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Antituberculous Therapy in Pregnancy

Risks to the Fetus

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A total of 1,939 reported births to mothers who received isoniazid ethambutol, rifampin and streptomycin alone or in combination, for all or part of their pregnancies, were surveyed to determine teratogenicity of these agents. There was no significant increase in birth defects with isoniazid, ethambutol and rifampin, in contrast to the use of streptomycin which was associated with mild auditory and vestibular defects. Guidelines for the treatment of active tuberculosis in pregnancy are therefore established.

THE MANAGEMENT of pulmonary tuberculosis is becoming more and more the responsibility of internists. A recurrent problem encountered is that of women who become pregnant while receiving antituberculous chemotherapy. The purpose of this report is to suggest guidelines for the management of such patients. To this end, the available data on teratogenicity of the four major antituberculous drugs (isoniazid [INH], ethambutol [EMB], rifampin [RMP] and streptomycin [SM]) are reviewed.

Results

Isoniazid

The widespread use of INH in both prophylaxis and treatment of tuberculosis has allowed the accumulation of a large body of data on its administration during pregnancy. The findings in 1,079 births to women who received the drug alone or in combination with other antituberculous medications, from ten series, are summarized in Table 1. The usual 300 mg per day dosage was administered in most of the studies.

Because of a possible effect on fertility in animals, large early studies examined the outcome of pregnancies in which either parent received INH alone.[1,2] During the first five years of observation, no significant differences were found between the INH and placebo groups in birth rates, sex ratios or birth weights. Specifically, there were no birth abnormalities recorded during the first year of follow-up; that is, in births to women who received INH throughout their pregnancy.

Lowe[3] in Wales compared the outcome of 71 pregnancies during which INH was administered and 167 pregnancies with no drug administration. The two birth defects (2.8 percent) in the INH group were a myelomeningocele in a female infant, and hypospadias in a male. The former infant was born to a mother who had two previous normal births after pregnancies throughout which she received INH. In the group which received no drugs, seven infants were found to have birth defects (4.1 percent).

Hammond and co-workers,[4] in studying the

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ABBEVIATIONS USED IN TEXT

EMB = ethambutol
IHN = isoniazid
RMP = rifampin
SM = streptomycin

TABLE 1.—*Isoniazid (INH) Administration During Pregnancy*

Authors	Births to Patients Receiving INH	Control Group	Birth Defects Treated	Birth Defects Controls
Wilson et al[18]	8	..	0	..
Ludford et al[1]	26	35	0	0
Lowe, CR[3]	71	167	2	7
Hammond et al[4]	660	..	0	..
Jentgens, H[5]	300	432	3	0
Verbist et al[9]	4	..	0	..
Rocher et al[11]	5	..	0	..
Reimers, D[10]	1	..	0	..
Bobrowitz et al[6]	3	..	0	..
Place, VA[7]	1	..	0	..
TOTALS	1,079	640	5	7

possible carcinogenic effects of INH therapy, were able to trace 660 children exposed *in utero,* some to the age of 13 years. None had cancer. One was a mongoloid, and one was described as a "slow baby."

A large survey in Germany[5] compared the births to 2,051 women who received antituberculous chemotherapy during pregnancy with the births to 432 tuberculous women who were not treated while pregnant. There were no differences in birth defects between the two groups. In this study over 300 women received INH, with only three reported defects: a ventricular septal defect in one child, hammer toe in one and a deformed lower extremity in one.

Most other studies[6-11] involve smaller numbers, but with results similar to those above.

Ethambutol

Findings in live births to mothers after EMB administration during human pregnancy are summarized in Table 2. Lewit and associates[12] reported no signs of maldevelopment of the eye, nervous system or other organs in embryos up to 12 weeks gestation obtained from mothers who had received therapeutic dosages of EMB. The authors questioned whether EMB might have affected later morphofunctional differentiation.

In the report of Pyle,[13] four women received EMB during pregnancy, two throughout gestation.

