Fetal growth retardation: Associated malformations and chromosomal abnormalities

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OBJECTIVE: Our objective was to determine the incidence and pattern of chromosomal abormalities in fetal growth retardation.
STUDY DESIGN: Blood karyotyping was performed in 458 fetuses referred to us for further assessment of growth retardation at 17 to 39 weeks' gestation.
RESULTS: The fetal karyotype was normal in 369 and abnormal in 89 (19%) of the cases. The most common chromosomal defect in the group referred at <26 weeks' gestation was triploidy; in those referred at ≥26 weeks, it was trisomy 18. The incidence of fetal autosomal chromosome aberrations increased, whereas the incidence of triploidy did not change, with maternal age. Ninety-six percent of chromosomally abnormal fetuses had multisystem fetal defects that were characteristic of the different types of chromosomal abnormalities. Compared with those fetuses with a normal karyotype, the chromosomally abnormal group had a higher mean head circumference/abdominal circumference ratio, a higher incidence of normal or increased amniotic fluid volume, and normal waveforms from the uterine or umbilical arteries or both.
CONCLUSION: The findings of the different types of chromosomal abnormalities and their ultrasonographically detectable phenotypic expression provide the background for prospective studies to determine the incidence of chromosomal abnormalities in unselected populations of small-for-gestational-age fetuses. (Am J Obstet Gynecol 1993;168:547-55.)

Key words: Fetal growth retardation, prenatal diagnosis, ultrasonography, fetal karyotype, cordocentesis

Although low birth weight is a common feature of many chromosomal abnormalities,[1, 2] the incidence of chromosomal defects in small-for-gestational-age neonates is < 10%.[3, 4] However, data derived from postnatal studies may underestimate the association between chromosomal abnormalities and growth retardation because many pregnancies with chromosomally abnormal fetuses result in spontaneous abortion or intrauterine death.[5] Furthermore, because in the more lethal types of chromosomal abormalities the degree of growth retardation is generally more severe,[2] it is expected that in antenatally diagnosed, early-onset, severe growth retardation the types of chromosomal abnormalities will be different from those abnormalities recognized at birth.

The aim of our study was to determine the incidence and patterns of chromosomal abnormalities in a large series of antenatally diagnosed fetal growth retardation. Detailed ultrasonographic examination, uterine and umbilical artery Doppler studies, and fetal karyotyping were carried out to investigate whether the risk of chromosomal abnormalities was related to (1) maternal age, (2) gestation at diagnosis of growth retardation, (3) the degree of fetal growth retardation, (4) fetal body proportionality, (5) the presence of fetal malformations, (6) amniotic fluid volume, and (7) increased impedance to flow in the placental circulation.

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Material and methods

This was a cross-sectional study involving the analysis of data from 458 patients with singleton pregnancies who were referred to our unit at 17 to 40 (mean 29) weeks' gestation for further assessment because of fetal growth retardation of uncertain cause. The patients were seen between September 1985 and August 1991, and the criteria for entry into this study included: (1) reliable gestational age from maternal menstrual history (n = 394) or, for patients with uncertain dates or irregular cycles, from ultrasonographic examination in the first trimester of pregnancy (n = 64); (2) no fetal abnormalities other than an abdominal circumference <5th percentile detected at routine scan, (3) birth

Table I. Fetal karyotype in 458 growth-retarded fetuses

Karyotype	*No. of fetuses*
Normal	
46,XY	192
46,XY	177
Autosomal aberrations	
47,XX+22	1
47,XX+21	5
47,XY+21	3
47,XX+18	14
47,XY+18	18
47,XX+13	1
47,XY+13	4
46,XX,del(4p)+der(4)	1
46,XY,del(4p)	3
46,XY,t(4;15)+der(15)	1
46,XY,t(11;12)+der(11)	1
46,XY,t(17;19)+der(17)	1
Triploidy	
69,XXX	26
69,XXY	10

weight <5th percentile of the appropriate reference range for gestation, and (4) available results from fetal blood chromosome analysis.

