Sonography of Placental Abnormalities and Oligohydramnios in Women with Elevated Alpha-fetoprotein Levels: Comparison with Control Subjects

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To evaluate the relationship of placental and amniotic fluid findings to elevated maternal serum alpha-fetoprotein (MS-AFP) levels, we compared sonograms made between 18 and 24 weeks gestational age in 76 women with elevated MS-AFP levels with sonograms of a control group. Patients with fetal malformations, incorrect dates, twins, or lack of follow-up were excluded. Overall, 27 (36%) of 76 patients with elevated MS-AFP levels had placental or amniotic fluid abnormalities compared with only three (3%) of 87 control subjects. Significant differences (p < .01) were noted in the frequency of periplasental hemorrhage (9% vs 0%), intraplaclental sonoluencies greater than or equal to 1.5 cm in diameter (18% vs 3%) and moderate or severe oligohydramnios (17% vs 0%). More patients with elevated MS-AFP levels had placenta previa (4%) or placental thickness greater than or equal to 3.5 cm (12%) than did those in the control group (1% and 5%, respectively), although these differences did not reach statistical significance. Seven (28%) of the 27 patients had more than one abnormality.

We conclude that placental and/or amniotic fluid abnormalities are frequently shown on sonograms in women who are examined because of elevated MS-AFP levels.

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Women with elevated levels of maternal serum alpha-fetoprotein (MS-AFP) commonly undergo prenatal sonography for detection of possible fetal malformations, notably neural tube defects. Other common reasons for elevated MS-AFP levels include incorrect gestational age, multiple gestations, and death of the fetus [1]. However, even when accounting for these conditions, no apparent explanation is found in the vast majority of women with abnormally elevated MS-AFP levels [1].

Recent reports suggest that placental abnormalities [2–6] and oligohydramnios [7–9] may be associated with elevated MS-AFP levels. However, the frequency of such observations is uncertain because of the small number of published series. In order to determine the frequency of placental abnormalities and oligohydramnios in women with an apparently normal fetus and an elevated MS-AFP level, we compared sonographic findings in these patients with findings in a control population.

Materials and Methods

The initial study population consisted of 107 consecutive patients referred for sonographic evaluation during a 3-year period (1985–1987) with the clinical indication of an MS-AFP level greater than or equal to 2.5 multiples of the median level. If necessary, corrections for maternal weight or diabetes were made. All serum samples were obtained between 16 and 20 weeks gestational age. Twenty-two patients were excluded because of fetal anomalies (eight cases), incorrect dates (10 cases), or twins (four cases) that explained the elevated MS-AFP level. Nine other patients were eliminated from the study group because of a lack of follow-up (four cases) or referral to sonography after 24 weeks gestational age (five cases),
leaving a total of 76 patients in the study group. All sonograms in these 76 patients were obtained between 18 and 24 weeks gestational age.

The control group consisted of 87 consecutive women who had sonograms made between 18 and 24 weeks gestational age and in whom MS-AFP values were known to be normal. The indications for sonography in these patients included genetic amniocentesis due to advanced maternal age (24 cases), uncertain dates (18 cases), uterine size discordant with dates (14 cases), history of a prior abnormal pregnancy (17 cases), and other routine obstetric indications (14 cases).

Sonograms were obtained with commercially available real-time and static equipment. Each sonogram was reviewed retrospectively and randomly by two experienced sonographers without knowledge of the clinical indication or outcome. When more than one examination was performed, only the first sonogram was evaluated. In each case, the presence of periplacental hemorrhage (retroplacental or subchorionic), placenta previa, intraplacental sonolucencies greater than or equal to 1.5 cm in diameter, and placental thickness greater than or equal to 3.5 cm were noted. A subjective determination of moderate to severe oligohydramnios was also made on the basis of a paucity of amniotic fluid, poor fetal/fluid interfaces, and crowding of fetal parts.

Sonographic findings were then correlated with clinical indications and outcome. The outcome was determined by follow-up sonograms, a review of the medical records, and correspondence with the referring physician.

