

# Biometry of Face and Brain in Fetuses with Trisomy 21

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**ABSTRACT:** The aim of this study was to specify the early setting of the particular craniofacial morphology in Down syndrome during the fetal period from data based on postmortem examinations. The study included 1277 fetuses at 15–38 gestational weeks (GW): 922 control fetuses and 355 fetuses with trisomy 21, selected from fetopathology units in Paris. Body weight (BW) and nine dimensions of the face, skull, and brain were recorded: the outer and inner canthal distances (OCD, ICD), biparietal diameter (BPD), head circumference (HC), brain weight (BrW), occipitofrontal diameters of left and right hemispheres (IOFD, rOFD), weight of the infratentorial part of the brain (IBW), and maximal transversal diameter of the cerebellum (CTD). Four ratios were computed: BPD/HC, OCD/BPD, BrW/BW, IBW/BrW. Differences between trisomic fetuses and control fetuses were tested by age interval. Results showed that BW, rOFD, and IOFD were lower in trisomic fetuses as early as 15 GW. Cerebellar hypoplasia included lower IBW and CTD in trisomic fetuses. The IBW/BrW ratio was higher in trisomic fetuses, showing that growth restriction affected the infratentorial part of the brain less than the supratentorial part. Early brachycephaly was found in trisomic fetuses, with higher values of BPD and BPD/HC from 15 GW. ICD and OCD were not significantly different in the two groups, but OCD/DBP ratio was lower in trisomic fetuses. These results confirm the early phenotypical expression of trisomy 21 on craniofacial morphology, associated with a marked restriction of brain growth, especially in the supratentorial part. (*Pediatr Res* 59: 33–38, 2006)

The distinctive features of craniofacial and brain morphology in trisomy 21 have been well documented in children and adults. Numerous structural abnormalities including reduced BrW, alteration of configuration, and maturation delay were found in the postnatal period. Concerning fetuses, most studies were performed to improve the diagnosis of Down syndrome, and mainly involve ultrasound records. Since cerebellar hypoplasia in trisomy 21 has been found in the postnatal period, much attention has been focused on cerebellum dimensions in fetuses, but the results are contradictory: some studies failed to observe cerebellar hypoplasia (1,2), unlike others (3–5). Other cerebral structures have been studied in fetuses with Down syndrome. Hypoplasia of the frontal lobes has been found in ultrasound studies of trisomy 21 (6,7) but was not confirmed in a postmortem pathologic study (8). Craniofacial dysmorphology was also assessed using skull and

face dimensions ratios: brachycephaly was assessed based on the cephalic index (9). In all ultrasonographic studies (10–12) but one (13), brachycephaly was identical in fetuses with and without trisomy 21. Very few data have been collected concerning the BrW of fetuses with trisomy (8), and no significant difference in BrW was detected before birth.

The purpose of this study was to complete the information on the specificities of craniofacial and cerebral growth in fetuses with Down syndrome. It was based on postmortem pathologic examinations and consequently provided data absent from the literature, such as the weights of different parts of the brain, linear dimensions of the brain and face, and craniofacial proportions. Such data are of particular interest since they give information about the early mode of setting of the particular phenotype of trisomy 21, and in this way contribute to the knowledge of the physiopathology of Down syndrome.

## PATIENTS AND METHODS

**Selection of the sample.** Subjects came from a large data set including more than 4000 fetuses autopsied in fetopathology units of pediatric hospitals in Paris between 1986 and 2003. From these data, 1277 subjects (922 normal fetuses and 355 fetuses with trisomy 21) were carefully selected according to several criteria. The control population was selected as previously described (14,15). We excluded multiple pregnancies; macerated fetuses; fetuses with any dysmorphic feature, malformation, or disruptive macroscopic lesion (except isolated minor malformations, e.g. polydactyly, single umbilical artery, or Meckel diverticulum); fetuses from diabetic mothers; fetuses with severe septicemia, toxoplasmosis, listeriosis, or cytomegalic inclusion disease, as it is well-known that such diseases may have a major effect on fetal growth and organ structure, especially at the brain and head levels. However, subjects with minor pulmonary infections related to recent chorioamnionitis were retained in the study. For at least 30% of the control fetuses, a normal karyotype was obtained antenatally. For the others, the cytogenetic study was not considered useful in fetopathologic examination because of the slight risk of a chromosomal anomaly in a phenotypically normal fetus.

