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Correlation of ultrasound and pathologic findings of placental anomalies in pregnancies with elevated maternal serum α-fetoprotein

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Summary

Twenty pregnancies with elevated maternal serum α-fetoprotein (MSAFP), a normal fetus and unusual or abnormal placental/cord sonographic features are reported. These include: (A) gigantic enlargement with multiple sonolucent spaces of different size and shape (n = 2; Swiss cheese); (B) placental masses of variable echogenicity (n = 5); (C) cord masses with central echo-dense zone and peripheral hypoechoic areas (n = 2); (D) enlarged placentas with patchy decrease of echogenicity (n = 6; jelly-like); and (E) large sonolucent spaces with turbulent blood flow surrounded by normal placental tissue (n = 5; placental lakes). After delivery, these ultrasound features were compared with pathologic findings. Diffuse mesenchymal hyperplasia of the stem villi were found in the gigantic placentas (n = 2). The placental masses corresponded to chorioangiomas (n = 3), infarct (n = 1) or subamniotic hematoma (n = 1) and the cord masses to angiomyxomas (n = 2). The 'jelly-like' placentas were related to subchorial thrombosis (n = 2), massive fibrin deposition (n = 1) or hypertrophy with no obvious abnormalities (n = 3). Large subchorial thrombosis (n = 2), or no obvious abnormalities (n = 3) were observed in placentas with large lakes. These findings suggest that a large range of placental and cord anomalies are associated with elevated MSAFP and are potentially diagnosable by routine sonographic examination at the time of AFP screening.

Ultrasonography; Placenta; Umbilical cord; Maternal serum α-fetoprotein

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Introduction

Placental abnormalities have been previously investigated in pregnancies presenting with elevated maternal serum α-fetoprotein (MSAFP) and an anatomically normal fetus [1–4]. However, these studies did not attempt to correlate antenatal and postnatal findings. Thus, pathologic studies of placentas from pregnancies complicated by elevated midtrimester MSAFP have showed an increase in the mean placental volume and a higher incidence of chronic villitis, infarcts and intervillous thrombosis [1,2]. In contrast, antenatal sonographic studies have reported the presence of placental sonolucent areas in some pregnancies, with elevated MSAFP in the second trimester [3,4]. The authors postulate that these placental sonolucent spaces represent an anomalous vascular interdigitation of maternal and fetal blood pools [3], or that they are zones of placental haemorrhage with secondary fetomaternal admixture of blood and/or intra-amniotic bleeding [4]. However, no pathologic confirmation of these placental lesions was reported at delivery.

The aim of the present study is to correlate the different antenatal ultrasonographic features with postnatal pathologic findings, in placentas from pregnancies with elevated MSAFP and a normal fetus.

Materials and methods

Detailed pathologic investigations were performed on placentas and umbilical cords from 20 pregnancies where antenatal ultrasound examination had demonstrated a variety of unusual or abnormal placental/cord features. These cases were obtained from a total number of 358 patients referred from their prenatal care providers after elevated MSAFP levels (> 2.5 multiple of the median (MoM) on two repeated samples). A systematic examination of the placenta and the cord was performed, and the various abnormalities were documented. The pregnancies described in this study were singleton, and in each case the gestational age and the absence of fetal structural malformation were confirmed by ultrasound.

The placentas were trimmed and weighed immediately after delivery. They were immersed in 4% formaldehyde for 2 weeks and then examined macroscopically. Subsequently, they were cut into parallel and vertical slices 1 cm thick. Several blocks of both macroscopically normal and abnormal placental tissues were processed for routine histologic examination.

Results

The sonographic features, pregnancy outcome and the pathologic findings are summarized in Table I. All but one infant (vide infra) were anatomically normal. Nineteen infants were born alive and did not present neonatal complications; one was stillborn and autopsy confirmed the absence of structural anomalies. In seven cases the birth weight, adjusted for sex and parity, was below the 10th percentile of the Kloosterman charts [5].

