Prenatal Diagnosis of Craniomaxillofacial Malformations: A Characterization of Phenotypes in Trisomies 13, 18, and 21 by Ultrasound and Pathology

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Objective: To determine the relationship between trisomies 13, 18, and 21 and craniofacial malformations detected by prenatal sonography.

Design: During a 29-year period (1976 through 2004), prenatal sonographic findings of 69 fetuses with trisomy 13; 171 fetuses with trisomy 18; 302 fetuses with trisomy 21; and 17 fetuses with other trisomies were evaluated retrospectively, after fetal karyotype identification. Sonographic findings were compared with autopsy results in 209 patients (trisomy 13, n = 39; trisomy 18, n = 64; and trisomy 21, n = 106).

Results: For trisomy 13, cleft deformities were detected prenatally in 65.2%, and of the 39 cases with pathological information, 76.9% were found to have a cleft deformity. Ocular and orbital abnormalities were found in 28%. Malformations of the jaws and abnormal profiles were more frequently diagnosed postnatally than prenatally. For trisomy 18, abnormal profiles (41.5%) and ear abnormalities (5.3%) were the most noticeable ultrasound markers, next to abnormalities of the neurocranium (36.8%) and cranial bone configuration (21.6%). Dysmorphisms of the eye, ear, or nose were detected more frequently in autopsy cases. For trisomy 21, ultrasound showed an aberrant shape of the skull in 14.2% of fetuses. In general, the ocular-orbital and nasal abnormalities in fetuses with trisomy 18 or 21 were more evident in pathological examination than in prenatal ultrasound imaging.

Conclusions: Facial anomalies are common in the major trisomies, and their prenatal sonographic identification should be improved. The above-mentioned facial anomalies provide sufficient reason to consider performing cytogenetic evaluation.

KEY WORDS: *facial malformations, fetal aneuploidy, prenatal sonography, trisomy*

Trisomies 21, 18, and 13 are the most commonly diagnosed autosomal trisomies in liveborn infants. Although these conditions are associated with a high degree

of infant mortality, longer survival, especially in the case of trisomy 21, is quite common nowadays (Rasmussen et al., 2003).

Each trisomic condition has a typical phenotype that nevertheless shows a wide variation in phenotypic expression. However, the face in particular plays an important role in defining the phenotype. Facial abnormalities are, for example, quite common among fetuses with trisomy 21. In 2002, Sonek and Nicolaides reported three cases of trisomy 21 with an absence of or shorter nasal bone than would be expected for the gestational age (Sonek and Nicolaides, 2002). Trisomy 18 is associated with typical facial abnormalities such as short ear length, an abnormal profile, micrognathia, and hypotelorism (Yeo et al., 2003). Also, facial abnormalities due to holoprosencephaly as well as different types of facial clefts as typical signs of trisomy 13 have been described (Nicolaides et al., 1993b; Nyberg and Souter, 2001). With the improving quality of ultrasound equipment and standards of scanning, craniofacial dysmorphisms are more likely to be detected, even by routine ultrasound examination.

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TABLE 1 Screening Index of Markers for Detecting Trisomies 13, 18, and 21

Abnormal skull	Facial clefts, cleft lip, or cleft palate
Macrocephaly or microcephaly	Median cleft
Brachycephaly	Microstomia
Strawberry skull	Ocular or orbital abnormalities
Polyhydramnion*	Anophthalmia
Abnormal neurocranium	Microphthalmia
Holoprosencephaly	Hypotelorism or hypertelorism
Hydrocephalus	Nasal abnormalities
Choroid plexus cysts	Single nostril
Nuchal edema or translucency	No nasal bone
Facial defects	Ear abnormalities
Flat forehead	Retrocaudal positioning of the ears
Flat or abnormal profile	Low-set ears or small ears
Micrognathia	Cardiac abnormality*
Macroglossia	

* Not included in this study.

The aim of this study was to determine the relationship between major trisomic conditions and prenatally detected craniofacial malformations.

PATIENTS AND METHODS

The patients were recruited at the Department of Obstetrics and Gynecology, Division of Prenatal Diagnosis and Therapy in a Level III hospital from 1976 through 2004. During the study period, 559 fetuses with trisomies 21 ($n = 302$), 18 ($n = 171$), 13 ($n = 69$), and others ($n = 17$) were evaluated sonographically according to an index of facial and cranial markers for detecting trisomies (Table 1). Postnatal autopsies were performed in a subset of 209 fetuses. All the cytogenetic and ultrasound records of these fetuses were reviewed and analyzed retrospectively. In the first years of the study, besides sonographic examination, the patients underwent an amniocentesis between gestational weeks 12 and 39 in order to determine the fetal karyotype. Since 1987, the techniques of cordocentesis and placental biopsy also have been used.