The trisomic fetuses were included in the study on the basis of cytogenetic examinations performed before or at autopsy. More than half of pregnancies were terminated after amniocentesis was performed due to maternal age, one third after ultrasound screening, and about 15% after blood analysis of biochemical markers.

The age of each subject was calculated in weeks from the beginning of the last menstrual period (GW), fine-tuned or rectified by the first trimester ultrasound crown-rump length measurement, and confirmed on autopsy by the estimation of organ maturation (16). In cases of a discrepancy of more than 2 wk between the two estimations of fetal age, the subject was excluded from

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**Abbreviations:** BPD, biparietal diameter; BrW, brain weight; BW, body weight; CTD, maximal transversal diameter of the cerebellum GW, gestational weeks; HC, head circumference; IBW, weight of the infratentorial part of the brain; IOFD, rOFD, occipitofrontal diameters of left and right hemispheres; OCD, ICD, outer and inner canthal distances;

the study. Fetal age ranged from 15 to 38 GW, with a prevalence of fetuses in the first half of gestation. Considering the small sample size in late gestation, the subjects were grouped in 2-wk intervals until 30 wk and in 4-wk intervals thereafter (Table 1). For the same reason, we did not consider the males and females separately. For smoothing purposes, the subjects are grouped by 4-wk intervals in the figures.

**Data recording and statistical processing.** Fetal examinations and measurements were all performed by one medical team (F.M., A.L.D.), according to the same procedure. All external dimensions were measured in the first step of the pathologic examination, before evisceration and fixation. Four linear dimensions of the face and skull were measured: OCD and ICD, BPD, and HC. The BW was recorded before fixation. Visceral dissection was undertaken in two steps: evisceration was performed as soon as the fetus arrived at the laboratory; until dissection, the brain was immersed in a solution of 4% formalin with 0.3% zinc and 0.9% NaCl for 10–20 d, depending on the fetal gestational age (the delay of the fixation was quite similar for fetuses of identical ages). After fixation, BrW was recorded. Then, the IBW, including the brainstem and cerebellum, was cut just below the inferior colliculi and weighed separately. BrW and IBW were weighed with a precision of 0.1 g, BW with a precision of 1 g. The rOFD and IOFD and the CTD were measured. All measurements were made with a calliper square, except HC, which was measured with a tape with a precision of  $\pm 5$  mm.

Some ratios, potentially indicative of the dysmorphism associated with trisomy 21, were computed: BPD/HC, OCD/BPD, BrW/BW, IBW/BrW.

Student's *t* test was used to test for each variable in each age interval the differences between the control fetuses and the fetuses with trisomy 21.

## RESULTS

**Trisomy 21 and craniofacial growth.** No significant differences in HC were observed between control and trisomic fetuses during the prenatal period (Table 2). On the contrary, BPD was significantly higher in fetuses with trisomy 21 in all intervals between 17 and 22 wk and in the 27–28 wk interval (Table 2). Consequently, the BPD/HC ratio computed in each patient (Table 2, Fig. 1) was significantly higher in patients with Down syndrome in the second gestational trimester (except in the 25–26 interval, Table 2). This difference in proportion revealed a more brachycephalic skull in trisomic fetuses. From the 31–34-wk interval, the number of trisomic fetuses was too small to make any conclusions.

The ICD was not significantly different in the two groups, whatever the fetal age (Table 2). The OCD was significantly smaller in trisomic fetuses only in the 19–20-wk interval (Table 2). However, the OCD/BPD ratio, representative of the relative widths of the face and skull, was lower in trisomic fetuses in most age intervals in the second gestational trimester (Table 2, Fig. 2). It is noteworthy that this ratio decreased in both groups all over the prenatal period, in relation to the increasing volume of the skull.

**Trisomy 21 and brain growth.** BrW was significantly smaller in trisomic fetuses in most periods from the beginning of the second gestational trimester (Table 3, Fig. 3). On the other hand, significant differences in BW were only found in the 27–28 GW age interval (Table 3). These findings explain why the BrW/BW ratio was considerably lower in trisomic fetuses (Fig. 4), in all age intervals from 15 wk on, except in the 29–30 interval, which comprised only five trisomic fetuses (Table 3). In both groups, the ratio decreased throughout gestation, which corresponds to a change in body-head proportions.