The patients were divided into five groups according to the sonographic appearances of their placenta or cord:

TABLE I

Sonographic and follow-up data of 20 pregnancies with raised MSAFP, a structurally normal fetus and placental or cord anomalies

Case	MSAFP (MoM)	Sonographic diagnosis	Evaluation time (wks)	Prenatal complications	Pregnancy outcome	P/F weight (g) & Sex	Pathologic results
1	4.2/4.4	Gigantic Swiss cheese enlargement	20	None	Preterm delivery at 36 wks	1 200/2 200 (F)	Diffuse mesenchymal hyperplasia
2	3.4/3.6	Gigantic Swiss cheese enlargement	22	None	NSVD at 37 wks	3 280/2 940 (F)	Diffuse mesenchymal hyperplasia
3	7.6/8.2	Placental mass (7×6×6 cm)	20	None	NSVD at 39 wks	830/3 750 (M)	Large chorioangioma (8×7×6 cm)
4	8.5/9.2	Placental mass (4×3×3 cm)	23	Polyhydramnios	Preterm delivery at 36 wks	430/3 120 (F)	Small chorioangioma (3×3×3 cm)
5	6.2/7.4	Placental mass	18	IUGR Breech	C/S at 37 wks	455/2 230 (M)	Large chorioangioma (5×4×4 cm)
6	10.2/11	Placental mass (5.5×4×4 cm)	18	None	NSVD at 37 wks; IUGR	420/2 150 (F)	Subamniotic hematoma (8×5×2 cm). Massive fibrin depositions
7	8.3/9.8	Placental mass (4.5×4×4 cm); Major Previa	19	Oligoamnios Hypoxia	IUD at 27 wks IUGR	384/480 (M)	Placental infarct (5×4×5 cm) Normal fetal autopsy
8	3.3/3.1	Diffuse cord mass with two pseudocysts	21	Short cord	C/S at 38 wks Skin angiomas	840/3 690 (M)	Angiomyxoma infiltrating the entire cord length (580 g)
9	6.2/6.5	Nodular cord mass	18	Short cord	C/S at 38 wks	420/2 750 (F)	Nodular angiomyxoma of 125 g (15×16×13 cm)
10	5.2/7.2	Jelly-like enlargement	17	Vaginal bleeding	C/S at 28 wks	420/780 (M)	Large subchorial thrombosis (7×4×4 cm); P/F > 90th Pct.
11	3.3/9.0	Jelly-like enlargement	22	None	NSVD at 40 wks; IUGR	380/2 740 (F)	Large suchorial thrombosis (3×2.5×2)
12	4.6/6.9	Jelly-like enlargement	23	None	NSVD at 38 wks; IUGR	355/1 960 (F)	Massive fibrin deposition
13	8.8/9.1	Jelly-like enlargement	23	PROM	Preterm delivery at 32 wks	620/1 294 (F)	No lesion; P/F > 90th Pct
14	2.8/3.2	Jelly-like enlargement	20	None	NSVD at 41 wks	850/3 620 (M)	No lesion; P/F > 90th Pct
15	3.8/4.2	Jelly-like enlargement	20	None	NSVD at 40 wks	760/3 450 (M)	No lesion; P/F > 90th Pct
16	3.2/3.3	Large lakes	18	None	NSVD at 40 wks; IUGR	410/2 490 (M)	Large subchorial thrombosis (3×2×2 cm); chronic villitis
17	3.6/3.8	Large lakes	18	None	NSVD at 40 wks	525/3 320 (F)	No lesion
18	3.2/3.4	Large lakes	20	None	NSVD at 37 wks	485/2 929 (F)	No lesion
19	3.4/3.5	Large lakes	23	None	NSVD at 37 wks	383/3 390 (M)	Large subchorial thrombosis (4×4×2 cm)
20	3.5/2.9	Large lakes	18	None	IUGR at 39 wks	425/2 335 (F)	No lesion

MSAFP MoM, maternal serum α-fetoprotein multiples of the median; IUGR, intra-uterine growth retardation; P/F, placental/fetal; C/S, Cesarean section; NSVD, normal spontaneous vaginal delivery; IUD, intra-uterine death; M, male; F, female; Pct, percentile.