In our unit detailed ultrasonographic examination was performed for fetal biometry, assessment of amniotic fluid volume, and the detection of fetal malformations (Aloka SSD-650, Tokyo, or Hitachi EUB 340, Tokyo, 3.5 MHz or 5 MHz curvilinear transducer). Continuous-wave Doppler ultrasonography (Doptek Ltd., Chichester, England) was used to obtain flow velocity waveforms from the uterine and umbilical arteries, and waveforms were examined for absence or presence of an early diastolic notch and presence or absence of end-diastolic frequencies, respectively.[6, 7] Fetal karyotyping was performed by cytogenetic analysis of fetal blood obtained by cordocentesis.[8, 9] Maternal contamination of fetal blood was excluded by Betke-Kleihauer testing.

The head circumference, abdominal circumference, femur length, head circumference/abdominal circumference ratio, and head circumference/femur length ratio of the chromosomally normal and abnormal growth-retarded fetuses were compared with the appropriate normal mean for gestation of our reference ranges established from the cross-sectional study of 1010 normal fetuses from singleton pregnancies.

The results of the ultasonographic examinations and fetal karyotypes were given to the referring obstetricians, who undertook further management of the patients. Details on the outcomes of pregnancies were obtained from the referring hospitals.

Statistical analysis. Individual values for the biometric parameters examined were expressed as the number of SDs by which the parameters differed from the appropriate normal mean for gestation; the two-tailed Student t test was used to examine the significance of the differences between chromosomally normal and abnormal fetuses. The χ^2 test was applied to examine the significance of differences in the incidence of chromosomal abnormalities (1) at <26 and ≥26 weeks' gestation; (2) with increased or normal and reduced or absent amniotic fluid, and (3) with normal and abnormal uterine or umbilical artery waveforms. Scheffé's trend/contrast analysis was applied to examine the significance of changes in the incidence of different types of chromosomal abnormalities with maternal age.

Results

The fetal karyotype was normal in 369 and abnormal in 89 (19%) of the cases (Table I). The incidence of chromosomal abnormalities was significantly higher in patients referred at 18 to 25 weeks than in those referred at later gestations (Table II; 50 of 132 vs 39 of 326, $\chi^2 = 40.3$, $p < 0.001$). The most common chromosomal defect in the group referred at <26 weeks' gestation was triploidy (58%); in the group referred ≥26 weeks, it was trisomy 18 (46%). The incidence of fetal autosomal chromosome aberrations increased ($z = 2.27$, $p < 0.05$); the incidence of triploidy did not change significantly with maternal age (Table III; $z = -1.31$).

Abnormal karyotypes were more often encountered when there was ultrasonographic evidence of fetal malformations (85 of 215 cases, 40%), than with isolated growth retardation (4 of 243 cases, 2%; $\chi^2 = 104.6$, $p < 0.001$). Table IV illustrates the pattern of chromosomal abnormalities found in association with various fetal malformations. The characteristic Swiss cheese appearance of a molar placenta was found in only 6 of the 36 fetuses with triploidy.

In chromosomally normal growth-retarded fetuses the mean head circumference, abdominal circumference, and femur length were significantly lower than the appropriate normal mean for gestation, and the mean head circumference/abdominal circumference and head circumference/femur length ratio were increased (Table V; Figs. 1 through 4). In triploid fetuses with normal-looking placentas the mean abdominal circumference was significantly lower and the head circumference/abdominal circumference was higher than in the chromosomally normal group; in the six cases where fetal triploidy was accompanied by the presence of a molar placenta, the mean abdominal circumference was significantly higher and the mean head circumference/abdominal circumference ratio was lower (Table V; Figs. 1 and 4). In the fetuses with autosomal chromosome aberrations the degree of growth retardation (change in abdominal circumference) and the degree of asymmetry (change in head circumference/abdominal circumference ratio) increased significantly with gesta-

Table II. Relationship between gestational age and incidence of chromosomal abnormalities in growth-retarded fetuses

Gestational age (wk)	No.	Abnormal fetal karyotype							
		All		Triploidy		Trisomy 18		Other	
		No.	%	No.	%	No.	%	No.	%
18-25	132	50	38	29	22	14	11	7	5
26-33	208	21	10	7	3	9	4	5	2
34-41	118	18	15	0	0	9	8	9	8
TOTAL	458	89	19	36	8	32	7	21	5

Table III. Relationship of maternal age and incidence of chromosomal abnormalities in growth-retarded fetuses