The cerebral hemispheres were also shorter in trisomic fetuses: rOFD and IOFD were significantly shorter in most periods from 17 wk (Table 3), corresponding to the appearance of a fetal brachyencephaly. The weight of the IBW was

**Table 1.** Sample size by period

Period (wk)	No. of normal fetuses	No. of fetuses with trisomy 21
15–16	86	29
17–18	124	62
19–20	133	98
21–22	165	59
23–24	177	40
25–26	77	19
27–28	40	12
29–30	21	7
31–34	47	18
35–38	52	11

significantly lower in trisomic fetuses only in one period: 21–22 wk (Table 3). As observed in a previous study (17), the ratio IBW/BrW decreased until the end of the second gestational trimester and sharply increased afterward (Table 3, Fig. 5). Until 26 GW, the infratentorial part of the brain (mainly cerebellum) grew less quickly than the supratentorial part (decreasing ratio). Afterward, the cerebellum grew faster than the whole brain, therefore, the IBW/BrW ratio increased quickly. In the present study, this ratio was significantly higher in trisomic fetuses in three age intervals: 17–18, 19–20, 23–24 wk (Table 3).

The CTD was shorter in trisomic fetuses as early as 15 wk. This difference was significant in four age intervals: 15–16, 17–18, 19–20, 25–26 (Table 3).

## DISCUSSION

This study was the first to consider so many biometric variables to characterize the craniofacial growth of fetuses with trisomy 21. In addition to various linear dimensions or weights of the fetal brain and face, special attention has been paid to dimension ratios, providing specific information on craniofacial proportions. The number of trisomic fetuses in the first two trimesters was large enough to divide the sample in 2-wk intervals. Thus, this study provides the first growth standards of various biometric parameters for trisomic fetuses. However, it should be noted that the number of trisomic fetuses decreased abruptly after 28 wk, including less than 10 fetuses in late gestation in many variables. Consequently, the results concerning the third trimester should be interpreted with caution.

In this study, the brain growth in trisomic fetuses was clearly impaired. BrW was significantly smaller as early as the beginning of the second gestational trimester. This restriction of brain growth was also observed by Schmidt-Sidor *et al.* (8) in a smaller group of 17 fetuses, aged 15–22 wk. The lengths of the cerebral hemispheres were also shorter in trisomic fetuses in the second gestational trimester, which had not been previously observed. These observations confirm that brachyencephaly is an early manifestation of Down syndrome. The length of the frontal lobes has been found to be smaller in Down syndrome cases in the second trimester of gestation (5–7).

To determine whether cerebellar hypoplasia is established in the prenatal period, several variables have been studied.

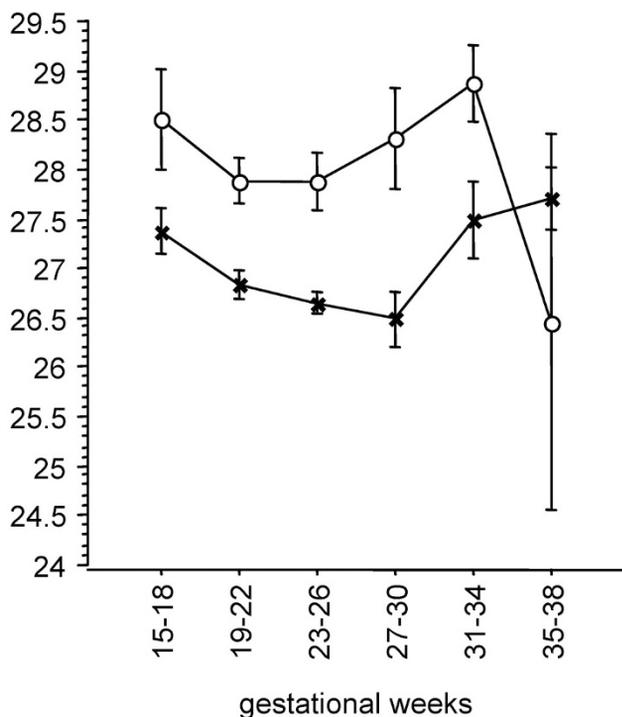
**Table 2.** Differences in craniofacial biometry between control (Contr) and trisomic (Tri) fetuses