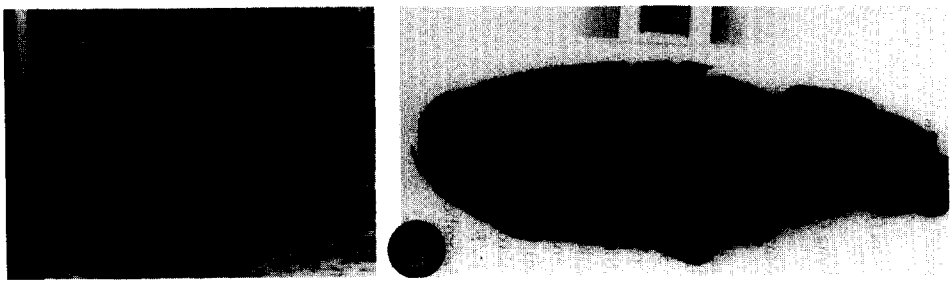

Fig. 1. Transverse sonogram (A) at 22 weeks' gestation in case 2 showing gigantic enlargement of the placenta with Swiss cheese appearance related to dilatation of the chorionic and the main villous vessels and myxoid degeneration of the stem villi (B).

Group A (n = 2)

Included are two cases presenting with gigantic enlargement of the placentas (thickness of 45 and 60 mm at 20 and 22 weeks, respectively) accompanied by diffuse intraplacental sonolucent spaces of various sizes and shapes (Fig. 1A). In both cases, serum levels of hCG at the time of ultrasound examination were within normal limits. Serial ultrasound examinations demonstrated normal fetal growth and no evidence of hydrops, while the placentas continued to enlarge. From the end of the second trimester, blood flow could be observed by real-time imaging in some of the sonolucent spaces.

The placental weights were 1200 and 3280 g, respectively. In both cases, the chorionic arteries and veins were dilated. Serial slicing revealed gelatinous structures, mainly located under the chorionic plate, with a clear plane of cleavage and dilated vessels within the placental mass (Fig. 1B). Microscopic examination demonstrated poorly vascularized stem villi composed of loose cellular connective tissue and containing a few ill-formed vessels. The largest trunks were undergoing central myxoid degeneration. Terminal villi showed no significant abnormalities. In particular, no trophoblastic hyperplasia could be observed. Chromosome analysis of placental tissue demonstrated a normal karyotype (46, XX), in both cases.

Group B (n = 5)

This group included five placental masses. In cases 3 and 4, the masses were hypoechoic and well circumscribed from the rest of the placental tissue. They were located near the umbilical cord insertion in cases 3 and 4, and at the placental margin in case 5. Serial ultrasound examinations demonstrated from 28 weeks' gestation a progressive increase of the mass echogenicity in cases 3 and 5 (Fig. 2A). Case 4 was complicated by polyhydramnios and premature delivery without obvious modification of the sonographic appearance of the mass. None of these three cases presented increased fetal heart size or signs of fetal hydrops. In case 6, sonographic examination of the placenta showed, at 18 weeks' gestation, an hypoechoic mass near the cord insertion (Fig. 3). The shape of this lesion was easily modified by fetal movements or abdominal pressure. From the end of the second trimester the fetal growth was slow but Doppler studies of the fetal circulation showed normal flow velocity waveforms. In case 7, ultrasound examination revealed, at 19 weeks'