The statistical significance of sonographic findings was determined with the Fisher two-tailed exact test. Because of the limited size of the study groups, no attempt was made to match abnormal and control populations for maternal factors (i.e., diabetes, hypertension, age, parity, history of tobacco smoking, or previous loss of a pregnancy) that could possibly influence the results.

**Results**

The results of the study are compiled in Table 1. Intraplacental sonolucencies greater than or equal to 1.5 cm in diameter were noted in 14 women (18%) with elevated MS-AFP levels (Fig. 1) compared with only three women (3%) in the control group ($p < .01$). Seven patients (9%) with an elevated MS-AFP level had evidence of periplacental hemorrhage (Fig. 2), and 13 had evidence of moderate (11 cases) or severe (2 cases) oligohydramnios (Fig. 3). In comparison, none of the control patients had sonographic evidence of periplacental hemorrhage ($p < .01$) or oligohydramnios ($p < .001$).

In all, 27 (36%) of 76 patients with an elevated MS-AFP level had one or more placental abnormalities or oligohydramnios compared with only three (3%) of 87 patients in the control group. Seven (26%) of these 27 patients had more than one abnormality. Four patients had both periplacental hemorrhage and intraplacental sonolucencies, and three patients had periplacental hemorrhage and oligohydramnios.

Placenta previa was identified by sonography in three patients (4%) with elevated MS-AFP levels and in one patient (1%) in the control group. However, when only complete previa at the time of delivery is considered, two patients with

**TABLE 1: Comparison of Sonographic Findings in Patients with Elevated Maternal Serum Alpha-fetoprotein (MS-AFP) and Control Subjects**

<table>
<thead>
<tr>
<th>Sonographic Finding</th>
<th>Increased MS-AFP (n = 76)</th>
<th>Control Subjects (n = 87)</th>
<th>$p$ Value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraplacental sonolucencies</td>
<td>14 (18%)</td>
<td>3 (3%)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Periplacental hemorrhage</td>
<td>7 (9%)</td>
<td>0 (0%)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Oligohydramnios (moderate to severe)</td>
<td>13 (17%)</td>
<td>0 (0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>3 (4%)</td>
<td>1 (1%)</td>
<td>.34</td>
</tr>
<tr>
<td>Placental thickness $\geq$3.5 cm</td>
<td>9 (12%)</td>
<td>4 (5%)</td>
<td>.23</td>
</tr>
</tbody>
</table>

$^a$ Fisher two-tailed exact test.

Fig. 1—Sonogram made at 18 weeks gestational age in a woman with elevated level of maternal serum alpha-fetoprotein shows several intraplacental sonolucencies (arrows). Fetus died at 26 weeks gestation. Placental infarcts were described in pathology report.

Fig. 2—A, Sonogram made at 18 weeks gestational age shows placental sonolucencies (arrows) beneath chorionic plate in a woman with elevated maternal serum alpha-fetoprotein. B, Different view of same patient shows a hypoechogenic area consistent with hemorrhage (H) beneath chorionic membrane (arrows). F = fetus, P = placenta.
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Fig. 3.—Sonogram made at 17 weeks gestational age shows marked oligohydramnios in a woman with elevated level of maternal serum alpha-fetoprotein. Follow-up sonograms showed no change in these findings, leading to decision to terminate pregnancy at 21 weeks. F = fetus; B = maternal bladder.

Fig. 4.—Sonogram made at 19 weeks gestational age in a woman with elevated level of maternal serum alpha-fetoprotein shows marked thickening (arrows) of placenta (P).

Elevated MS-AFP levels had a previa compared with no control patients (p = .22).

An abnormally thickened placenta (≥3.5 cm) was found in nine patients (12%) with elevated MS-AFP levels (Fig. 4) compared with four control patients (5%) (p = .23).

In patients with elevated MS-AFP levels, clinical outcome included normal delivery in 53 cases (70%), fetal or neonatal death in 11 cases (15%), intrauterine growth retardation in four cases (5%), premature delivery (<36 weeks gestation) in five cases (7%), and congenital anomalies in three cases (4%). These three anomalies included two cases of cleft lip and palate and one case of amputation of several digits of the hand. No major congenital anomaly such as neural-tube defect or anterior abdominal wall defect was missed by sonography in either the group of patients with elevated MS-AFP levels or the control group.