GW		HC		BPD		BPD/HC		ICD		OCD		OCD/BPD	
		Tri	Contr	Tri	Contr	Tri	Contr	Tri	Contr	Tri	Contr	Tri	Contr
15-16	M	111.5	114.71	31.3	32.89	0.28	0.28	8.9	9.23	22.3	23.03	0.71	0.71
	S	21.48	13.43	7.48	4.17	0.04	0.02	1.79	1.95	5.33	2.85	0.06	0.07
17-18	M	137.22	144.36	39.5 *	37.29	0.28 **	0.26	1.94	1.6	27.33	27.47	0.69 **	0.74
	S	12.51	18.38	4.00	3.76	0.01	0.02	2.55	1.63	3.83	3.47	0.06	0.07
19-20	M	167.92	164.12	46.5 **	44.19	0.27 *	0.26	12.34	12.36	31.64 *	32.74	0.68 **	0.75
	S	14.94	11.65	4.17	4.17	0.02	0.02	1.80	1.93	2.99	3.04	0.05	0.06
21-22	M	189.36	187.98	52.64 *	5.68	0.27 **	0.26	14.04	13.51	36.36	36.89	0.69 **	0.73
	S	13.99	12.5	4.29	4.69	0.02	0.02	2.44	1.82	3.27	3.25	0.05	0.06
23-24	M	209.83	212.49	58.5	56.65	0.28 **	0.26	15.26	14.98	39.53	41.05	0.68 **	0.73
	S	9.2	12.48	4.53	4.33	0.01	0.01	1.37	2.32	2.46	3.52	0.05	0.06
25-26	M	235.00	234.33	64.4	62.2	0.27	0.26	17.00	15.81	44.4	44.52	0.69	0.72
	S	10.00	11.97	2.07	4.83	0.01	0.01	1.87	2.03	2.51	3.66	0.05	0.05
27-28	M	263.75	25.77	76.75 **	66.86	0.291 **	0.263	16.50	16.62	5.25	47.13	0.65	0.71
	S	4.79	13.26	2.06	4.52	0.01	0.01	1.91	1.56	2.87	3.05	0.02	0.05
29-30	M	282.5	272.89	77.75	75.1	0.275	0.27	18.25	17.9	51.25	51.9	0.66	0.69
	S	9.57	9.9	4.57	5.15	0.01	0.01	1.89	2.51	2.75	4.25	0.07	0.04
31-34	M	303.00	298.89	87.40	83.25	0.29	0.275	18.60	19.52	55.00	56.95	0.63 **	0.69
	S	12.55	19.09	3.20	6.60	0.01	0.02	0.89	1.83	2.55	3.10	0.05	0.03
35-38	M	332.50	324.26	88.00	89.87	0.26	0.277	22.00	2.29	58.50	63.14	0.67	0.71
	S	3.53	14.18	9.89	5.19	0.03	0.01	1.41	1.26	0.71	4.52	0.08	0.05

\*  $p \leq 0.05$ ; \*\*  $p \leq 0.01$ .

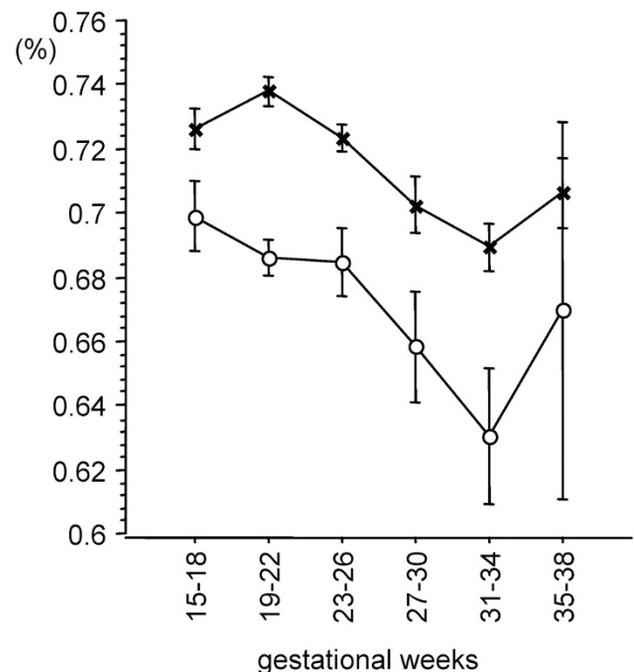
M, mean; S, standard deviation.

