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## RESUMEN

**Objetivo:** Evaluar la asociación entre exposición a ribostamicina en etapas tempranas del embarazo y ototoxicidad en el producto. **Métodos:** 85 mujeres que estuvieron expuestas en forma inadvertida a ribostamicina durante el primer trimestre del embarazo y 170 mujeres control de edades y número de embarazos similares fueron voluntariamente incluidas en el estudio de cohorte prospectiva. Los recién nacidos fueron examinados clínicamente al nacimiento por un neonatólogo y mediante estudios de imagen en caso de que alguna posible anomalía fuera identificada. La capacidad auditiva fue evaluada mediante la respuesta auditiva del tallo cerebral. **Resultados:** Ninguno de los bebés nacidos en el grupo expuesto presentó ototoxicidad neonatal (0/70) mientras que en el grupo control hubo un caso (1/160; 0.6%) ( $P = 0.5$ ). **Conclusiones:** La exposición a ribostamicina durante el primer trimestre del embarazo no parece estar asociada con ototoxicidad neonatal. Aunque la exposición ocurrió a muy tempranas etapas del desarrollo fetal, cuando el oído interno aún no estaba desarrollado, nuestros hallazgos pueden ser útiles para dar el consejo adecuado a mujeres expuestas en forma inadvertida a este aminoglucósido en etapas tempranas del embarazo.

### Palabras clave

Aminoglucósidos; Exposición materna; Exposición transplacentaria

## INTRODUCTION

Ribostamycin is an aminoglycoside antibiotic used to treat infections caused by gram-negative organisms such as *Neisseria gonorrhoeae*, *Escherichia coli*, *Klebsiella* spp., and *Proteus* spp. [1]. It has similar efficacy and reduced ototoxicity when compared to other major aminoglycosides [2]. It is primarily used to treat infections such as pelvic inflammatory disease (PID), cystitis, and severe upper respiratory tract infections (URTI), and is administered intramuscularly, once a day, at doses of 500-1,000 mg [3].

Approximately four decades ago, a study in 17 children between the age of 6 and 13 years whose mothers had received streptomycin during pregnancy reported that although there was no apparent deafness at speech frequencies, 8 children had minor abnormalities of eighth-nerve function on caloric test or audiograms [4]. In addition, two cases of congenital deafness after *in utero* exposure to gentamicin 80 mg three times daily for two days and to 100 mg three times a day for a single day, respectively, have been reported elsewhere [5] [6]. In contrast, a recent study in 40 infants who were exposed *in utero* to gentamicin documented no case of hearing loss [7].

The present study was conducted to investigate a potential association between inadvertent exposure to ribostamycin in early pregnancy with adverse fetal outcomes and ototoxicity in the offspring. The first part of the study assessing major and minor malformations of babies born to exposed women was submitted for publication elsewhere [8]; the current paper assessed the potential ototoxicity in the offspring.

## METHODS

The protocol was approved by the Institutional Review Board at Cheil General Hospital and Women's Healthcare Center, Seoul, Korea; the study was performed between January 1999 and February 2008 at the Korean Motherisk Program.

### Subjects

Pregnant women who were inadvertently exposed to ribostamycin were invited to participate into the study; 85 women were enrolled. Pregnancy was confirmed by transvaginal ultrasound examination. In all cases, fetal age was estimated according to the somatometric results of the transvaginal ultrasound examination, and the time of exposure to ribostamycin was calculated accordingly. In addition, a large group of pregnant women who were not exposed to any aminoglycoside or to any known or potential human teratogen were followed-up prospectively as potential controls. From this group, two consenting controls were enrolled for each case, after matching for age ( $\pm 2$  years that of the control) and gravidity.

### Study outcomes

As a marker of ototoxicity, hearing was assessed in the newborns with the automated auditory brainstem response (AABR) method ALGO 1 (Natus Medical Inc., San Carlos CA, USA) [9]. The system delivered thousands of soft 'click' sounds at 35 dB within a normal hearing level (normal acoustic frequency spectrum: 70 to 5,000 Hz) through disposable earphones in order to evoke a series of identifiable brain waves from auditory brainstem. All infants with abnormal AABR results were reexamined 1-2 days later. Infants with repeated abnormal test results were referred to a tertiary care center for further evaluation.

### Statistical analysis

Continuous variables including gestational age at birth (weeks) and birth weight (grams), were compared between groups by a Student t test. The rate of babies with altered hearing test ototoxicity was compared between groups by means of a

Fisher's exact test. A  $P < 0.05$  was considered as statistically significant.

