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Limb deformity in a newborn. Is rifampicin just an innocent bystander?

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Abstract. – OBJECTIVE: The first-line antituberculous agents for use during pregnancy have minimal teratogenic effects. The possibility of limb deformity during rifampin use, however, was reported by some researchers.

CASE REPORT: A male newborn was born with a hypoplastic right forearm to a mother with tuberculosis who used isoniazid and rifampicin in the first two months of her pregnancy.

CONCLUSIONS: The limb anomaly in our case might be attributed to rifampicin usage during the first 2 months of pregnancy. Caution should be given with regard to possible congenital malformations which could be associated with the treatment of pregnant women with antituberculous drugs.

Key Words:
Tuberculosis, Pregnancy, Teratogenicity, Rifampicin, Limb deformity.

Introduction

Tuberculosis is one of the oldest diseases in the human history. The disease is caused by an aerobic bacillus, *Mycobacterium tuberculosis*, and mostly transmitted by inhalation of aerosolized particles. The incidence of tuberculosis increases during childbearing age in females. The higher incidence of tuberculosis in that age group has also been suggested to be associated with the increased incidence of Human Immunodeficiency Virus (HIV) infection in this age group since HIV infection increases the risk of tuberculosis infection due to weakened immune system[1].

Pregnancy may lead to a delay in diagnosis of tuberculosis due to the nonspecific nature of symptoms or reluctance to perform radiography, a low index of suspicion and higher proportions of non-pulmonary tuberculosis in pregnant women than in nonpregnant women although pulmonary TB is the commonest manifestation[1]. When diagnosed, treatment should directly be started because the disease itself causes more harm to the mother and the baby including low birth weight, preterm labor, preeclampsia and early fetal death than do the drugs used for treatment[2].

Herein, we report a male infant with hypoplastic right forearm who was born to a mother with tuberculosis and used isoniazid and rifampicin in the first two months of her pregnancy. This case may suggest the possible teratogenic effects of anti-tuberculous drug usage during pregnancy.

Case Report

A 19 year-old woman admitted to the Perinatology Department of Kanuni Sultan Suleyman Teaching and Research Hospital, Istanbul, Turkey at 26 weeks of gestation for prenatal screening. She had a history of pulmonary tuberculosis diagnosed 4 months before her pregnancy. She was started isoniazid, rifampicin, ethambutol and pyrazinamide combination therapy for 2 months, then isoniazid and rifampicin continued for 4 months. At the 4th month of the two-drug regimen, she stopped these medications without consulting his physician as she realized that she was pregnant. The prenatal ultrasonography at 26 weeks of gestation showed hypoplasia of the right forearm of the fetus. No associated amniotic bands or any other abnormality involving the placenta or membranes were detected. No other risk factors such as exposure to medications other than antituberculous drugs, any chronic disease of the mother as diabetes mellitus, smoking history, any viral infections before or after conception or any affected family member were revealed. Parents refused any further screening and did not admit to the hospital until labor.

At 38 weeks of gestation, the mother delivered a 2850 g (10-50th centile) male infant with normal vaginal delivery with Apgar scores 7 and 8 at

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minute 1 and 5, respectively. The length and head circumference of the infant were 47 cm (25-50th centile) and 33 cm (25-50th centile), respectively. The infant had a hypoplastic right forearm and other physical examination findings were found to be normal (Figure 1). The abdominal ultrasonography showed bilateral renal calculi without any other abnormality. Blood tests were all normal. At the follow-up, the infant did not have any signs of growth retardation as his weight, height and head circumference were at 25th percentile.

Discussion

Tuberculosis is one of the major infectious causes of morbidity and mortality in women of reproductive age, especially in developing countries. As proposed by CDC (Centers for Disease Control and Prevention) in 2003, untreated tuberculosis represents a far greater hazard for both pregnant woman and fetus than does the treatment of tuberculosis[2]. Maternal and neonatal mortality rates in untreated tuberculosis range between 30-40%. Several studies reported a significant reduction in obstetric morbidity and mortality when the treatment is started early in pregnancy[1,3].

Usual treatment strategy involves isoniazid, rifampicin, ethambutol and pyrazinamide combination therapy for 2 months which is followed by combination of isoniazid and rifampicin for 4 months. If pyrazinamide is not used in the first phase, continuation therapy should be given for 7 months, instead of 4 months. Pyridoxine should be added to the therapy when isoniazid is used[4].