The transverse cerebellar diameter, commonly measured in ultrasound routine screening, was found to be decreased in the second gestational trimester. This result confirms the findings



**Figure 1.** Differences in BPD/HC ratio between trisomic (○) and control (●) fetuses during the prenatal period. Differences were statistically significant ( $p \leq 0.05$ ) in the 15-18, 19-22, 23-26, and 27-30 age intervals.

of previous ultrasonographic studies (4,5) but contradicts others (1,2). Furthermore, the IBW was found to be lower in all age intervals, and more significantly in the second gestational trimester (19-22 GW). These results provide an argument for impaired growth of the IBW in trisomic fetuses, in agreement

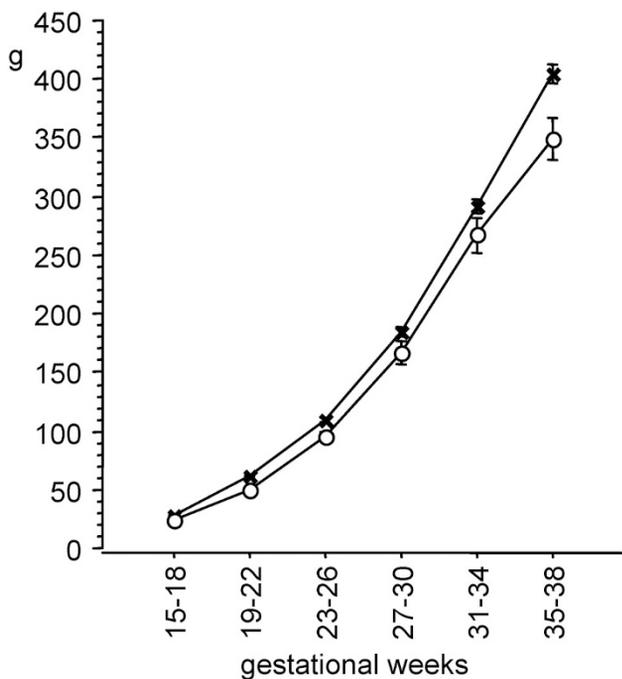


**Figure 2.** Differences in OCD/BPD ratio between trisomic (○) and control (●) fetuses during the prenatal period. Differences were statistically significant ( $p \leq 0.05$ ) in all age intervals, except 35-38.

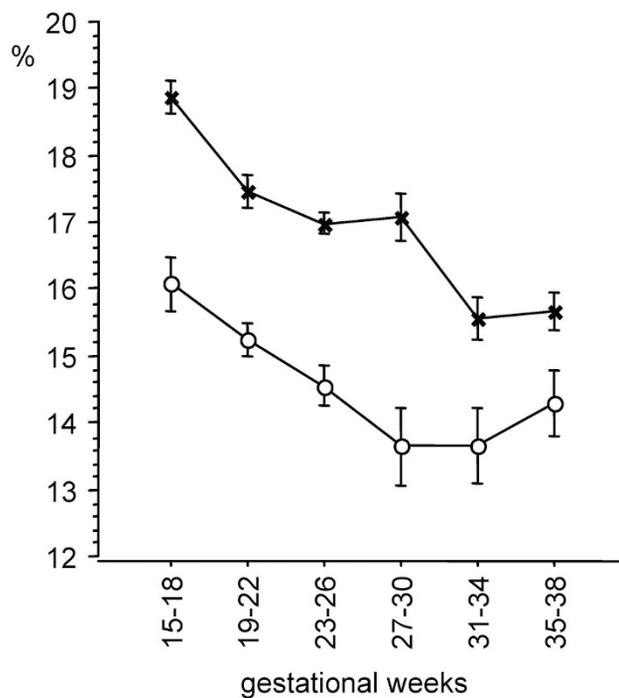
**Table 3.** Differences in BW and brain biometry between control (Contr) and trisomic (Tri) fetuses