Examination of the fetal face was done by a transabdominal ultrasound technique and performed by well-trained obstetricians. Different types of ultrasound systems equipped with different transducers were used (e.g., the Sonoline SL 1 and 2 [Siemens AG, Erlangen, Germany]; Acuson 128 [3.5-MHz linear-array transducer], Acuson Aspen [5- to 7-MHz variable-focus transducer], and Acuson Sequoia 512 [5- to 8-MHz sector probes, linear; Acuson Corp., Mountain View, CA]; color doppler ultrasound HDI 5000 [Philips, type ATL, Bothell, WA]; Kretz Combison 530 D [5.0-MHz annular array transducer; Kretztechnik, Zipf, Austria]; Examination of the face always included the midsagittal view for profile analysis and serial axial scans at the level of the forehead, eyes, nose, and upper and lower lips (Hansmann et al., 1991).

The sonograms (usually reports, videotapes, digital data media, and thermal prints) of each case were evaluated for the nature of facial dysmorphism and associated anomalies. If the circumference of the head was below the fifth

percentile for the corresponding gestational age, microcephaly was diagnosed. The diagnosis of hydrocephalus was based on an evaluation of the posterior horn of a lateral ventricle. Nuchal edema of more than 3 mm in the first trimester was regarded as pathological, and, in the case of profound retrognathia, the diagnosis of micrognathia was made without precise measurements. Positioning of the tongue between the lips during most of the time of the ultrasound examination was regarded as macroglossia.

In the case of microphthalmia, the diameter of the eye was smaller than reference values (Hansmann et al., 1991). Hypotelorism was defined as a decreased interocular distance of more than one diameter of the orbita.

The data were obtained by review of the charts, sonograms, and pathological and cytogenetic records. Sonographic data were compared with the autopsy data in case of interruption or neonatal death or with the postnatal clinical findings and detailed information obtained from medical records of the newborn child.

This protocol was approved by our institutional review board, and informed consent was obtained from each patient.

RESULTS

In cases of fetal trisomy, 69 fetuses with trisomy 13 (12.3%); 171 fetuses with trisomy 18 (30.6%); and 302 fetuses with trisomy 21 (54.0%) were found. Seventeen cases (3.0%) showed other, less common trisomies. Thirty-six, 259, and 264 fetuses were scanned in the periods 1976 through 1983, 1984 through 1992, and 1993 through 2004, respectively. The median gestational age at the time of sonographic examination was 22 (range, 12 to 35) weeks. The mean $\pm$ SD maternal age was 33 ± 5 years for trisomy 13; 32 ± 6 years for trisomy 18; and 36 ± 5 years for trisomy 21.

Trisomy 13 ($n = 69$)

On detailed ultrasonographic examination, 20 of the 69 fetuses with trisomy 13 showed abnormalities of the shape of the skull such as microcephaly ($n = 10$, 14.5%), brachycephaly ($n = 9$, 13.0%), or a strawberry-shaped head ($n = 4$, 5.8%). In 28 cases (40.6%) an abnormal neurocranium was detected, together with holoprosencephaly ($n = 16$, 23.2%) or hydrocephalus ($n = 13$, 18.8%) (Table 2).

Eighteen fetuses had a flat profile (26.1%), and eight fetuses (11.6%) showed micrognathia. Facial clefts were observed in 45 cases (65.2%), with a predominance of cleft lip and palate in 36 fetuses (52.2%). Sonographic examination revealed ocular and orbital abnormalities in 21 fetuses, most frequently microphthalmia ($n = 15$, 21.7%), followed by hypotelorism and hypertelorism ($n = 4$, 5.8% each). Using ultrasound only, nasal defects were detected in 13.0% ($n = 9$) and ear malformations in 4.3% ($n = 3$) (Table 3).