The clinical outcome of patients with elevated MS-AFP levels was particularly poor in association with oligohydramnios. Of 13 patients with oligohydramnios, the outcome included fetal or neonatal death in seven cases, intrauterine growth retardation in two cases, premature delivery at 25 weeks in one case, and normal term delivery in three cases. Seven patients with oligohydramnios had a history of vaginal bleeding, and two patients had sonographic evidence of periplacental hemorrhage.

Correlation of sonographic findings with pathologic findings was limited because of a lack of adequate examination of the placenta. Also, periplacental and intraplacental hemorrhage often resolve by the time of delivery. We recognize the limitations of pathologic examination, but report that placental blood clots were found at delivery in five cases and placental infarcts were identified in two additional cases. Both patients with placental infarcts had intraplacental sonolucencies. Of the five patients with pathologic evidence of retroplacental clot, sonographic findings suggested periplacental hemorrhage in two cases and marked oligohydramnios in two additional cases. The remaining patient had a normal-appearing placenta at 22 weeks gestational age, but one week later the patient developed acute clinical symptoms consistent with retroplacental abruption. The sonogram at this time showed a markedly thickened and heterogeneous placenta consistent with a retroplacental hemorrhage.

Discussion

Alpha-fetoprotein (AFP) is a fetal-specific protein that is first produced by the yolk sac and later by the fetal gastrointestinal tract and liver [1]. AFP reaches the amniotic fluid by excretion in fetal urine and by diffusion across fetal skin capillaries. In turn, AFP in the amniotic fluid diffuses across placental membranes to reach the maternal circulation. Because of this diffusion gradient, concentrations of AFP in the fetal serum are 100--200 times greater than that found in the amniotic fluid and 100,000 times greater than that found in the maternal serum at 16--20 gestational weeks [1].

Up to 4% of all women with an aneconically normal fetus have elevated levels of MS-AFP [1]. Fetal-maternal hemorrhage has long been suspected as the underlying cause of elevated MS-AFP levels in many of these patients. Because the concentration of AFP in the fetal serum is 100,000 times greater than that in maternal serum at 16--20 weeks gestational age, elevation of the MS-AFP level is a sensitive marker for fetal-maternal hemorrhage [10--12]. Therefore, an elevated MS-AFP level may be a sign of an underlying placental abnormality. Women with elevated MS-AFP levels are known to be at increased risk of placental abruption, intrauterine growth retardation, premature labor, and death of the fetus [1, 3, 7, 13].

As our study shows, placental abnormalities and oligohydramnios are frequently seen in women with elevated MS-AFP levels and an aneconically normal fetus. Intraplacental sonolucencies (Fig. 1) were the most common sonographic abnormal findings in this study. The frequency of intraplacental sonolucencies in women with elevated MS-AFP levels (18%) agrees with the results of Perkes et al. [2], who reported intraplacental sonolucencies in 18.5% of patients with elevated MS-AFP levels and in 2.3% of a control group.

Although intraplacental sonolucencies may represent various pathologic findings, Spirit et al. [14] and others [2, 3, 15--18] have shown that they correlate best with intervillous thrombi. Intervillous thrombi represent intraplacental fetal hemorrhage resulting from rupture of villous capillaries [14, 15]. Devi et al. [18] showed a strong correlation between intervillous thrombi and the presence of fetal RBCs in the maternal circulation. Because intervillous thrombosis repro-
sents a site of fetal-maternal hemorrhage, it also has been associated with Rh sensitization and erythroblastosis in Rh-negative women [15–18]. An association also has been observed between intervillous thrombi and placental abruption, spontaneous abortion, and premature delivery [15–18].

The prevalence and significance of intervillous thrombs appear to vary with gestational age. Javert and Reiss [15] reported pathologic findings of intervillous thrombi in 7.7% of all placentas up to 22 weeks gestation, including 1.2% of placentas from therapeutic abortions and 10.6% from spontaneous abortions. In comparison, these authors found intervillous thrombi in 28.5% of term placentas [15]. Similarly, intraplacental sonoluencies are frequently shown in the third trimester on prenatal sonography, but were observed in only 3% of control subjects before 24 weeks gestation in this study.

