA, USA (12) establish that pregnant women with the following characteristics must be screened for TB: patients at risk or infected with HIV; close contacts of persons known or suspected of having TB; women with medical or immunosuppressive risk factors known to increase the risk of disease if infection has occurred; alcoholics and drug abusers, and low-income populations.

The majority of reports concerning pregnancy and TB provide information on women with pulmonary localization of the infection; in the current article, nearly 50% of the mothers had extrapulmonary TB, and the newborn infants of these women had fewer complications than neonates of mothers with pulmonary TB. Margono et al. (13) reported six cases of pregnant women with extrapulmonary TB and 10 with pulmonary infection: there were five cases of premature newborns and five cases of fetal growth retardation, but the authors made no analysis associated with localization of TB.

The results obtained from this study show that congenital TB is not the main problem in pregnancies complicated by TB; this is a rare entity, with only 29 cases reported in the English-language literature from 1980–1994 (14). Although coinfection with HIV may increase the risk of congenital infection (15), in this study only one pregnant woman was HIV seropositive.

The increased risk of morbidity and mortality of newborn infants born to mothers with TB demands emphasis on preventive measures. Because prevalence of TB in low-income countries remains high, it is mandatory to be highly suspicious of TB for successful management of this infectious disease in the pregnant women.

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