Among the 39 fetuses with trisomy 13 in which an autopsy was performed, 33.3% ($n = 13$) had an abnormal

TABLE 2 Frequency of Abnormal Sonographic (Sono) and Pathological (Patho) Cranial Findings in Fetuses With Aneuploidy

Finding	Trisomy 13				Trisomy 18				Trisomy 21			
	Sono (n = 69)		Palho (n = 39)		Sono (n = 171)		Patho (n = 64)		Sono (n = 302)		Patho (n = 106)	
	n (%)	GA* (mean ± SD)	n (%)	GA (mean ± SD)	n (%)	GA (mean ± SD)	n (%)	GA (mean ± SD)	n (%)	GA (mean ± SD)	n (%)	GA (mean ± SD)
Abnormal shape of the skull	20 (29.0)	26 ± 7	14 (35.9)	23 ± 6	37 (21.6)	24 ± 6	33 (51.6)	25 ± 6	43 (14.2)	19 ± 4	81 (76.4)	21 ± 5
Brachycephaly	9 (13.0)	25 ± 7	6 (15.4)	24 ± 5	17 (9.9)	23 ± 5	7 (10.9)	21 ± 4	42 (13.9)	19 ± 4	71 (67.0)	20 ± 4
Strawberry skull	4 (5.8)	22 ± 8	—	—	14 (8.2)	22 ± 4	1 (1.6)	19	0 (0)	—	2 (1.9)	—
Microcephaly	10 (14.5)	29 ± 4	10 (25.6)	23 ± 7	9 (5.3)	28 ± 9	5 (7.8)	29 ± 8	1 (0.3)	17	10 (9.4)	20 ± 3
Abnormal neurocranium	28 (40.6)	23 ± 7	11 (28.2)	23 ± 6	63 (36.8)	23 ± 6	28 (43.8)	24 ± 6	22 (7.3)	20 ± 4	10 (9.4)	21 ± 4
Holoprosencephaly	16 (23.2)	21 ± 7	10 (25.6)	23 ± 7	1 (0.6)	24	1 (1.6)	20	1 (0.3)	25	1 (0.9)	26
Hydrocephalus	13 (18.8)	25 ± 7	0 (0)	—	13 (7.6)	27 ± 5	2 (3.1)	23 ± 2	5 (1.7)	22 ± 4	0 (0.0)	—
Choroid plexus cysts	—	—	—	—	32 (18.7)	20 ± 4	3 (4.7)	22 ± 8	8 (2.6)	17 ± 2	2 (1.9)	20 ± 0
Nuchal edema	13 (18.8)	16 ± 5	2 (5.1)	15 ± 3	26 (15.2)	15 ± 4	4 (6.3)	21 ± 6	69 (22.8)	17 ± 4	25 (23.6)	19 ± 3

* The mean GA in the Sono column refers to mean gestational age at ultrasound; in the Patho column it refers to autopsy; – indicates no patient data.

shape of the skull, and 25.6% (n = 10) had holoprosencephaly. High incidences of flat profile (n = 29, 74.4%) and facial clefts (n = 30, 76.9%) were found, including 23 (59.0%) fetuses with cleft lip and palate. Ocular-orbital and nasal abnormalities were each found in 11 fetuses (28.2%) and ear malformations were found in five (12.8%).

Trisomy 18 (n = 171)

Thirty-seven fetuses with trisomy 18 (21.6%) showed abnormalities of the shape of the skull, including brachycephaly (n = 17, 9.9%), strawberry-shaped skull (n = 14, 8.2%), and microcephaly (n = 9, 5.3%).

The incidence of a flat profile was 41.5% (n = 71), clearly more frequent ($p = .025$, χ^2 test) than in trisomy 13 (26.1%) (Tables 2 and 3). Sonographic micrognathia was found in 35 fetuses (20.5%). Thirteen (7.6%) of the fetuses were suspected prenatally to have a cleft lip and palate, whereas ocular (n = 7, 4.1%), nasal (n = 5, 2.9%), and ear abnormalities (n = 9, 5.3%) were rarely found.

Among the 64 fetuses (37.4%) who underwent autopsy, 33 (51.6%) showed abnormalities of the shape of the skull, and 28 (43.8%) had an abnormal profile; 10 fetuses (15.6%) presented with a flat forehead, and 17 (26.6%) showed a vertical forehead. A flat occiput was described in 15.6% (n = 10). Fetal cleft lip and palate was identified postnatally in 19 fetuses (29.7%) (Table 3). In contrast with ultrasound findings, 48 fetuses (75.0%) showed abnormal anatomical ocular and orbital findings. Forty-seven fetuses (73.4%) were diagnosed with ear malformation, and 41 fetuses (64.1%) with nasal malformation. Autopsy data revealed micrognathia in 32 fetuses (50%); whereas, microstomia was diagnosed in 27 cases (42.2%).