Maternal age (wk)	No.	Abnormal fetal karyotype							
		All		Triploidy		Trisomy 18		Other	
		No.	%	No.	%	No.	%	No.	%
16-19	28	2	8	1	4	1	4	0	0
20-23	90	16	22	8	9	6	7	2	2
24-27	110	22	25	9	8	6	5	7	6
28-31	108	22	26	12	11	7	6	3	3
32-35	79	15	23	5	6	5	9	5	6
36-39	32	6	23	1	3	3	9	2	6
40-43	11	6	55	0	0	4	40	2	18
TOTAL	458	89	19	36	8	32	7	21	5

tion ($r = -0.603$, $p < 0.0001$ and $r = 0.599$, $p < 0.0001$, respectively). At ≤30 weeks' gestation the mean change in abdominal circumference was higher and the change in the head circumference/abdominal circumference ratio was lower than in the chromosomally normal group; at >30 weeks' gestation the mean change in abdominal circumference was similar and the head circumference/abdominal circumference ratio was higher (Table V; Figs. 1 and 4).

The amniotic fluid volume was subjectively assessed by ultrasonography and classified as normal, reduced, absent (no vertical pool free of umbilical cord >1 cm), or increased. The incidence of chromosomal abnormalities was higher in the group with normal or increased amniotic fluid volume (40%) than in those with reduced or absent amniotic fluid (8%; $\chi^2 = 24.0$, $p < 0.001$; Table VI). Among pregnancies with increased or excessive amounts of amniotic fluid the incidence of esophageal atresia or diaphragmatic hernia was significantly higher (6 of 21) than among those with normal or reduced amniotic fluid volume (3 of 457; $\chi^2 = 7.1$, $p < 0.01$).

The flow velocity waveforms from the uterine and umbilical arteries were examined, and the patients were subdivided according to the presence or absence of a notch in the waveform from at least one of the uterine arteries and the presence or absence of end-diastolic frequencies in the umbilical arteries. The incidence of chromosomal abnormalities in the subgroup with normal waveforms from the uterine and umbilical arteries was higher (44%) than in the subgroup with abnormal waveforms in both types of vessels (8%; $\chi^2 = 54.3$, $p < 0.001$) and in those where either the umbilical or uterine artery waveforms were abnormal (15%; $\chi^2 = 26.5$, $p < 0.001$; Table VII).

In the chromosomally abnormal group there were 59 elective terminations of pregnancy; 17 intrauterine deaths, 7 neonatal deaths, and 1 infant death; 5 (6%) babies are alive. In the chromosomally normal group there were 20 elective terminations of pregnancy, 70 intrauterine deaths, 35 neonatal deaths, and 13 infant deaths; 231 (63%) babies are alive.

Comment

Our study establishes that with severe growth retardation the risk of a chromosomal abnormality is substantially increased if (1) there are fetal defects, (2) there is an inappropriately normal or increased volume of amniotic fluid, or (3) there is no evidence of impaired perfusion in the uteroplacental or fetoplacental circulations. Additionally, our findings indicate that the pattern and incidence of chromosomal defects are associated with specific multisystem malformations and alterations in body proportionality.

Although in our series the indication for referral was unexplained growth retardation, detailed ultrasono-

Table IV. Incidence and pattern of chromosomal abnormalities in presence of ultrasonographically detectable defects

		Abnormal fetal karyotype				
		All				
	No.	*No.*	*%*	*Triploidy*	*Trisomy 18*	*Other*
Skull, brain, or both						
Brachycephaly	28	8	32	1	6	1
Strawberry-shaped head	18	17	94	1	16	–
Cloverleaf-shaped head	1	1	100	–	–	1
Ventriculomegaly	28	20	71	11	4	5
Choroid plexus cysts	13	11	85	–	11	–
Posterior fossa cyst	11	10	91	3	5	2
Absent corpus callosum	2	1	50	–	1	–
Face, neck, or both						
Facial cleft	8	7	88	1	3	3
Micrognathia	21	19	90	7	11	1
Macroglossia	1	1	100	–	–	1
Anophthalmia	1	–	–	–	–	–
Single nostril	1	–	–	–	–	–
Nuchal edema	13	6	46	2	1	3
Chest						
Diaphragmatic hernia	7	7	100	1	5	1
Heart defect	28	23	82	3	15	5
Abdomen						
Mild hydronephrosis	20	9	45	–	5	4
Multicystic kidney	5	5	100	–	3	2
Absent stomach bubble	11	11	100	–	11	–
Bowel obstruction	3	1	33	–	–	1
Exomphalos	6	6	100	–	4	2
Spine, skeleton, or both						
Spina bifida	3	3	100	3	–	–
Phocomelia	1	–	–	–	–	–
Absent fibula	1	–	–	–	–	–
Relative short femur	122	36	30	27	4	5
Talipes	16	14	88	2	8	4
Rocker-bottom feet	7	7	100	–	6	1
Sandal gap	2	1	50	–	–	1
Overlapping fingers	29	28	97	–	25	3
Syndactyly	32	28	88	28	–	–
Clinodactyly	3	3	100	–	1	2
Polydactyly	3	3	100	1	–	2
TOTAL	215	85	40	36	32	17