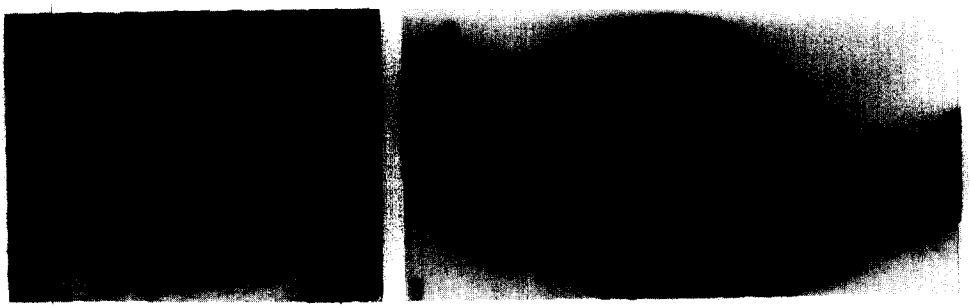

Fig. 2. Longitudinal sonogram (A) at 30 weeks' gestation in case 3 showing a large subchorionic mass (7×6×6 cm) corresponding to a chorioangioma (B). Half of the lesion was grooved by bands of fibrous tissue (*).

gestation, a large mass under the chorionic plate. This mass was more echogenic than the rest of the placenta but had no clear plane of cleavage. Subsequent ultrasound examinations at 22, 24 and 26 weeks' gestation demonstrated severe fetal growth retardation and oligohydramnios. Doppler studies revealed reversed end-diastolic flow in the umbilical arteries and in the fetal descending aorta from 24 weeks. Uterine arteries blood-flow waveforms were always normal. An uneventful cordocentesis was performed at 26 weeks' gestation which confirmed severe fetal hypoxia and acidosis (pH = 7.195, pO_2 = 18.7, pCO_2 = 53.4). A conservative management was adopted after discussion with the parents. The fetus died in utero during the 27th week of gestation.

Pathologic investigations showed a single mixed placental chorioangioma in cases 3, 4 and 5. The lesion was partially grooved by bands of fibrous tissue in cases 3 (Fig. 2B) and deeply fibrotic in cases 4 and 5. In case 6, a large subamniotic

Fig. 3. Longitudinal sonogram in case 6 at 18 weeks' gestation (left) showing an hypoechoic subamniotic mass and longitudinal and transverse sonogram at 24 weeks (middle and right) showing the presence of a central echogenic area. Pathologic examination revealed an old subamniotic hematoma.

Fig. 4. A and B (Case 8), longitudinal and transverse sonograms of the cord at 22 weeks' gestation showing a central echodense zone (*) surrounded by a hypoechoic pseudocystic mass (p); C and D (case 9), longitudinal and transverse sonograms of the cord at 20 and 34 weeks' gestation respectively, showing a similar structure (*) infiltrating the cord longitudinally. E. Pathologic demonstration of an extended angiomyxoma in case 9.

hematoma surrounded by amniotic membranes was observed near the cord insertion; this was associated with underlying massive fibrin depositions. In case 7, examination demonstrated a large chronic infarct under the fetal plate. The maternal plate and the rest of the placental tissue were unremarkable.

Group C (n = 2)

Included two cord masses. Sonographically, these masses were heterogeneous, consisting of a strong echogenic central area, embedding the umbilical vessels and surrounded by large hypoechoic areas (Fig. 4). In both cases, the masses were found near the placental insertion of the cord. In case 8 (Fig. 4A and B), the same enlarged