Trisomy 21 (n = 302)

Brachycephaly was diagnosed prenatally in 42 fetuses (13.9%). Besides a flat profile in 29.1% (n = 88), nuchal edema (n = 69, 22.8%) was a frequent marker for trisomy 21. Sonographically detected ocular-orbital abnormalities and nasal malformations were rare, with 13 occurrences (4.3%) each, and ear malformations (n = 1, 0.3%) were very rare. Macroglossia (n = 7) and micrognathia (n = 7) were observed ultrasonographically in 2.3% of the fetuses and facial clefts in 1% (n = 3).

Pathological and postnatal clinical examination (n = 106, 35.1%) revealed an abnormally shaped skull in 81 cases (76.4%), with a majority of brachycephaly (n = 71, 67.0%). Fifty-five (51.9%) had a flat profile, 17 (16.0%) micrognathia, and 41 (38.7%) macroglossia. Nuchal edema could be observed in 25 fetuses (23.6%).

In contrast to sonographic indications, evaluation of the macroscopic anatomy showed a high percentage of ocular-orbital (n = 91, 85.8%), nasal (n = 84, 79.2%), and ear malformations (n = 41, 38.7%). Among these malformations, hypertelorism (n = 81, 76.4% versus n = 4, 1.3% in

TABLE 3 Frequency of Abnormal Sonographic (Sono) and Pathological (Patho) Facial Findings in Fetuses With Aneuploidy

Finding	Trisomy 13				Trisomy 18				Trisomy 21			
	Sono (n = 69)		Patho (n = 39)		Sono (n = 171)		Patho (n = 64)		Sono (n = 302)		Patho (n = 106)	
	n (%)	GA* (mean ± SD)	n (%)	GA (mean ± SD)	n (%)	GA (mean ± SD)	n (%)	GA (mean ± SD)	n (%)	GA (mean ± SD)	n (%)	GA (mean ± SD)
Facial defects												
Flat profile	18 (26.1)	23 ± 7	29 (74.4)	25 ± 8	71 (41.5)	23 ± 6	28 (43.8)	26 ± 1	88 (29.1)	19 ± 4	55 (51.9)	23 ± 6
Micrognathia	8 (11.6)	22 ± 7	3 (7.7)	23 ± 7	35 (20.5)	22 ± 5	32 (50.0)	24 ± 7	7 (2.3)	19 ± 2	17 (16.0)	22 ± 5
Macroglossia	0 (0.0)	—	0 (0.0)	—	0 (0.0)	—	1 (1.6)	29	7 (2.3)	22 ± 7	41 (38.7)	22 ± 6
Abnormal mid/lower face	—	—	28 (71.8)	25 ± 8	—	—	8 (12.5)	25 ± 7	—	—	9 (8.4)	27 ± 7
Facial clefts	45 (65.2)	22 ± 7	30 (76.9)	25 ± 8	14 (8.2)	26 ± 9	22 (34.4)	27 ± 7	3 (1.0)	22 ± 9	17 (16.0)	22 ± 6
Median cleft	9 (13)	24 ± 8	7 (17.9)	22 ± 3	1 (0.6)	29 ± 0	3 (4.7)	36 ± 5	1 (0.3)	13	1 (0.9)	19
Cleft lip and palate	36 (52.2)	22 ± 7	23 (59)	25 ± 8	13 (7.6)	26 ± 9	19 (29.7)	26 ± 6	2 (0.7)	27 ± 11	16 (15.1)	29 ± 9
Ocular abnormalities	21 (30.4)	26 ± 7	11 (28.2)	24 ± 6	7 (4.1)	29 ± 9	48 (75.0)	25 ± 7	13 (4.3)	20 ± 7	91 (85.8)	21 ± 5
Microphthalmia	15 (21.7)	26 ± 7	5 (12.8)	23 ± 2	1 (0.6)	37 ± 0	4 (6.3)	27 ± 10	0 (0.0)	—	3 (2.8)	18 ± 4
Hypotelorism	4 (5.8)	28 ± 6	5 (12.8)	25 ± 9	2 (1.2)	30 ± 2	42 (65.6)	23 ± 5	1 (0.3)	26	0 (0)	—
Hypertelorism	4 (5.8)	25 ± 8	3 (7.7)	25 ± 6	1 (0.6)	27 ± 0	1 (1.6)	39	4 (1.3)	15 ± 2	81 (76.4)	21 ± 5
Nasal abnormalities	9 (13.0)	21 ± 7	11 (28.2)	28 ± 7	5 (2.9)	23 ± 6	41 (64.1)	24 ± 6	13 (4.3)	18 ± 3	84 (79.2)	21 ± 5
Minor	4 (5.8)	18 ± 3	4 (10.3)	26 ± 8	4 (2.3)	23 ± 7	37 (57.8)	24 ± 6	13 (4.3)	18 ± 3	31 (29.2)	20 ± 5
Major	5 (7.2)	24 ± 8	7 (17.9)	31 ± 4	1 (0.6)	21 ± 0	4 (6.3)	25 ± 7	0 (0.0)	—	53 (50.0)	20 ± 6
Single nostril	1 (1.4)	22	0 (0.0)	—	1 (0.6)	—	0 (0.0)	—	0 (0.0)	—	0 (0.0)	—
No nasal bone	3 (4.3)	29 ± 4	7 (17.9)	31 ± 4	0 (0.0)	21 ± 0	4 (6.3)	23 ± 9	0 (0.0)	—	1 (0.9)	—
Ear abnormalities	3 (4.3)	33 ± 1	5 (12.8)	24 ± 7	9 (5.3)	33 ± 4	47 (73.4)	25 ± 6	1 (0.3)	13	41 (38.7)	21 ± 6
Retrocandal positioning	—	—	—	—	—	—	20 (31.3)	26 ± 7	—	—	19 (17.9)	24 ± 6
Small ears	—	—	—	—	—	—	14 (21.9)	24 ± 6	—	—	12 (11.3)	22 ± 4
Low-set ears	1 (1.4)	33	3 (7.7)	28 ± 7	4 (2.3)	32 ± 4	31 (48.4)	24 ± 6	1 (0.3)	13	23 (21.7)	20 ± 7