## RESULTS

We recruited 85 pregnant women who were inadvertently exposed to ribostamycin at the  $3.9 \pm 1.5$  (mean  $\pm$  SD) weeks of gestation (median: 4.1 weeks) at a dose ranging from 250 mg to 1 g per

day (mean duration of exposure: 2.4 days) (Table 1). In the exposed group, there were 85 births (83.3%), 6 spontaneous abortions (5.9%), 8 voluntary abortions (7.8%), 1 ongoing pregnancy (1.0%) and 2 cases were lost to follow-up (2.0%).

**Table 1** Maternal characteristics, dose and duration of exposure to ribostamycin in pregnancy, and fetal outcome

	Exposed (n= 85)	Control (n= 170)	P value
Age (years)	$30.6 \pm 3.0$	$31.0 \pm 3.2$	0.4
Gestational age at exposure (weeks)	$3.9 \pm 1.5$ (range: 0.5 - 8.0)	-	-
Dose of ribostamycin (mg/day)	250 - 1,000	-	-
Duration of exposure (days)	$2.4 \pm 2.6$	-	-
Ototoxicity in neonates/infants	0/70	1/160 (0.6%)	0.5

The AABR test for hearing ability was obtained in 70 infants in the exposed group and 160 infants in the control group. The test was performed at postnatal age between one to five days. Only one infant (0.6%) had an abnormal test in the control group compared to none in the exposed group (Table 1). We were not able to assess the AABR hearing test in 15 infants from the exposed group and 10 from the control group.

## DISCUSSION

This appears to be the first prospective cohort study to examine the hearing outcome of infants exposed to ribostamycin in early pregnancy. The rate of hearing impairment in general population is approximately 1 to 2 per 1,000 uncomplicated births [10]; however, in infants at risk, the prevalence of neonatal hearing disorders may increase 10- to 50-fold. At the Cheil General Hospital in Seoul, the calculated incidence of abnormal hearing tests is 4.5 per 1,000 healthy babies. Hearing loss is associated with exposure to other ototoxic drugs (e.g. furosemide, indomethacin, or ibuprofen) [7] [10], genetic disorders such as Turner syndrome or osteogenesis imperfecta [11], intrauterine infections such as rubella or toxoplasmosis [10] [11], or exposure to alcohol or cocaine [11]. Prematurity, craniofacial malformations, hyperbilirubinemia, hypoxia, bacterial infections, mumps, low Apgar scores, and low birth weight can also be associated with hearing deficits [4] [10] [11].

The AABR test has a sensitivity of 98% and specificity of approximately 96% and have proved

to be an effective screening tool in evaluation of hearing in the newborns [9] [10] [12] [13] [14] [15]. According to the previous reports [16], aminoglycoside induced ototoxicity leads to permanent bilaterally severe, high-frequency sensorineural hearing loss and temporary vestibular hypofunction accompanied by degeneration of hair cells and neurons in the cochlea of the internal ear. The onset of development of otic placode occurs on 24th day of fetal development (38th gestational age, or 5th gestational week). However, the onset of otic invagination occurs on the 30th day of fetal development, while the onset of development of otic vesicle is on the 34th day of gestation age [17]. The target of aminoglycoside toxicity is the hair cells of cochlea which starts to develop after the 34th day of organogenesis, i.e. after the 48th gestational day (at the end of 6th gestational week).

In our study, the mean gestational age at exposure was approximately 4 weeks, at a time when the development of inner ear has not yet started. Therefore, our results cannot be extrapolated to women requiring anti-infective treatment at later stages of fetal development. Treatment with other antimicrobials with proven safety and efficacy in pregnancy should still be preferred over ribostamycin. However, our study is relevant for counseling women who were inadvertently exposed to this drug at early stages of pregnancy in order to avoid unnecessary pregnancy terminations and to reduce the level of anxiety because of the exposure.

## CONCLUSIONS

Exposure to ribostamycin during the first-trimester of pregnancy does not appear to be associated with ototoxicity in the offspring. Although exposure occurred at very early stages of fetal development, when the inner ear was not yet developed, our findings may be valuable when counseling women inadvertently exposed to this aminoglycoside in early pregnancy.

## AUTHORS' PARTICIPATION

SW L, JY H, HJ L & JS C provided teratogenic risk counseling and reviewed the literature. HK A, MH K, & HM R did the medical and obstetrical follow-up of participants, JY H, AA N-O, & G K designed the study. All the authors drafted the manuscript and discussed findings.

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None to declare.

## CONFLICT OF INTERESTS/DISCLAIMERS

JY H, AA N-O, and G K are members of the Editorial Board of the journal. The study was not supported in any form by any pharmaceutical company.

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