The first-line agents suggested by the CDC for use during pregnancy (isoniazid, rifampin, and ethambutol) seem to have minimal teratogenic effects including congenital anomalies. Isoniazid and ethambutol are considered as the safest agents for maternal use. Although isoniazid may cross the placenta, it is accepted to be safe even in the first trimester[3]. Rifampicin is also considered to be safe in pregnancy. Bleeding attributed to hypoprothrombinemia has been reported in infants and mothers following the use of rifampicin in late pregnancy. Therefore, vitamin K administration is recommended for both mother and the infant during postpartum period, if rifampicin has been used in the last few weeks of pregnancy[3]. Early studies in mice or rats that were exposed to 2.5-10 times higher than the usual human dose of ripampicin in utero reported no increase in the incidence of congenital abnormalities[5]. In one study including 442 pregnant women exposed to rifampicin, 109 of whom used it during the first trimester, no increase in the rate of congenital anomalies were found[6]. However, in one study[7], malformations including hydrocephalus, anencephaly and limb defects associated with rifampicin use were detected in 4.4% of 204 pregnancies which was higher than 1.8% rate that was reported in other studies[6]. But no cases of limb reduction defects have apparently been reported in association with maternal rifampin treatment in the subsequent 35 years, despite continued use of this medication in pregnant women.

Figure 1. Limb deformity involving the right forearm.

Although ethambutol may cause ocular toxicity (retrobulbar neuritis) in adults, there is no data about this adverse effect on fetal ophthalmological development if the standard dose is used in pregnancy[3]. Pyrazinamide is another important anti-tuberculous drug as it shortens the treatment period. The use of pyrazinamide in pregnancy was avoided until recently due to lack of adequate data on its teratogenicity. However, its use is now recommended since to date, no significant adverse events have been reported regarding its use in pregnant women[4]. Streptomycin should not be used in pregnant women due to its ototoxic effects on the fetus ranging from mild hearing loss to bilateral deafness[3]. Pregnant women with multidrug-resistant tuberculosis may require second line drugs most of which have teratogenic risks[3,4].

In a recent trial, Awodele et al[8] assessed the teratogenic effect of fixed-dose combined antituberculous drugs containing rifampicin, isoniazid, pyrazinamide and ethambutol on the organogenesis stage of fetal development in an animal model. They showed that fixed-dose combined antituberculous agents had no effect on the morphology of the fetuses but led to a significantly low birth weight of the fetuses of

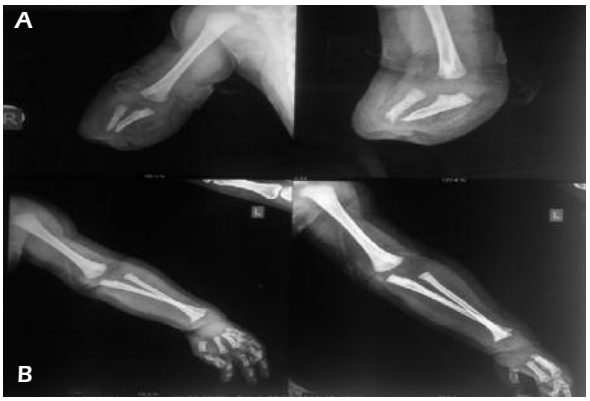

Figure 2. A, Radiographs of the right arm with short and rudimentary radius and ulna without metacarpals and phalanges. ***B,*** Radiographs of the uninvolved left arm with normal bone structures.

the animals, also led to a reduction in platelet and neutrophile counts and to significant elevations in the levels of aspartate aminotransferase (AST) and alkaline phosphatase (ALP) in the fetuses of the animals. They concluded that fixed-dose combined antituberculous agents might have teratogenic potential.

In our case, the mother used isoniazid and rifampicin combination therapy during the first 2 months of her pregnancy. The infant was born with a limb deformity involving the right forearm. Although some researchers reported the possibility of limb deformity due to rifampicin use during pregnancy this rate, however, was reported to be similar to the normal population[4]. Most isolated transverse terminal limb reduction defects occur sporadically and without any apparent cause[9]. Although the maternal treatment and the limb reduction defect in the infant reported might be coincidental, we presume that the limb deformity in our case might be attributed to rifampicin usage during the first 2 months of pregnancy since no other risk factors including exposure to medications other than antituberculous drugs, any chronic disease of the mother as diabetes mellitus, smoking history, any viral infections before or after conception or any affected family member as well as the presence of any associated amniotic bands or any other abnormality involving the placenta or membranes were revealed.

Conclusions

We suggest that it will be reasonable to evaluate the fetus for the possible congenital anomalies during tuberculosis treatment and share the risk and benefit ratio of treatment with the family to make them aware of the possible teratogenic potential of antituberculous drugs.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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