GW		BW		BrW		BrW/BW		IOFD		rOFD		IBW		IBW/BrW		CTD	
		Tri	Contr	Tri	Contr	Tri	Contr	Tri	Contr	Tri	Contr	Tri	Contr	Tri	Contr	Tri	Contr
15-16	M	92.74	98.84	16.83 *	19.43	0.167**	0.192	36.29	36.35	36.15	37.58	1.17	1.07	0.68	0.61	14.96 *	16.1
	S	28.74	32.17	3.24	5.3	2.46	3.02	2.74	5.68	3.23	4.78	0.38	0.32	0.26	0.26	0.54	1.55
17-18	M	178.92	176.55	26.63 **	32.14	0.157**	0.186	42.49 **	45.58	42.86 **	45.43	1.55	1.64	0.58**	0.52	17.45**	19.03
	S	50.46	43.86	5.44	6.94	3.67	3.86	3.69	4.42	3.78	3.92	0.4	0.43	0.16	0.1	1.58	1.26
19-20	M	289.30	275.79	43.07 **	48.78	0.151**	0.182	49.9 **	52.94	49.7 **	52.7	2.24	2.38	0.53**	0.49	19.72 *	2.59
	S	58.69	61.83	7.74	9.22	2.04	5.75	4.14	4.38	4.13	4.31	0.47	0.54	0.08	0.08	1.39	1.54
21-22	M	411.07	418.50	61.36 **	7.07	0.153**	0.168	57.02 **	6.64	56.7 **	6.36	2.96 **	3.36	0.49	0.48	22.33	22.59
	S	75.91	69.41	12.68	12.00	3.23	2.21	4.48	5.35	4.01	4.34	0.55	0.6	0.08	0.07	1.63	1.47
23-24	M	607.75	586.57	87.43 **	99.07	0.145**	0.17	64.36 **	68.15	64.28 **	67.8	4.51	4.63	0.52**	0.46	25.91	26.13
	S	106.16	99.74	11.07	15.7	2.04	2.52	4.86	5.07	4.61	4.78	1.06	0.81	0.11	0.05	2.12	1.82
25-26	M	796.39	793.88	114.38**	132.39	0.144**	0.169	72.00	75.08	71.18 **	74.64	5.64	6.16	0.52	.47	27.86 **	3.2
	S	78.97	123.21	15.71	16.39	1.77	2.29	3.77	5.48	3.76	4.69	0.81	0.9	0.09	0.07	1.35	1.74
27-28	M	1116.92**	972.62	15.26 *	170.00	0.136**	0.178	77.25 *	82.71	76.2 *	82.07	7.81	8.31	0.10	0.47	34.5	34.3
	S	143.26	120.66	2.46	21.23	1.19	2.57	3.86	5.16	3.83	4.73	1.55	1.29	0.05	0.07	3.54	1.81
29-30	M	1310.71	1342.05	187.00	209.11	0.136	0.157	85.6	87.11	84.2	89.38	9.1	1.82	0.48	0.52	30.00	36.44
	S	179.82	227.92	37.12	33.94	2.76	2.37	7.4	8.08	7.05	7.45	1.27	1.94	0.07	0.07		2.51
31-34	M	1955.35	1913.30	267.28	291.20	0.136**	0.155	96.20	94.69	96.20	97.04	15.41	16.52	0.59	0.55	43.20	43.00
	S	263.45	338.05	48.91	39.79	1.88	2.07	7.72	1.26	7.68	6.51	3.32	3.66	0.07	0.07	5.07	3.61
35-38	M	2475.45	2604.31	348.88**	404.70	0.142 *	0.156	102.33 *	108.29	1.66 **	108.54	21.40	24.76	0.62	0.61	48.37	47.90
	S	283.64	372.46	58.47	52.59	1.55	2.04	6.70	7.69	7.38	6.78	3.74	4.29	0.04	0.08	4.24	3.83

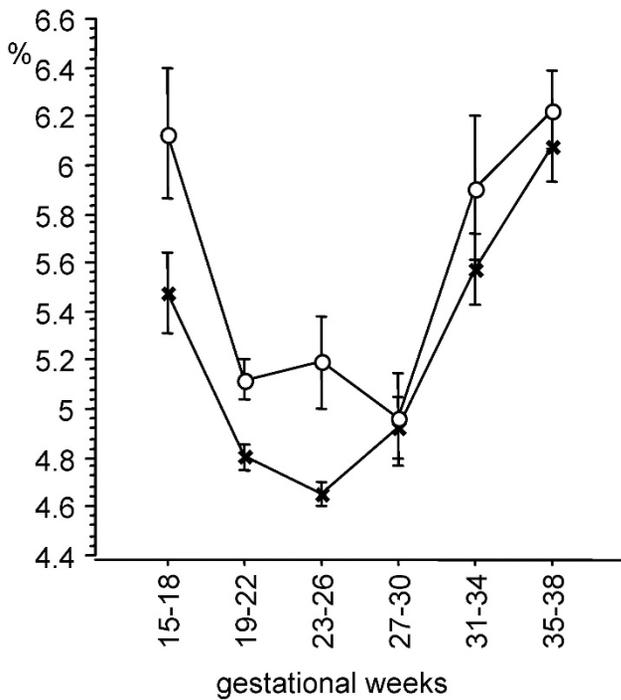
\*  $p \leq 0.05$ ; \*\*  $p \leq 0.01$ .  
M, mean; S, standard deviation.



