Streptomycin ototoxicity in the unborn child

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Summary

Streptomycin has been used in pregnant patients for more than 30 years. Some doubt, however, still exists with regard to its effects on the ear of the unborn child. Thirty-three children whose mothers had received streptomycin during pregnancy were followed up and their hearing tested. A minor degree of hearing loss which could possibly be due to the action of streptomycin was found in only 2 children.

S. Afr. med. J., **60**, 316 (1981).

A pregnant patient may present with active tuberculosis requiring treatment. Despite the development of a number of new antituberculosis drugs, streptomycin sulphate (SM) continues to play an important part in the first-line treatment of tuberculosis and is often used during pregnancy.

SM is known to have toxic effects upon the inner ear, and it has been suggested that the unborn child might be more susceptible to these than the adult.[1] SM crosses the placenta,[2,3] and levels up to 50% of those found in the mother's circulation have been reached in the fetal circulation.[4] Fetal inner ear damage following the use of SM in pregnancy is therefore possible.

Watson and Stow[5] were the first to report the follow-up of children whose mothers had received SM during pregnancy. They found normal hearing and vestibular function in 2 children whose mothers had received SM and had themselves developed loss of vestibular function. Since then at least 8 reports of deafness in children whose mothers received SM or dihydrostreptomycin (DHSM) in pregnancy have appeared (Table I). Most of these children had marked loss of hearing and in 4 cases vestibular function was affected.

In contrast, follow-up of groups of children at risk from the use of SM and DHSM in pregnancy (Table II) has tended to show that loss of hearing, when found, is high-tone and outside the speech frequencies. Likewise vestibular dysfunction, when found, has not been serious and is not usually associated with any clinical disability. Despite these reports, the number of children so far followed up has been insufficient to permit any definite conclusion whether SM is in fact toxic to the fetal inner ear when given to the mother in pregnancy.

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Date received: 2 December 1980.

Subjects and methods

During the period 1960-1976, 82 Cape Coloured and 5 White patients received SM during pregnancy while being treated for tuberculosis at the City Hospital for Infectious Diseases, Green Point, Cape Town. SM was given to these patients for at least 1 month at a dosage of 1 g/d. Up to 1974, SM was without exception combined with para-aminosalicylic acid and isoniazid. Since 1974, other drugs — ethionamide, rifampicin and ethambutol — have, when indicated, been used to supplement SM.

It proved possible to trace 30 of the 87 mothers who had been treated and 33 children. They were asked to attend the Department of Otorhinolaryngology at Groote Schuur Hospital for hearing tests and routine ear, nose and throat examination; the children's ages at the time of examination ranged from 1 to 16 years.

Results

The results of the hearing tests are set out in Table III, together with details of treatment and the stage of pregnancy during

TABLE I. STREPTOMYCIN OTOTOXICITY IN THE UNBORN CHILD — CASE REPORTS

Authors	No. of cases	Affected children	Drug used	Nature of defects
Le Roux[6]*	1	1	SM	Absent otopalpebral reflex but normal caloric responses
Moulonguet (quoted by Kreibich[7])*	1	1	SM	Loss of hearing
Bolletti and Croato[8]	1	1	SM	Severe bilateral sensorineural hearing loss and deficient vestibular function
Kern[9]	1	1	DHSM	Severe bilateral sensorineural hearing loss and deficient vestibular function
Robinson and Cambon[10]	2	2	SM	Both severe bilateral sensory hearing loss and deficient vestibular function
Khanna and Bhatia[11]	1	1	SM	Congenital deaf-mutism
Sellars *et al.*[12]	1	1	SM	Profound bilateral deafness

* In 1954 Kreibich reviewed 37 reported cases in which streptomycin had been administered during pregnancy. Two of the children were found to be deaf and are the cases of Le Roux and Moulonguet mentioned above.

TABLE II. STREPTOMYCIN OTOTOXICITY IN THE UNBORN CHILD — FOLLOW-UP OF GROUPS OF CHILDREN AT RISK

Authors	No. of cases	No. of affected children: Loss of hearing	No. of affected children: Vestibular dysfunction	Drug used	Nature of defects
Rebattu *et al.*[13]	6	1	1	SM DHSM	High-tone hearing loss in both cases No clinical disability of hearing or vestibular function
Lenzi and Ancona[14]	10	3	0	SM	Mild bilateral sensorineural hearing loss
Conway and Birt[15]	17	4	6	SM DHSM	Unilateral high-tone loss outside of speech frequencies in all cases. No clinical vestibular dysfunction
Rasmussen[16]	36	2	0	SM DHSM	High-tone unilateral hearing loss in 1 case, bilateral high-tone loss, probably a result of noise trauma, in the other
Varpela *et al.*[17]	40	1	2	SM DHSM	High-tone sensorineural loss. Possible vestibular dysfunction in 1 child
Ganguin and Rempt[18]	44	5	0	SM	Only higher frequencies outside normal speech frequencies affected

In 1963 Grande and Vespa[19] reported a series of 14 children whose mothers had been treated with DHSM. Seven were found to have a degree of deafness within the speech frequencies.