TABLE 2.—*Ethambutol (EMB) Administration During Pregnancy*

Authors	Births to Patients Receiving EMB	Control Group	Birth Defects Treated	Birth Defects Controls
Jentgens, H[5]	313	432	0	0
Wilson et al[18]	1	..	0	..
Marino et al[14]	1	..	0	..
Pyle, M[13]	4	..	0	..
Bobrowitz et al[6]	3	..	0	..
Place, VA[7]	1	..	0	..
Bobrowitz, ID[8]	42	..	8	..
Wilson, T[15]	1	..	0	..
Johnston, R[15]	1	..	0	..
Other*	2	..	0	..
TOTALS	369	432	8	0

*Unpublished data, Lederle Laboratories

All were delivered of healthy infants who developed normally, the oldest being five years of age at the last follow-up.

Bobrowitz[8] reviewed the medical records of all tuberculous pregnant patients over 11 years. In all, 38 patients had received EMB during some portion of their 42 pregnancies. Dosages ranged from 15 to 25 mg per kg of body weight. In 34 of the 42 children there were no defects at birth or in the follow-up period. In eight infants (19 percent), abnormalities were described, including supernumerary nipple, small umbilical hernia, withdrawal syndrome, mild right tibial torsion, congenital dislocation of the hip, left hydrocele, minimal metatarsus adductus, skin tags of the left fifth digit and two "strawberry marks." The author noted no pattern in these abnormalities nor increased incidence when compared with births to untreated mothers.

In the survey in Germany,[5] analysis of case histories of 182 women and of questionnaires completed by 131 women who had received EMB or RMP, or both, during pregnancy failed to show any evidence that either of these drugs had an embryotoxic effect.

Other published[6,7,14,15] and unpublished* reports involving EMB dosages of up to 25 mg per kg of body weight throughout or at various stages of pregnancy have not shown teratogenic effects of the drug.

Rifampin

Animal experiments with RMP in pregnancy yield conflicting results, depending on the species tested. Very high dosages (150 to 250 mg per kg of body weight per day) in rats and mice result

*Lederle Laboratories, Pearl River, N. Y.

in congenital malformations, primarily spina bifida and cleft palate.[16] Similar studies in rabbits produced no such defects.[17]

The number of patients reported after exposure to RMP in pregnancy has not been great, because of the relatively short time of the drug's availability, but the results of over 100 such cases are summarized in Table 3. In every trial except one,[9] the dosage was 600 mg per day. In one report two tuberculous women were unintentionally treated in the first trimester of pregnancy.[10] One bore a healthy child at term, and the other had a therapeutic abortion at five months gestation. Histological examination of the fetus showed no abnormality. The authors knew of 34 other cases in which no harmful effects of RMP administration during pregnancy were noted.

Eighty-four patients in the study in Germany[5] received RMP in combination with other antituberculous drugs with no adverse effects on their progeny. Rocher and co-workers[11] report five cases of normal children born to mothers treated with RMP during all or part of their pregnancy, including four who received the drug during the first trimester.

The small number of cases in other reports[9,18] show no teratogenic effects.

Streptomycin

Streptomycin crosses the placental barrier variably, with fetal levels reaching as high as 50% of the maternal concentration. Factors which influence this level include deficiencies of maternal excretion or detoxification, increased permeability of the placenta due to structural abnormalities, and other diseases of the mother or fetus.[19] Early animal experiments to establish definite auditory and vestibular toxicity in offspring after administration of SM during pregnancy have been inconclusive. In guinea pigs administration of SM in dosages comparable to human dosage failed to produce abnormalities in function or histologic abnormalities. Higher dosages, however, produced vestibular damage. In mice even massive SM dosage failed to produce damaged offspring, while in rats mild but definite damage was produced.[19]

The results of SM administration during pregnancy in humans in eight studies involving small numbers of patients are summarized in Table 4. A dosage of 1 gram per day was most commonly used, with total doses ranging from 10 to over 200 grams. While the testing itself is difficult in