graphic examination revealed that in many cases there were fetal defects, and the presence of fetal defects was associated with a high incidence of chromosomal abnormalities. The incidence of chromosomal abnormalities with isolated growth retardation was lower (4%) than previously reported (7%).[10] A possible explanation for this difference is that in our study both major and minor abnormalities, such as overlapping fingers and syndactyly, were considered. In triploidy there was a high incidence of ventriculomegaly, short femur, and syndactyly; a molar placenta was observed in only 6 of the 36 affected fetuses. In fetuses with trisomy 18 associated malformations included choroid plexus cysts, micrognathia, heart defects, exomphalos, and overlapping fingers and talipes; in those with trisomy 21, associated defects included nuchal edema, macroglossia, clinodactyly, and sandal gap.

Small-for-gestational-age fetuses are either normally small or they are growth retarded because of impaired placental function or fetal abnormalities. Pregnancies with normally small fetuses are characterized by symmetrically small, anatomically and chromosomally normal fetuses with normal amniotic fluid volume and normal Doppler waveforms from the uterine and umbilical arteries and normal perinatal outcome. Although in unselected population-based studies this group must constitute the great majority of small-for-gestational age fetuses, very few (< 2%) of our fetuses fulfilled these criteria because our population was highly preselected by the referring obstetricians.

Growth retardation as a result of placental insufficiency is characterized by increased impedance to flow in the uterine or umbilical arteries with consequent fetal hypoxemia, redistribution in the fetal circulation, impaired renal perfusion, and reduced urine production and amniotic fluid volume.[11, 12] Our study indicates that