* The mean GA in the Sono column refers to mean gestational age at ultrasound; in the Patho column it refers to autopsy; — indicates no patient data.

TABLE 4 Comparison of Ultrasound Diagnosis With Pathological Result Among the 209 Cases in Which Pathological Follow-Up Information Was Available*

Finding	False Negative, n (%)	False Positive, n (%)	True Negative, n (%)	True Positive, n (%)	Sensitivity (%)	Specificity (%)
Shape of the skull	41 (19.6)	21 (10.0)	61 (29.2)	86 (41.2)	67.7	74.4
Brachycephaly	71 (34.0)	17 (8.1)	107 (51.2)	14 (6.7)	16.5	86.3
Strawberry skull	1 (0.5)	6 (2.9)	201 (96.1)	1 (0.5)	50.0	97.1
Microcephaly	19 (9.1)	4 (1.9)	182 (87.1)	4 (1.9)	17.4	97.9
Abnormal neurocranium	19 (9.1)	26 (12.4)	135 (64.6)	29 (13.9)	60.4	83.9
Holoprosencephaly	4 (1.9)	2 (1.0)	195 (93.3)	8 (3.8)	66.7	99.0
Hydrocephalus	1 (0.5)	14 (6.7)	192 (91.8)	2 (1.0)	66.7	93.2
Choroid plexus cysts	1 (0.5)	17 (8.1)	187 (89.5)	4 (1.9)	80.0	91.6
Nuchal edema	19 (9.1)	33 (15.8)	145 (69.4)	12 (5.7)	38.7	81.5
Facial defects						
Flat profile	70 (33.5)	26 (12.4)	65 (31.1)	48 (23.0)	40.7	71.4
Micrognathia	45 (21.5)	11 (5.3)	146 (69.9)	7 (3.3)	13.5	93.0
Macroglossia	40 (19.1)	1 (0.5)	167 (79.9)	1 (0.5)	2.4	99.4
Facial clefts						
Median cleft	5 (2.4)	2 (1.0)	196 (93.7)	6 (2.9)	54.6	99.0
Cleft lip and palate	17 (8.1)	5 (2.4)	154 (73.7)	33 (15.8)	66.0	96.9
Ocular abnormalities						
Microphthalmia	9 (4.3)	9 (4.3)	189 (73.7)	2 (1.0)	18.2	95.5
Hypotelorism	5 (2.4)	5 (2.4)	198 (90.4)	1 (0.5)	16.7	97.5
Hypertelorism	126 (60.3)	5 (2.4)	75 (35.9)	3 (1.4)	2.3	93.8
Nasal abnormalities						
Minor nasal abnormalities	11 (52.6)	6 (2.9)	89 (42.6)	4 (1.4)	3.5	93.7
Major nasal abnormalities	9 (4.3)	5 (2.4)	192 (91.9)	3 (1.9)	25.0	97.5
Single nostril	0 (0.0)	0 (0.0)	209 (100.0)	0 (0.0)	—	100.0
No nasal bone	1 (0.5)	0 (0.0)	172 (82.3)	36 (17.2)	97.3	100.0
Ear abnormalities						
Low-set ears	57 (27.3)	1 (0.5)	151 (72.2)	0 (0.0)	0.00	99.3