**Figure 3.** Differences in BrW between trisomic (○) and control (x) fetuses during the prenatal period. Differences were statistically significant ( $p \leq 0.05$ ) in the 15-18, 19-22, 23-26, and 35-38 age intervals.



**Figure 4.** Differences in BrW/BW ratio between trisomic (○) and control (x) fetuses during the prenatal period. Differences were statistically significant ( $p \leq 0.05$ ) in all age intervals.



**Figure 5.** Differences in IBW/BrW ratio between trisomic (○) and control (x) fetuses during the prenatal period. Differences were statistically significant ( $p \leq 0.05$ ) in the 15–18, 19–22, and 23–26 age intervals.

with a previous fetopathologic study concerning the whole “neuro-osteological cerebellar field” (3). In addition, the IBW/BrW ratio was significantly higher in trisomic fetuses during the second gestational trimester. It can be concluded that the growth restriction affects the infratentorial part of the brain less than the supratentorial part. In children, on the contrary, it was observed that the IBW/BrW ratio was lower in patients with trisomy than in controls (18). This apparent discrepancy between these two periods of the life probably reflects that the cerebellum development intervenes later than that of the brain (17), corresponding to a delayed histogenesis of the cerebellum with regard to that of the cerebral cortex.

Craniofacial measurements have shown an early brachycephaly in trisomic fetuses. The enlargement of trisomic skulls was apparent in absolute values of BPD, and confirmed by the increase of the cephalic index BPD/HC. This brachycephaly, parallel to the brachyencephaly, was found as early as 15 wk. This result diverges from a majority of the ultrasound evaluations of the cephalic index in trisomy 21 (6–8,9–12), in which no significant difference was found between the two groups during the second gestational trimester. It is worth noting that all the previous studies included a low number of trisomic fetuses (8 to 38) compared with the 355 examined in the present study. Furthermore, the BPD is not measured in the same manner in fetopathologic and in ultrasound studies. In fetopathologic studies, the BPD is defined as the maximal width of fetal head. In ultrasound studies, the cerebral landmarks used to define the transaxial plane in which the BPD is measured are fixed, so that it does not necessarily coincide with the maximal head width measured at autopsy. This may explain the discordance between

our study and others and makes our results concerning the early brachycephaly in trisomy 21 very reliable.

A paradoxical finding concerned the HC. HC was not significantly smaller in trisomic fetuses, which seems to be at odds with the impaired growth of BrW. It might be that another dimension of the skull, not included in this study (such as the skull height) is smaller in trisomic fetuses, and the global size of the brain thus reduced. The differences in BrW might also correspond to qualitative, not quantitative, differences in brain composition. Specific histologic comparisons between trisomic and normal fetal brains would bring decisive elements to understand the morphologic development pattern of the trisomic brain.

Differences in face width between normal and trisomic fetuses were not found. The ICD and OCD were not significantly different in the two groups, except for OCD in one age interval. However, the OCD/DBP ratio was lower in trisomic fetuses, indicating a specific morphologic pattern associating a nearly normal growing face with skull enlargement, in a context of global volume restriction of brain growth. The smaller OCD observed in the largest age group of trisomic fetuses may also be ascribed to the up-slanting of their palpebral fissures.

In conclusion, this study addresses, in a large cohort of fetuses, the setting of the specific craniofacial phenotype of trisomy 21 cases from the beginning of the second gestational trimester. This phenotype is associated with a marked restriction of brain growth, especially in the supratentorial region and in the frontooccipital dimension, with skull brachycephaly. One of the most early morphologic signs of trisomy 21 is an increased skull width and consequent augmentation of the cephalic index. Such observations confirm the early determination of the Down syndrome phenotype and would be of some interest 1) to understand the relationships between triplication of chromosome 21 genes and anomalies of cephalic and cerebral morphogenesis and 2) to improve the prenatal diagnosis of Down syndrome.

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