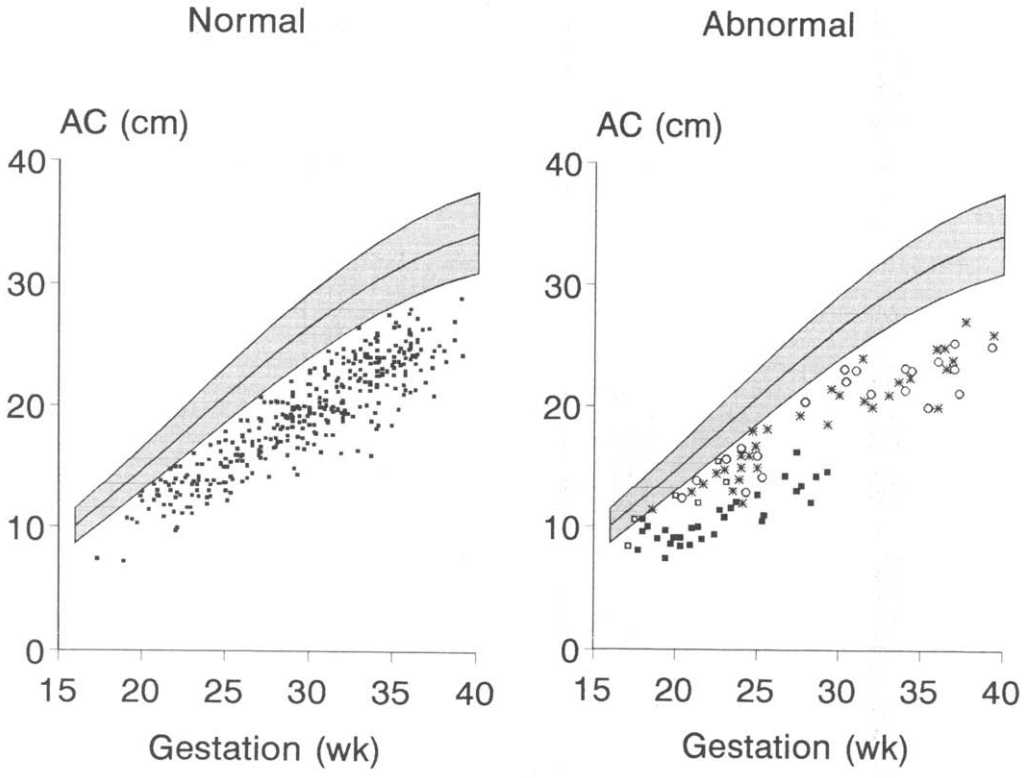

Fig. 1. Abdominal circumference *(AC)* of chromosomally normal *(left)* and abnormal *(right)* growth-retarded fetuses plotted on appropriate reference range (mean 95th and 5th percentiles) for gestation. *Open squares,* Triploidy with molar placenta; *solid squares,* triploidy without molar placenta; *stars,* trisomy 18; *open circles,* other.

Table V. Mean change in measurements in chromosomally normal and abnormal growth-retarded fetuses expressed as number of SDs by which values differed from appropriate normal mean for gestation

Karyotype	*No.*	*Mean change in SD*				
		AC	*HC*	*FL*	*HC/AC*	*HC/FL*
≤30 weeks' gestation						
Normal	200	−4.6	−3.1	−3.4	2.3	1.5
Abnormal	66	−4.8	−2.6*	−3.1	3.3†	2.0
Triploidy I	6	−2.9*	−4.4	−4.2	−0.9	3.1*
Triploidy II	30	−6.6‡	−2.6	−3.6	5.8‡	2.9‡
Trisomy 18	19	−3.3‡	−2.2*	−2.3†	1.6*	0.8‡
Other	11	−3.3*	−2.4	−2.4	1.5*	0.8
>30 weeks' gestation						
Normal	169	−4.7	−3.2	−2.9	2.6	0.4
Abnormal	23	−5.1	−3.2	−3.5	3.3*	1.0*
Trisomy 18	13	−4.9	−2.3*	−2.8	3.5*	0.9
Other	10	−5.3	−4.2	−4.4	3.0	1.1

Student *t* test was applied to determine significance of differences between chromosomally abnormal fetuses and normal fetuses. *AC,* Abdominal circumference; *HC,* head circumference; *FL,* femur length; *HC/AC,* head circumference/abdominal circumference ratio; *HC/FL,* head circumference/femur length ratio; *I,* molar placenta; *II,* normal placenta.

*$p < 0.05$.
†$p < 0.001$.
‡$p < 0.0001$.

the incidence of chromosomal abnormalities is much lower in the group with abnormal Doppler results (12%) and reduced amniotic fluid volume (8%) than in those where growth retardation is accompanied by normal Doppler results (44%) and normal or increased amniotic fluid (40%). In our study the incidence of increased or excessive amniotic fluid volume was 4%; 95% of these cases had multiple malformations and chromosomal