* — indicates no patient data available.

ultrasound) and mongoloid palpebral fissures ($n = 43$, 41.7% versus $n = 5$, 1.7% in ultrasound) were noted frequently; whereas, retrocaudally positioned ears ($n = 19$, 17.9% versus $n = 0$, 0% in ultrasound), low-set ears ($n = 23$, 21.7% versus $n = 1$, 0.3% in ultrasound), low nasal root ($n = 19$, 18.4% versus $n = 1$, 0.3% in ultrasound), and flat nasal bridge ($n = 39$, 37.9% versus $n = 1$, 0.3% in ultrasound) were seen less frequently. An anteversion nostril ($n = 2$, 22.3%) and triangular nostril ($n = 16$,

15.5%) were described only in the clinical pathological or postnatal examination.

In all 209 cases in which information from a pathological follow-up after ultrasound was available, the comparisons of the ultrasound diagnosis and pathological results were analyzed (Table 4). All sonographic findings were compared with the corresponding clinical conditions regarding accuracy (Fig. 1). One has to take into account that it was difficult for four reasons to make a clear statement about

FIGURE 1 Comparison of ultrasound diagnosis with pathological follow-up among the 209 fetuses that underwent both, n (%).

sensitivity and specificity. First, not all the women who were investigated during the study period (approximately 30,000) could be reviewed. Second, because this study involved a level III hospital, there was already a positive selection for fetuses at risk. Third, not all sonographic findings could be compared with postnatal autopsy results, and fourth, the medical technology experienced an impressive innovation in the three decades spanned by the study.

DISCUSSION

Facial dysmorphisms seen in individuals with trisomies 13, 18, or 21 vary considerably. As a result of continuous advancements in ultrasound techniques, it has become possible to detect craniofacial malformations as early as the 11th week of gestation. In the literature, the largest karyotyped series of fetuses with sonographically detected craniomaxillofacial anomalies included 146 cases (Nicolaidis et al., 1993a). The present study involved 559 trisomic fetuses.

Ocular Abnormalities

Ocular and orbital anomalies have been associated with several chromosomal abnormalities. According to the studies by Denis et al. (1993) and Trout et al. (1994), the inner and outer orbital measurements are useful for identifying fetuses with chromosomal defects. Similar to the findings of Nicolaidis et al. (1993b), the occurrence of ocular and orbital pathology (especially microphthalmia and hypotelorism) was about 30% at sonography as well as at autopsy in trisomy 13 fetuses (Table 3). In a pathomorphological study, Siliaeva (1990) found ocular pathologies such as dysplasia of the retina, colobomas, cataract, and luxations of the lens in 25 out of 28 trisomy 13 fetuses (89.3%). In contrast with the findings between sonography and autopsy in trisomy 13 fetuses, there was a large discrepancy between clinical pathology and ultrasound examination in trisomy 18 and 21 fetuses, with only 70% (trisomy 18) to 80% (trisomy 21) of the ocular pathology being demonstrated by ultrasonography in this study.

Nasal Abnormalities

Absence and hypoplasia of the nasal bones have been proposed recently as important markers for the detection of trisomy 21 (Bunduki et al., 2003; Vintzileos et al., 2003; Zoppi et al., 2003). In order to be accurate, this finding must be assessed using a midsagittal section of the face (Bergé et al., 2001). One limitation of our study is that the assessment of this sonographic marker may not be optimal because the data were collected over a long period of time, and a specific effort to examine nasal bones with current imaging standards was not part of our examination protocol.