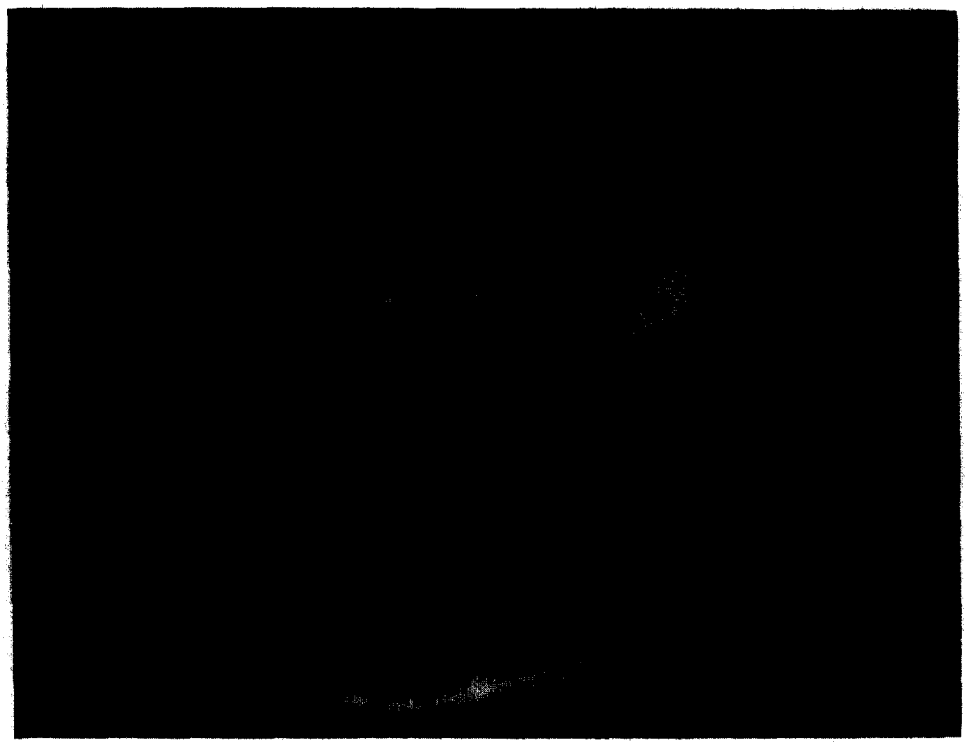

Fig. 4 continued.

to reach 20 cm in its largest diameter at term. In case 9 (Fig. 4C and D), the tumor developed longitudinally towards the fetus, involving the entire length of the cord at term. The cord appeared as continuous rigid structure and could be followed by successive longitudinal sonograms. Their length at term was estimated around 30 cm, and the two patients were delivered by Cesarean section. Examination of the neonate in case 9 revealed multiple flat superficial portwine skin angiomas. The baby was otherwise normal and at 6 months of age is well.

Pathologic investigation demonstrated the presence of a cord angiomyxoma in both cases (Fig. 4E). The cord lengths were 33 cm in case 8 and 26 cm in case 7. Histologically, both tumors were composed of an abundant capillary proliferation distributed in a dense myxoid stroma and surrounded by edematous Wharton's jelly that had undergone myxomatous degeneration.

Group D (n = 6)

Included six placentas with 'jelly-like' appearances (Fig. 5A, C, D and E). The placentas were enlarged (mean thickness ranging between 30 and 45 mm), with patchy decrease of echogenicity and quivering like jelly to sharp abdominal pressure. In all cases, large sonolucent spaces (> 1 cm in their largest diameter) were observed with turbulent blood flow pattern on real time imaging.

Fig. 5. Transverse sonograms in case 10 (A) and 12 (C, D and E) at 17 and 23 weeks' gestation, respectively, showing thick placentas with patchy decrease of echogenicity and large lakes. In case 10, the sonographic features were related at delivery to an 8 cm thick placentas (B) with a large subchorial thrombosis (arrows).

Fig. 6. Large placental lake under the chorionic plate in case 7, at 18 (A) and 22 weeks (B); on real-time imaging this contained turbulent blood flow. No lesion was observed after delivery.

Pathologic examination revealed a large subchorial thrombosis in cases 10 (Fig. 5B) and 11. In case 12, massive perivillous fibrin depositions were found. The placenta/fetal weight ratio was above the 90th percentile of Kloostermann table in four of the six cases in this group. There were no other reported abnormalities for these cases.