TABLE III. STREPTOMYCIN OTOTOXICITY IN THE UNBORN CHILD — RESULTS OF FOLLOW-UP OF 33 CHILDREN AND 30 MOTHERS

Case No.	Details of treatment: Duration (mo.)	Details of treatment: Stage of pregnancy	Other drugs	Age at testing (yrs): Mother	Age at testing (yrs): Child	Result of hearing test: Mother	Result of hearing test: Child
1	3	3rd trimester	INH, PAS	42	16	Normal	Normal
2	1½	3rd trimester	INH, PAS	48	14	Perceptive loss in right ear (30-40 db)	Slight bilateral high-tone loss
3-7	1-5½	Various trimesters	INH, PAS	35-44	11-13	Normal	Normal
8	6	2nd and 3rd trimesters	INH, PAS	35	11	Bilateral conductive loss, right greater than left. Previous right radical mastoidectomy	Right normal, left slight high-tone loss
9	4	2nd and 3rd trimesters	INH, PAS	29	10	Normal	Normal
10	6	2nd and 3rd trimesters	INH, PAS	44	10	High-tone loss left and right	Normal
11-21	1-6	Various trimesters	INH, PAS	24-31*	5-8	Normal	Normal
22	5	2nd and 3rd trimesters	INH, PAS	31	4	Normal	Slight bilateral conductive loss. Right tympanic perforation, left tympanosclerosis
23	4	2nd and 3rd trimesters	INH, PAS	24	4	Normal	Normal
24-26	2½-3	Various trimesters	INH, ETH	25-46	4	Normal	Normal
29-31	1-4	Various trimesters	INH, EMB	19-26	1	Normal	Normal
32	2	3rd trimester	INH, RMP, EMB	26	1	Not tested	Normal
33	4	2nd and 3rd trimesters	INH, EMB	20	1	Normal	Normal
34	No streptomycin		INH, PZA, ETH, EMB, RMP	29	2½	Slight bilateral high-tone hearing loss	Slight bilateral high-tone hearing loss

* Two mothers in this group had died.
INH = isoniazid; PAS = para-aminosalicylic acid; ETH = ethionamide; EMB = ethambutol; RMP = rifampicin; PZA = pyrazinamide.

which SM had been given. Three mothers who had received SM and 3 children were found to have defective hearing. In 2 cases (cases 2 and 8) both mother and child were affected.

In case 2 the bilateral deafness of mother and child could be ascribed to the action of SM, but in case 8, while the child's unilateral defective hearing could have been due to SM, the mother's bilateral conductive hearing loss could not. SM could also be implicated in the bilateral high-tone loss of hearing of the mother in case 10, but could not have been the cause of hearing loss in the child in case 22, who had evidence of past middle ear disease.

Sixteen mothers had been treated during the 3rd trimester of pregnancy. One of the children in this group had slight bilateral high-tone hearing loss (case 2). Thirteen mothers had been treated in the 2nd and 3rd trimesters; 1 of their children had slight unilateral high-tone loss of hearing (case 8). One mother was treated in the 1st trimester only, 2 mothers in the 1st and 2nd trimesters and 1 mother for 7 months from the 1st trimester to the 3rd trimester; none of their children was found to suffer from deafness which could be ascribed to SM.

Discussion

The results of this follow-up do not differ greatly from those of previous surveys, and confirm that SM can possibly cause deafness in the unborn child when given to the mother in pregnancy. However, as in previous surveys, what deafness was found in the children was high-tone and outside the speech frequencies; the children in question were not handicapped by their defect.

Sensitivity to the ototoxic action of SM is subject to a wide range of individual variability, and in some cases has been found to be a familial trait.[20,21] It is therefore of interest to note that one mother and child pair in this survey (case 2) was found to have a degree of deafness which could possibly be ascribed to a familial susceptibility to the action of SM.

Vestibular function was not tested in these children, but none of them was noted to have any obvious disability. In a series of 17 children Conway and Birt[15] found 6 who had abnormal vestibular responses on caloric testing but not complete loss of labyrinthine function. None of the children experienced any disability in day-to-day activities. Rasmussen[16] followed up 16 children and found them all to have normal vestibular function, while in a series of 34 children Varpela *et al.*[17] found only 2 with vestibular defects. One of these was thought to have a degree of clinical disability.

The inadvisability of attributing abnormalities found in a survey such as this to the action of SM, or any other drug, is well illustrated by a further mother and child pair who were inadvertently asked to attend for testing (case 34). Both were found to suffer from high-tone deafness, but SM had not been used at all in the treatment of the mother's tuberculosis. She had received isoniazid, pyrazinamide, ethionamide, ethambutol and rifampicin.

On present evidence it would therefore appear that, when given to the mother in pregnancy in acceptable doses, SM can possibly cause a minor degree of deafness in the unborn child. The deafness, however, is usually high-tone and outside the speech frequencies. While the decision to use any drug in pregnancy should not be lightly taken, it would seem that SM may be used subject to the same considerations as would apply in a non-pregnant patient — it should therefore not be used in the presence of impaired renal function, and the performance of monthly audiograms is desirable to detect the first signs of ototoxicity, at which stage the drug should be withdrawn.

With regard to other possible toxic or teratogenic effects, SM has now been used in pregnancy for more than 30 years and in reports and reviews by a number of authors there has been very little suggestion that it has any toxic or teratogenic effects upon the fetus, other than its possible effect upon the inner ear, even when given in the early stages of pregnancy.[22-28]

The authors would like to thank Miss Janet Foxcroft of the City Hospital for Infectious Diseases for invaluable secretarial help and Dr T. Malherbe, Medical Superintendent of City Hospital, and Dr R. Coogan, Medical Officer of Health for the City of Cape Town, for permission to publish.

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