Ear Abnormalities

Abnormally small ears have been described previously in fetuses with aneuploidy (Birnholtz and Farrell, 1988; Lettieri et al., 1993; Awwad et al., 1994; Yeo et al., 2003). According to a study by Yeo et al. (2003), a short ear length—below the 10th percentile for gestational age—was accepted as a sensitive marker for trisomy 18 ($n = 26/27$, 96.3%); whereas, in a study by Chitkara et al. (2002), a short ear was a negative marker for fetuses with trisomy 18 ($n = 0/4$) and a positive marker for 3 out of 19 trisomy 21 fetuses (15.8%). For trisomy 21, this was confirmed by Vintzileos and Egan (1995) in a prospective study.

In a previous study, low-set ears were found to be one of the most frequent external anomalies ($n = 24$, 77.4%) in autopsy cases with trisomy 18 (Kinoshita et al., 1989). Similarly, almost 50% of our trisomy 18 cases were found at autopsy to have low-set ears.

In trisomy 21 fetuses at 11 to 14 weeks' gestation, ear length is reduced; however, the degree of deviation from normal has been found to be too small for this marker to be useful in screening for trisomy 21 (Sacchini et al., 2003).

Facial Clefts

In agreement with a previous study, the highest rate of median clefts revealed by ultrasound was found in fetuses with trisomy 13 ($n = 8/28$, 28.6%) (Bergé et al., 2001); whereas, the incidence of cleft lip and palate was quite uncommon in trisomy 21 (1%) (Lopoo et al., 1999). The importance of characterizing the type of facial cleft was demonstrated by Nyberg et al. (1995), indicating that the type and extension of the cleft correlate with fetal outcome and karyotype abnormalities. In a study to determine the correlation between prenatal diagnosis and postnatal findings, Sohan et al. (2001) could demonstrate that ultrasound is a useful tool in screening for cleft lip with or without cleft palate but not for an isolated cleft palate. Nevertheless, even an isolated case of cleft lip was thought to be more at risk for a chromosomal abnormality (Nyberg et al., 1995; Bergé et al., 2001).

Abnormal Profile/Micrognathia

The facial profile of fetuses with a trisomic condition can be characterized by an insufficient configuration of the nose or by micrognathia with markedly receding chin and an unusually small mandible. Micrognathia occurs secondary to abnormalities of the first branchial arch caused by deficiency or insufficient migration of neural crest cells in the fourth week of gestation (Mernagh et al., 1999). Besides trisomies 13 and 18, micrognathia is often part of other syndromes or sequences, such as Treacher Collins syndrome, Goldenhar syndrome, and Seckel or Pierre Robin sequence (Nicolaidis et al., 1993b; Bromley and Benacer-

raf, 1994). Regarding abnormal profiles, the results of this study—in which sonographic findings like micrognathia, a flat profile, and macroglossia are associated with an abnormal karyotype in 26% to 42% of the fetuses—correspond with the literature, in which the equivalent figure is 25% to 40% of fetuses (Benacerraf et al., 1986; Nicolaides et al., 1993a; Turner and Twining, 1993; Bromley and Benacerraf, 1994).

Sonographic diagnosis of fetal micrognathia should, therefore, lead to a further search for evidence of other, possibly associated anomalies; if positive, determining karyotype is highly recommended.

In summary, some isolated prenatal sonographic findings, such as facial clefts and profile abnormalities, are not necessarily indicative of aneuploidy; whereas, multiple facial abnormalities increase the likelihood of a trisomic condition (Nicolaides et al., 1992; Nicolaides et al., 1993b; Nyberg et al., 1993; Lehman et al., 1995; Hill, 1996; Hafner et al., 1997; Shields et al., 1998; Bergé et al., 2001). A detailed facial scan therefore improves the detection of a trisomy.

In accordance with the literature (Nyberg and Souter, 2001), sonographically detected facial pathology can be obtained in 90% of fetuses with trisomy 13, in 60% to 80% of fetuses with trisomy 18, and in 50% to 70% of fetuses with trisomy 21. An equally high identification rate is possible by evaluation of the facial pathology in fetuses with trisomy 13 and 18. Therefore, cytogenetic evaluation should be recommended when facial abnormalities are diagnosed prenatally.

This study confirms that craniofacial abnormalities are present in a substantial proportion of fetuses with trisomies 21, 18, and 13. Thus, a detailed ultrasonographic evaluation of the fetal cranium and face should be performed in every fetal anatomical survey, and prenatal diagnosis of craniofacial abnormalities should prompt consideration of a karyotype.

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