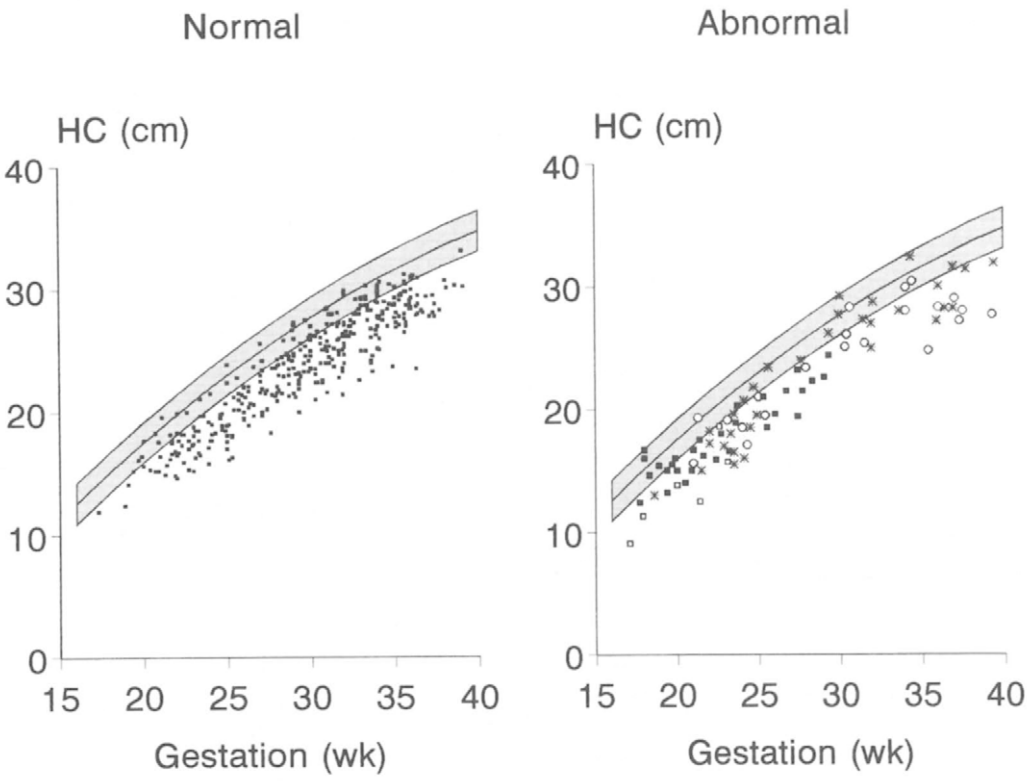

Fig. 2. Head circumference *(HC)* of chromosomally normal *(left)* and abnormal *(right)* growth-retarded fetuses plotted on appropriate reference range (mean 95th and 5th percentiles) for gestation. *Open squares,* Triploidy with molar placenta; *solid squares,* triploidy without molar placenta; *stars,* trisomy 18; *open circles,* other.

Table VI. Relationship between amniotic fluid volume and incidence of chromosomal abnormalities in growth-retarded fetuses

Amniotic fluid	*No.*	*Abnormal fetal karyotype*							
		All		*Triploidy*		*Trisomy 18*		*Other*	
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Increased	20	19	95	0	0	18	90	1	5
Normal	147	47	32	20	14	13	8	14	10
Reduced	159	16	10	10	6	1	1	5	3
Absent	132	7	5	6	5	0	0	1	1
TOTAL	458	89	19	36	8	32	7	21	5

abnormalities. Edyoux et al.[10] found polyhydramnios in 6% of their 374 growth-retarded fetuses; 41% of these had multiple malformations, and 35% had chromosomal abnormalities.

It has been previously suggested that assessment of body proportionality may provide information on the underlying pathophysiologic changes of fetal growth retardation.[13-16] Thus fetal causes of growth retardation such as chromosomal abnormalities were thought to be associated with early-onset, symmetric impairment in growth of all parts of the body. In contrast, placental insufficiency was considered to be associated with late-onset, asymmetric impairment in growth primarily affecting the abdomen and sparing the head and femur. However, our study indicates that relative shortening of the femur is found in both chromosomally normal and abnormal fetuses. Furthermore, fetuses with triploidy have severe, early-onset, asymmetric growth retarda-