Group E (n = 5)

Included five placentas with large lakes (Fig. 6A and B). Large sonolucent spaces (> 1 cm in their largest diameter) were found under the chorionic plate and/or within the placental substance. These lakes were surrounded by placental tissue of normal echogenicity.

Pathologic investigations revealed a large subchorial thrombosis in cases 16 and 19. In the latter, which was complicated by fetal growth retardation, microscopic examination showed diffuse chronic villitis. No abnormalities were demonstrated in the other cases.

Discussion

The α fetoprotein (AFP) is produced by the yolk sac and the fetal liver during the first trimester of pregnancy, but is nearly all of fetal hepatic origin during the second and third trimesters [6]. This glycoprotein is transferred from the fetal circulation to the maternal circulation, across the placental villous barrier. In addition to this major route, AFP is also excreted via the fetal urine in the amniotic fluid, and then transferred to the maternal circulation, through the free placental membranes [1,6].

Sonographic and macroscopic appearances of the first two cases reported in this study were suggestive of trophoblastic disease (Fig. 1A and B). However, the maternal serum hCG levels were within normal ranges, unlike the situation in triploidy, classical hydatidiform mole and partial diploid mole which are associated with elevated hCG levels [7–10]. Furthermore, triploidy was unlikely, as in this disorder the fetus almost always presents with fetal growth retardation and/or major congenital defects [7]. A dyzgotic twin pregnancy combining a complete mole and a normal pregnancy was also excluded, as in this condition sonographic examination shows the presence of a large vesicular area adjacent to normal placental tissue and fetus [8]. In our cases the cause of the Swiss cheese sonographic appearance was probably due to the swelling of some main villous trunks and to the dilatation of the chorionic vessels. Diffuse mesenchymal hyperplasia of the stem villi with persistence of vessels without areas of trophoblastic hyperplasia were suggestive of a non-trophoblastic tumor of the placental. Classically, this category of tumor includes placental chorioangiomas and chorioangiomatosis, a placental anomaly characterized by diffuse infiltration of the placenta by hemangiomatous tissue [11,12]. Our two cases presenting with diffuse mesenchymal hyperplasia without associated vascular proliferation might be considered as the cellular type of chorioangiomatosis.

The association of elevated MSAFP and placental or cord vascular tumors has been reported previously [13–16]. These lesions develop during embryonic life always before the time of AFP screening [11]. Chorioangiomas are found in 0.5 to

1% of the placentas examined at term [11,12]. These tumors have a different echogenicity (Fig. 2A) and appear to be well circumscribed from the rest of the placental tissue [14,17]. Increase in echogenicity of the tumor with gestation was related in our cases, with fibrotic degeneration of the lesion (Fig. 2B). When a placental mass consistent with a chorioangiomas is diagnosed antenatally it is important to perform serial sonographic examinations. These pregnancies may be complicated by an excess of amniotic fluid or by fetal growth retardation [11]. Furthermore, large tumors can also be complicated by fetal cardiac failure with hydrops due to the shunting of blood through the tumor [11,12]. Small chorioangiomas (less than 5 cm in diameter) accompanied by polyhydramnios, as observed in case 4 are unusual [11].

