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Congenital Absence of Salivary Glands in Fetuses with Trisomy 21

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ABSTRACT: **Background:** The congenital absence of salivary glands has been reported in children but never in fetuses with trisomy 21.
Objectives: To determine whether the congenital absence of salivary glands can be detected prenatally between 13 and 16 weeks of gestation in normal and trisomy 21 fetuses using transvaginal ultrasound.
Methods: We performed a retrospective analysis of recordings of normal and trisomy 21 fetuses. Inclusion criteria were a single viable fetus and good visualization of the anatomic area of the salivary glands on both sides of the fetal face. All videos were reviewed by one examiner who reported the presence or absence of one or more salivary glands and was blinded to the fetal karyotype.
Results: Of the 45 videos reviewed, 4 were excluded from the study: namely, a non-viable fetus, a twin pregnancy, and in 2 there was unsatisfactory visualization of the anatomic area of the salivary glands. Of the remaining 41 fetuses, 24 had trisomy 21 and 17 were normal. In the trisomy 21 fetuses, 8 (33.3%) had congenital absence of one or more salivary glands compared to 1 of 17 normal fetuses (5.9%) ($P < 0.05$).
Conclusions: Congenital absence of the salivary glands has a high specificity but low sensitivity for detecting trisomy 21 fetuses.

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KEY WORDS: congenital absence, salivary glands, Down syndrome, trisomy 21, ultrasound, prenatal diagnosis

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We recently reported the congenital absence of one or more salivary glands in children with trisomy 21 [1]. Congenital absence of one or more salivary glands has been reported in both normal and trisomy 21 children [2,3]. In trisomy 21 there are also differences in the composition of the saliva, with higher protein and sodium concentrations, and lower flow rate, amylase and peroxidase activities and potassium concentration [4]. We have shown that sonographic detection of the salivary glands is possible as early as 14–16 weeks of gestation [5]. We therefore undertook this study to determine whether congenital absence of salivary glands can be detected prenatally in fetuses with trisomy 21.

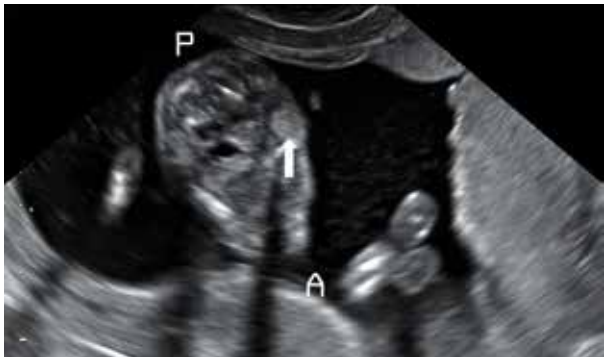
PATIENTS AND METHODS

We performed a retrospective analysis of video sonographic recordings of normal and trisomy 21 fetuses. The examiner was blind to the karyotype of the fetuses. Only recordings with a single viable fetus and good visualization of the anatomic area of the salivary glands on both sides of the fetal face were included in the study. As described elsewhere [5], the salivary glands can be viewed as echogenic structures medial to the external ear (the parotid gland) and further medial and also inferior to it (the submandibular gland) [Figures 1 and 2]. The sublingual glands cannot be demonstrated by ultrasound because they are actually a group of small salivary glands located beneath the tongue, whereas the parotid and submandibular glands are large solitary glands. Video recordings were arbitrarily chosen by the sonographer (M.B.) from his database and included normal fetuses with normal scan, fetuses with normal karyotype but with major and minor sonographic findings, and normal scans of fetuses with Down syndrome and minor and major sonographic findings, in order to assure the blindness of the examiner of the video recordings (M.O.) to the fetal karyotype. All videos were reviewed by one examiner (M.O.) who reported the presence or absence of one or more of the salivary glands. The karyotype was later disclosed by the physician (M.B.) who performed and recorded all examinations. All examinations were performed between 13 and 16 weeks of gestation using a Philips IU 22 3-9 MHZ transvaginal probe (Bothell, WA, USA). Most of the reviewed cases, with either trisomy 21 or normal karyotype, had several sonographic findings ("soft signs") or major malformations; few had a completely normal scan [Table 1]. All videos were chosen by the attending physician who intentionally included recordings with soft signs and major malformations as well as normal scans. When all salivary glands were visualized the review of the remaining recording was discontinued, thus some fetuses may have had other sonographic findings that were not detected.