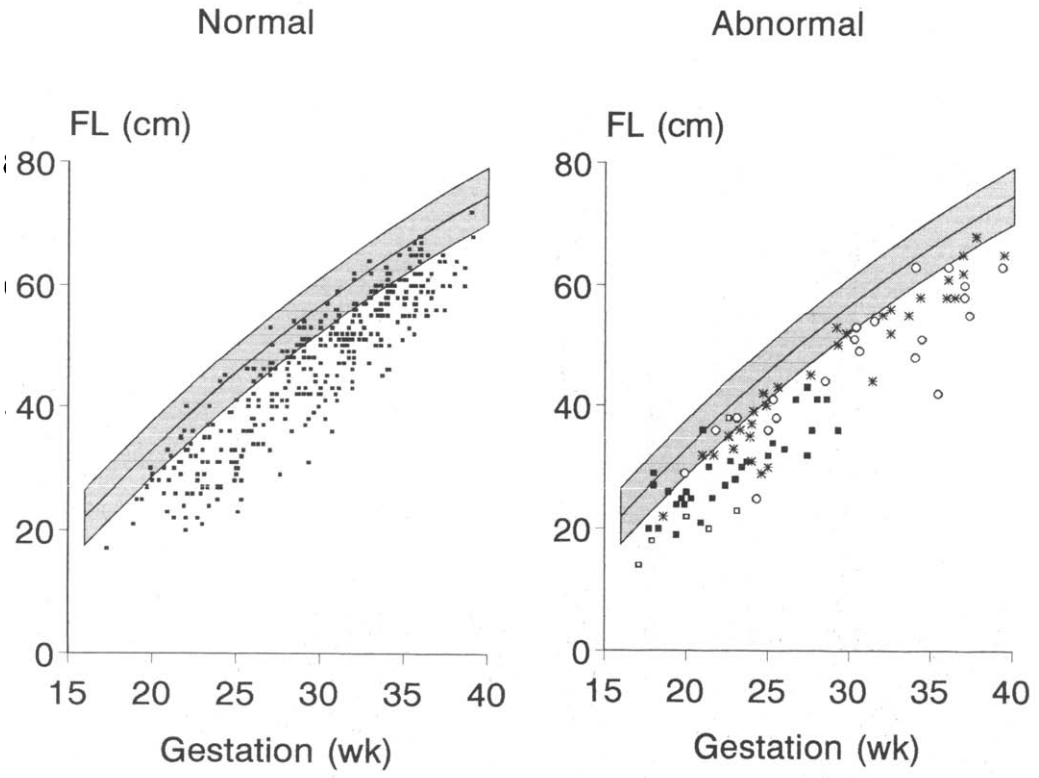

Fig. 3. Femur length *(FL)* of chromosomally normal *(left)* and abnormal *(right)* growth-retarded fetuses plotted on appropriate reference range (mean 95th and 5th percentiles) for gestation. *Open squares,* Triploidy with molar placenta; *solid squares,* triploidy without molar placenta; *stars,* trisomy 18; *open circles,* other.

Table VII. Relationship between chromosomal abnormalities in growth-retarded fetuses, absence or presence of notch in waveforms from uterine arteries, and presence or absence of end-diastolic frequencies in waveforms from umbilical arteries

Doppler findings	*No.*	*Abnormal fetal karyotype*							
		All		*Triploidy*		*Trisomy 18*		*Other*	
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
−NT, +EDF	111	49	44	17	15	20	18	12	11
−NT, −EDF	46	11	24	2	4	4	9	5	11
+NT, +EDF	113	14	12	10	10	3	3	1	1
+NT, −EDF	188	15	8	7	4	5	3	3	2
TOTAL	458	89	19	36	8	32	7	21	5

−, Absence; +, presence; *NT,* notch; *EDF,* end-diastolic frequencies.

tion, whereas fetuses with chromosomal abnormalities other than triploidy are symmetrically growth retarded at < 30 weeks; the ones diagnosed after this gestation are usually asymmetrically growth retarded.

It is possible that asymmetry in chromosomally abnormal fetuses results from superimposed starvation resulting from placental insufficiency; three previous studies demonstrated abnormal umbilical artery waveforms in seven of eight chromosomally abnormal fetuses examined.[17-19] However, in our study the incidence of abnormal waveforms from the uterine or umbilical arteries was low, suggesting that asymmetry may be the result of factors other than starvation. In normal pregnancy both head circumference and ab-