The discovery of a cord angiomyxoma is a rare event. Twenty cases were documented pathologically [18] and three cases were observed sonographically [13,19,20]. Only one of these cases was diagnosed in utero during the second trimester [13]. In the latter, the fetus died following puncture in utero of the tumor and thus no antenatal follow-up data was available. In our two cases the sonographic features and the pathologic findings could be easily correlated (Fig. 4B, C and D). The strong echogenic areas in intimate contact with the main umbilical vessels corresponded to dense angiomatous tissue. This was surrounded by large hypoechoic areas (Fig. 4A and C) related to the myxomatous degeneration of the Wharton's jelly. Ultrastructural studies of the umbilical cord amniotic epithelium reveal important differences from the placental amnion, suggesting that passage of fluid occurs with far less ease through the cord amnion [18]. This explains the essentially constant association of edema and myxomatous degeneration of Wharton's jelly with angiomyxomas compared with placental chorioangiomas [18]. The abnormal vascular pattern observed in angiomyxomas is well demonstrated in utero by color Doppler imaging and this new technique may be helpful in the early diagnosis of these tumors [21]. Potential fetal complications of cord tumors include vascular compression of the umbilical vessels with abnormal growth and possible intra-uterine death [18]. Extension of the lesion may also result, as in our cases, in shortening of the cord with possible complications during vaginal delivery.

Old subamniotic hematomas, due to the rupture of a chorionic vessel before delivery can be diagnosed in utero by ultrasound [22] and are sometimes associated with low birth weight and abnormal Doppler measurements [22,23]. In our case, fetal growth retardation was associated with massive perivillous fibrin deposition under the hematoma. Subamniotic hematomas have never been previously reported in the context of elevated MSAFP. Their incidence during pregnancy is unknown but most of them were found in third trimester placentas and are thought to occur during delivery [11].

Placental lesions due to disturbances of the intervillous circulation are less easily related to pathologic findings. The relative incidence at term of thrombosis, infarcts or fibrin deposition can not be extrapolated to the first half of pregnancy as they may occur anytime later in pregnancy. Furthermore, only extended infarcts and massive fibrin deposition are associated with pregnancy complications [11].

Placental infarcts have never been documented sonographically [17]. Although the sonographic lesion observed in our case was hyperechogenic and not well

circumscribed from the rest of the placental tissue, only pathologic investigation could exclude a chorioangioma. These lesions are secondary to thrombosis of maternal uteroplacental arteries [11]. Extended infarction involving more than 10% of the placental parenchyma is associated with a high incidence of growth retardation and intra-uterine death [11].

Placental lakes are found in 67% of the placentas examined by sonography from the first half of pregnancy until delivery [24]. To some extent, careful sonographic examination reveals small maternal lakes in virtually all placentas, mainly under the chorionic plate or in the marginal zone. Therefore, we only included in our study, placentas with lakes of more than 1 cm in the largest diameter where a turbulent blood flow could be observed on real-time ultrasonography. These large lakes were also present in all the cases labelled sonographically as 'jelly-like placentas'. These placentas were classified in a separate group as in these cases, increased placental volume in itself was sufficient to explain elevated MSAFP [1]. Massive perivillous fibrin deposition and large subchorial or marginal thrombosis were the main pathological findings in placentas containing large lakes and/or having a jelly-like appearance at the time of AFP screening. For the pathologist, these lesions reflect hemodynamic turbulence within the intervillous space with stasis of maternal blood but are thought to occur in placentas with good maternal uteroplacental blood flow [11]. Large placental lakes with or without a jelly-like appearance of the placenta could be an early sonographic clue to the development of these lesions. Furthermore, in groups D ($n = 6$) and E ($n = 5$), four fetuses were found to be growth-retarded at delivery and two pregnancies were complicated by premature delivery. Serial ultrasound examinations could therefore be recommended in the management of these pregnancies.

This study has demonstrated the pathologic basis for a variety of placental and cord sonographic features associated with elevated MSAFP. Vascular cord abnormalities, any alteration of the villous barrier, and increased placental size are all potential etiologies for elevated MSAFP if they develop at the time of AFP screening. The subset of 20 patients described in this study was obtained from a group of 358 patients referred from different hospitals because of elevated MSAFP. The extent to which patients had further local preselection can not be defined. Therefore, estimation from this study of the incidence of the different placental sonographic lesions associated with idiopathic elevation of MSAFP in the general obstetric population would be inaccurate. It is now necessary to investigate the incidence of these placental features and their relation to pregnancy outcome in an unselected group of patients.

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