As this was a retrospective study, we made no attempt to distinguish intraplacental sonoluencies with blood flow (“maternal lakes”) from those without evidence of flow. However, this distinction may be incomplete even when evaluated prospectively because slow flow may be difficult to see on sonography. Also, our own anecdotal experience suggests that maternal lakes seen before 24 gestational weeks also may be associated with elevated MS-AFP levels. We speculate that maternal lakes may form at sites of previous hemorrhage in this situation.

In addition to placental sonoluencies, sonographic evidence of periplacental hemorrhage was associated with elevated MS-AFP levels in the present study (Fig. 2). Seven patients (9%) with elevated MS-AFP levels had evidence of periplacental hemorrhage [19], and all hemorrhages were located near the margin of the placenta or beneath the chorionic membrane (Fig. 2). In comparison, Fleischer et al. [6] reported periplacental hematomas in 16 (64%) of 25 patients with an elevated MS-AFP level and a normal fetus. These authors also reported a high frequency of retroplacental hemorrhage. The reason for these discrepant results is unclear but possibly reflects differences in criteria for selection of patients or in sonographic interpretation. Periplacental hemorrhage apparently leads to an elevated MS-AFP level in a manner similar to that of intraplacental hemorrhage, with transfer of fetal RBCs to the maternal circulation [7, 17, 18]. This notion is supported by an association between circulating fetal RBCs and retroplacental hematomas examined at birth [18].

Thickened placentas (Fig. 4) and placenta previa were observed more often in patients with elevated MS-AFP levels than in the control group in the present study, although these associations did not reach statistical significance. Nevertheless, a thickened placenta or placenta previa in patients with an elevated MS-AFP level may be a helpful ancillary finding in conjunction with other sonographic abnormalities.

The association between midtrimester oligohydramnios and elevated MS-AFP level noted in the present study (Fig. 3) confirms earlier observations [7–9]. In the absence of genitourinary anomalies, the cause of oligohydramnios in these pregnancies is uncertain, but it has been suggested that it reflects an underlying uteroplacental insufficiency [9]. Fetal hypoxemia may result in shunting of blood away from the fetal kidneys and secondarily in decreased urine production and decreased amniotic fluid volume [9]. The frequent history of vaginal bleeding in association with oligohydramnios and elevated MS-AFP levels also implicates placental dysfunction as a contributing cause.

Regardless of the causes, severe midtrimester oligohydramnios is a predictor of poor fetal outcome due to pulmonary hypoplasia, intrauterine growth retardation, and prematurity [8–10]. In our 13 cases of oligohydramnios and elevated MS-AFP level, seven resulted in fetal or neonatal death, two resulted in intrauterine growth retardation, one resulted in premature delivery at 25 weeks, and only three (23%) resulted in a normal term delivery. A similar outcome has been observed by other authors [8–10]. Richards et al. [9] suggests that the risk of fetal death is increased when severe oligohydramnios persists longer than 2–4 weeks or when there is history of vaginal bleeding or amniotic fluid leakage.

Our findings carry important implications for counseling women found to have an elevated MS-AFP level. Although the protocol for evaluating such patients varies from institution to institution, our approach includes a thorough sonogram to identify possible fetal anomalies before a decision is made to perform amniocentesis. Few anomalies have been missed at our centers, particularly with awareness of characteristic cranial abnormalities that recently have been associated with myelomeningocele [20, 21]. However, amniocentesis is commonly performed to provide additional reassurance that a significant anomaly has not been missed. When placental abnormalities are shown that might explain the elevated MS-AFP level and the fetus appears anatomically normal, many women may decide that the benefits of amniocentesis do not justify its additional risk or expense.

In summary, a significant proportion of women with elevated MS-AFP levels but an anatomically normal fetus have intraplacental sonoluencies, periplacental hemorrhage, and/or oligohydramnios when compared with a control group. Current evidence suggests that these associations reflect fetal-maternal hemorrhage and placental dysfunction. Awareness of these sonographic findings may influence MS-AFP screening protocols.

REFERENCES

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