STATISTICAL ANALYSIS

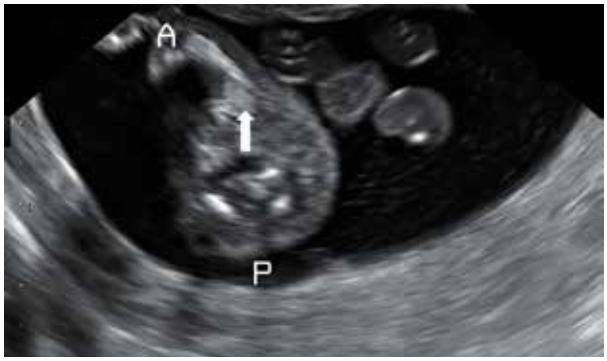
Fisher's exact test was used to compare the two groups, and $P < 0.05$ was considered significant.

Figure 1. The parotid gland (arrow) as observed in a fetus with normal karyotype



A = anterior, *P* = posterior

Figure 2. The submandibular gland (arrow) as observed in a fetus with normal karyotype



A = anterior, *P* = posterior

Table 1. Sonographic findings in fetuses with trisomy 21, with and without presence of all salivary glands

	Cervical cysts	Nuchal edema	Congenital heart malformation	Echogenic focus left ventricle	Tricuspid regurgitation	Pylectasis	Other findings	Normal scan
Trisomy 21 without congenital absence (n=16)	3 (18.7%)	6 (37.5%)	2 (12.5%)	6 (37.5%)	0	1 (6.3%)	1 (6.3%)	5 (31.3%)
Trisomy 21 with congenital absence (n=8)	5 (62.5%)	7 (87.5%)	0	1 (12.5%)	1 (12.5%)	1 (12.5%)	0	1 (12.5%)

RESULTS

Of the 45 videos reviewed, 4 were excluded from the study: 1 was a non-viable fetus, 1 a twin pregnancy and the other 2 were excluded because of unsatisfactory visualization of the anatomic area of the salivary glands. Of the remaining 41 fetuses, 24 had trisomy 21 and 17 had a normal karyotype. The genotype of all cases was determined by amniocentesis. Among the trisomy 21 fetuses, 8 (33.3%) had congenital absence of one or more salivary glands [Figures 1 and 2] compared to 1 of 17 normal fetuses (5.9%). The difference was statistically significant ($P < 0.05$). The submandibular gland was absent on both sides in six fetuses and only on one side in two. The parotid gland was missing in one fetus on one side, and in two fetuses the parotid glands on both sides were remarkably small but considered present. Table 1 shows additional sonographic findings in trisomy 21 fetuses without congenital absence of the salivary glands, compared to trisomy 21 fetuses with one or more absent salivary glands. This table was constructed in order to show the sonographic findings in fetuses with trisomy 21. We had no intention of determining the prevalence of sonographic findings in trisomy 21 fetuses.

DISCUSSION

To the best of our knowledge this the first report of congenital absence of the salivary glands in fetuses with Down's syndrome. The absence of salivary glands in children with Down's syndrome was reported by us earlier; we found that 28% of children with Down syndrome have congenital absence of at least one salivary gland [1]. One might argue that in some cases the absence of the salivary gland(s) may be due to acquired atrophy, rather than being congenital, but such absence has been reported in newborns with trisomy 21. This study confirms that the absence of the salivary glands is congenital in most cases. Moreover, in the current study the prenatal examiner was blinded to the karyotype, while the postnatal examiner could not be blinded to the syndrome manifestations for obvious reasons. The similarity between the two studies regarding the percentage of congenital absence of the salivary glands, i.e., 28% in trisomy 21 children [1] and 33% in trisomy 21 fetuses (in the current study) supports these findings.

Almost all examined fetuses had other sonographic findings, except for four fetuses that had a normal scan; of those, one had normal karyotype and three had trisomy 21. These recordings were intentionally included by the attending physician who chose normal and trisomy 21 fetuses with both soft signs and major malformations to ensure that the examiner could not tell or guess which fetus had trisomy 21. Thus, the blinding of the examiner was ensured by not knowing the karyotype and by not assuming the karyotype based on sonographic findings. Table 1 shows the findings in trisomy 21 fetuses with and without congenital absence of the salivary glands.

The weakness of our study is the lack of pathologic or postpartum confirmation of the absence or presence of the salivary glands due to the retrospective nature of the study. However,

due to the rarity of congenital absence of the salivary glands, our findings, although unconfirmed, are significant. This issue should be evaluated in a large prospective study.

Detection of the salivary glands as early as 14–16 weeks of gestation [5], and the fact that these glands are absent in about 28% of children with trisomy 21 [1] and in 33% of fetuses with trisomy 21 (as shown in this study), support the feasibility of using this finding for prospectively detecting fetuses at risk for trisomy 21.

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