TABLE 3.—*Rifampin (RMP) Administration During Pregnancy*

Authors	Births to Patients Receiving RMP	Control Group	Birth Defects	
			Treated	Controls
Wilson et al[18] ...	2	..	0	..
Jentgens, H[5]	84	432	0	0
Verbist, L[9]	4	..	0	..
Rocher, G[11]	5	..	0	..
Reimers, D[10]	1	..	0	..
Reimers, D[17]	5	..	0	..
TOTALS	101	432	0	0

children, no neurosensory hearing defects of serious degree (that is, greater than 30 decibels in the speech frequencies) were observed.[19-21] Abnormalities were present, although rare, and were confined to the higher frequencies, without clinical disability. For example, one of 40 children in one study was found to have a high frequency loss and in two of 34 children, a vestibular defect was detected.[20] There was no observable effect of the function of these children in their daily activities. The numbers are too small for statistical comparison, but the authors note that age matched Helsinki school children not exposed to SM have 3.3 to 9 percent inner ear hearing loss, depending on testing method used.

Isolated cases of varying degrees of deafness have been reported[22] as well as one case of congenital deaf mutism.[23] No other types of birth defects in conjunction with the administration of SM during pregnancy are recorded.[2,18,22]

Discussion

It is a general principle that the administration of any drugs to a pregnant patient is to be avoided, because of possible fetal damage. However, when tuberculosis complicates pregnancy, prompt and adequate antituberculous chemotherapy is mandatory. Also, pregnancy may occur during the treatment of active pulmonary tuberculosis. Under such circumstances the risk to the developing fetus must be considered in advising the expectant mother and her obstetrician.

The outcome of the administration of INH, EMB and RMP to pregnant tuberculous women (1,549 births included in Tables 1 through 3) with most cases representing multiple drug therapy, points to the safety of these three drugs throughout pregnancy. The greatest number of patients received INH so that its use can be recommended with the least reservation. Although less voluminous, the data clearly support the safety of EMB and RMP administration during preg-

nancy. Careful monitoring of liver and ocular toxicity, as is usual with any tuberculous patient receiving these drugs, is also important in pregnant women.

The 390 births to patients who received SM (Table 4) produced children with clinically minor, but definitely present auditory or vestibular damage. There seems to be a significant risk of such damage to the fetus, although controls are lacking in most studies. We would recommend that as organogenesis of the inner ear occurs at around the seventh intrauterine week, and differentiation of the cochlear cells continues up to the halfway point of pregnancy,[19] avoidance of SM during this period is particularly important. Further, high single doses and treatment of pregnant women with impairment of renal function or toxemia might be particularly deleterious. Children whose mothers have received SM in pregnancy should be checked for auditory and vestibular disturbance as early as possible, since they may be especially vulnerable to further damage upon subsequent administration of SM and other aminoglycosides.

In conclusion, the risk to the fetus from administration of INH, EMB and RMP during pregnancy is small, and the use of these agents is not contraindicated. A strong two or three drug regimen is therefore available for the treatment of tuberculosis in pregnancy. Further, the use of SM in a patient known to be pregnant can easily be avoided. If SM is used in the treatment of a nonpregnant woman in her childbearing years, she should be warned of the risk of becoming pregnant. Finally, if SM therapy has been administered to a woman during the first half of her pregnancy, a decision regarding termination of the pregnancy might be considered. A fully informed patient would presumably take into account a host of personal factors, weighing heavily the fact that defects reported with SM administration are mild. It is to be hoped that the best possible antituberculous therapy, coupled with the best possible obstetric and social outcome, would be the result of such informed deliberation.

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TABLE 4.—*Streptomycin (SM) Administration During Pregnancy*

Authors	*Births to Patients Receiving SM*	*Control Group*	*Birth Defects*		*Births to patients receiving SM with:*		
			Treated	*Controls*	*High Frequency Hearing Loss*	*Vestibular Defect*	*Clinical Disability*
Wilson et al[18]	5	..	0	..			
Lowe, CR[3]	12	173	0	7			
Jentgens, H[5]	220	432	0	0			
Varpela et al[19]	51	..	0	..	6	0	0
Varpela et al[20] ...	40	..	0	..	1	2	0
Ganguin et al[21] ...	44	..	0	..	5	..	..
Khanna et al[23]	1	..	1	..	..	..	1
Conway N[22]	17	..	2	..	4	6	0
TOTALS	390	605	3	7	16	8	1