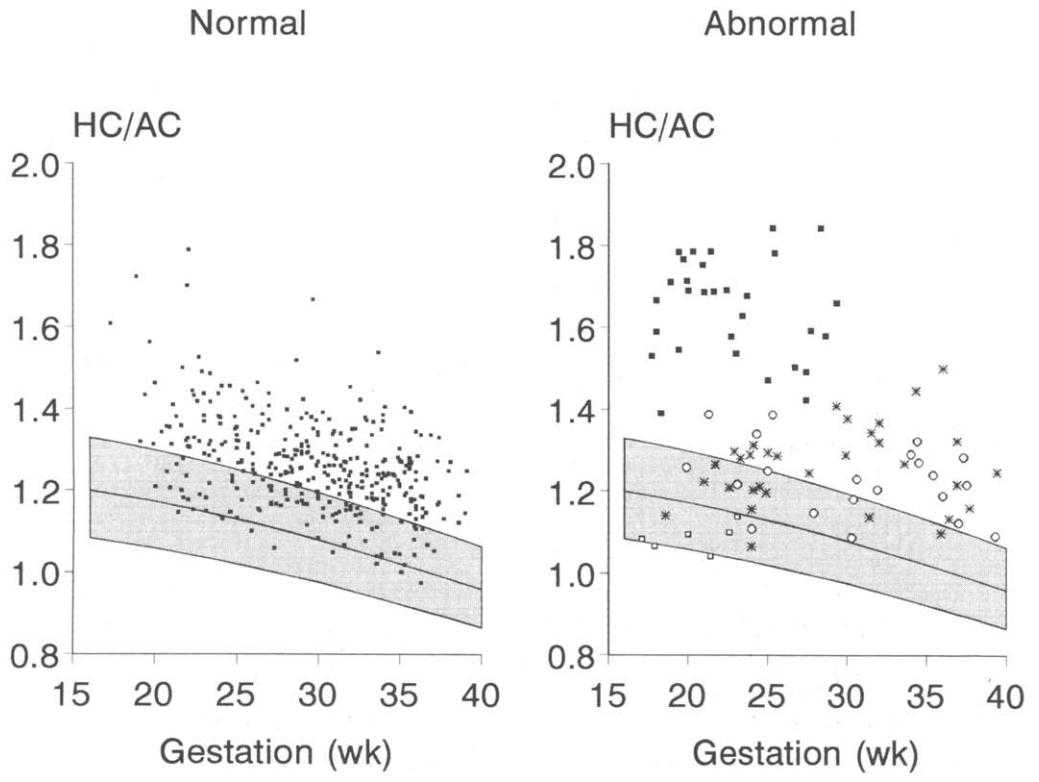

Fig. 4. Head circumference abdominal circumference *(HC/AC)* ratio of chromosomally normal *(left)* and abnormal *(right)* growth-retarded fetuses plotted on appropriate reference range (mean 95th and 5th percentiles) for gestation. Open squares, Triploidy with molar placenta; *solid squares*, triploidy without molar placenta; *stars*, trisomy 18; *open circles*, other.

dominal circumference increase with gestation, but the head circumference/abdominal circumference ratio decreases. It could be postulated that chromosomal abnormalities interfere with the developmental clock that controls the switch from preferential growth of the head to growth of the abdomen.

The change in relative frequency of the different types of chromosomal abnormalities with advancing gestation could be explained by their degree of lethality. Thus triploidy is a common chromosomal abnormality in spontaneous abortions and midtrimester growth retardation but is rarely seen postnatally.[20] Unlike the incidence of fetal trisomy, the incidence of triploidy was not significantly related to maternal age, which may indicate that the frequency of triploid conceptions does not change with maternal age, whereas the frequency of trisomic conceptions increases.

Although the true incidence of chromosomal abnormalities in unselected groups of small-for-gestational-age fetuses is likely to be lower than in our study, fetal karyotyping in growth retardation is essential both for defining prognosis and management of the present pregnancy and for accurate counseling of parents about the cause of the condition and the risk of recurrence.[20]

The findings of our study regarding the different types of chromosomal abnormalities and their ultrasonographically detectable phenotypic expression (fetal morphologic features and body proportionality, amount of amniotic fluid, and impedance to flow in the uterine and umbilical arteries) provide the background for prospective studies to determine the incidence of chromosomal abnormalities in unselected populations of small-for-gestational-age fetuses.

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Seeking early medical attention after vaginal bleeding will not assure mild disease in postmenopausal endometrial carcinoma

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We compared the length of time between the onset of vaginal bleeding and (1) initial visit to a physician and (2) hysterectomy in patients with endometrial carcinoma (mild vs advanced disease). There was no difference in these times. We conclude that patients with advanced endometrial carcinoma do not delay seeking medical attention when compared with patients with mild disease. (Am J Obstet Gynecol 1993;168:555-6.)

Key words: Vaginal bleeding, endometrial carcinoma

It is commonly believed that vaginal bleeding is an early symptom of endometrial carcinoma. It is also believed that women initially seen with mild disease seek medical attention early and women with more advanced disease have delayed seeking medical advice. We evaluated this concept.

Material and methods

All patients are a subset of those previously reported[1] and were ≥ 10 years postmenopausal. Therefore vaginal bleeding should have been interpreted as abnormal by all patients. All patients had endometrial carcinoma and underwent hysterectomy. Patients were divided into two groups: group A, grade 1 (well-differentiated) tumor plus <50% depth of invasion of the tumor into

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