

ALPHA-FETOPROTEIN AND DOWN SYNDROME

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ABSTRACT

We determined the concentration of alpha-fetoprotein by rocket immunoelectrophoresis in amniotic fluid obtained from second trimester pregnancies with several pathological fetuses according to their karyotype. We found low alpha-fetoprotein levels in 3 out of 6 fetuses with Down syndrome (trisomy 21). Two other fetuses with trisomies 13 and 18 showed alpha-fetoprotein levels similar to those detected in the amniotic fluid of fetuses with normal karyotypes.

INTRODUCTION

The observation that lower levels of maternal serum alpha-fetoprotein (AFP) tend to occur in second trimester pregnancies involving fetal chromosome abnormalities than in normal pregnancies was first reported by Merkatz *et al.* (1984). Cuckle *et al.* (1984), in a study of 61 pregnancies involving fetuses affected with Down syndrome, found lower maternal serum levels in this group but not in other trisomic fetuses. Both authors suggested that this finding indicates the potential of the serum AFP assay as a valuable screening test for fetal Down syndrome, especially for pregnant women aged 35 years or less who are not usually selected for prenatal cytogenetic diagnosis. This association has been confirmed by many authors (Baumgarten *et al.*, 1985; Macri *et al.*, 1986; Simpson *et al.*, 1986).

Guibaud *et al.* (1984) found that 10 of 13 samples of maternal serum and

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amniotic fluid (AF) from Down syndrome fetuses presented low AFP levels. Similar observations have been reported by Trigg *et al.* (1984), Tabor *et al.* (1984), Cuckle *et al.* (1985) and Davis *et al.* (1985). However, these data are in contrast to those reported by Seller (1984) who detected a low level of maternal serum AFP in only one of 8 pregnancies involving trisomy 21.

In the present paper we report AFP levels in the AF of pregnant women with Down syndrome fetuses or with fetuses carrying other chromosome aberrations and compare them with the levels detected in the AF of pregnant women with normal fetuses.

MATERIALS AND METHODS

A total of 153 AF samples were collected by amniocentesis from Brazilian pregnant women who presented a high risk for chromosome aberrations. Among these, 6 fetuses with Down syndrome were detected. Two additional AF samples from fetuses with trisomies 13 and 18 and 4 samples from fetuses with balanced translocations were also tested.

Fetal karyotypes were obtained by culturing amniotic fluid cells by the method of Nazareth *et al.* (1981). AFP was determined by the rocket immunoelectrophoresis technique of Laurell (1966) using reagents from Behringwerke AG (Marburg, West Germany). MoM (multiples of the median) values were used for each gestational age according to the Second Report of the UK Collaborative Study (1979). A previous study using the same method was undertaken by our laboratory as the first investigation of this type on the Brazilian population, and the results for normal pregnancies have been published elsewhere (Costanzi *et al.*, 1987).

RESULTS

Three out of 6 AF samples from fetuses with Down syndrome presented low AFP levels (≤ 0.6 MoM), whereas AF samples from fetuses with trisomy for chromosomes 13 and 18 showed normal AFP levels (Table I). These observations agree with those reported by Nelson and Petersen (1985) and Doran *et al.* (1986).

In fetuses with balanced translocations involving either chromosome 21 or other autosomes (t(8;11) and t(3;4)), the amniotic-fluid AFP concentration was within normal limits.

Approximately 20% of the AF samples from fetuses with normal karyotypes between the 13th and the 21st gestational week presented AFP levels ≤ 0.6 MoM (Costanzi *et al.*, 1987), while these low values were present in 3 out of 6 AF samples from fetuses with Down syndrome.

Table I - Alpha-fetoprotein levels in the amniotic fluid of fetuses with different chromosome aberrations.

Fetal karyotype	Gestational age	AFP ($\mu\text{g/ml}$)	MoM*	Indication for amniocentesis
47,XY,+21	16	13.5	0.66	advanced maternal age + previous child with Down syndrome
47,XY,+21	16	12.0	0.59	advanced maternal age + previous child with neural tube defect
47,XX,+21	19	5.6	0.47	advanced maternal age
47,XX,+21	16,5	11.5	0.56	advanced maternal age
47,XY,+21	19	11.6	0.97	previous child with Down syndrome
46,XY,t(14q;21q)	18	12.5	0.61	t(14;21) mat
47,XY,+13	16	17.5	0.86	advanced maternal age
47,XY,+18	16	25.0	1.23	advanced maternal age
45,XY,t(14q;21q)	16	20.3	1.0	t(14q;21q) mat
45,XY,t(14q;21q)	17	20.6	1.0	t(14q;21q) mat
46,XY,t(3;4)	15	34.5	1.48	t(3;4) mat
46,XY,t(8;11)	18	22.0	1.08	t(8;11) mat

*MoM - multiple of the median ($\bar{x}_{16-18} = 20.3 \mu\text{g/ml}$ $\bar{x}_{19-21} = 11.9 \mu\text{g/ml}$).

DISCUSSION

AFP is produced by the fetal liver from the beginning of intra-uterine life. It reaches the amniotic fluid through the fetal urine and arrives to the maternal blood by transplacental diffusion. The maternal serum AFP level can only be accurately measured after the 16th gestational week. By that time, AFP concentrations in fetal serum and in the AF are already decreasing owing to albumin synthesis by the fetal liver, growth of the conceptus and an increase in both body volume and transplacental diffusion area.

High AFP levels in maternal serum and in the AF of pregnant women whose fetuses have neural tube defects have been detected in prenatal diagnosis laboratories since the early seventies. However, the importance of low AFP levels has been pointed out in the literature only recently.

The reasons for the occurrence of low AFP concentrations in maternal serum and AF of Down syndrome fetuses have been discussed by many authors. The first proposal was that these fetuses have some problem in transplacental diffusion, since low AFP levels have been found in maternal serum and aneuploid fetuses are known to

have difficult diffusion. However, the AFP measurements performed in the AF by Guibaud *et al.* (1984) and Tabor *et al.* (1984) and the results of the present paper indicate that the AFP level is also reduced in the AF and this is not only a placental problem. Thus, the low AFP levels could be a consequence either of fetal immaturity or of accelerated growth of fetuses with trisomy 21.

Our median AFP level in the AF of Down syndrome pregnancies was 0.64 MoM, which is similar to the values obtained by Tabor *et al.* (1984) and Cuckle *et al.* (1985) and very similar to the 0.58 MoM value found by Hullin *et al.* (1985). Low AFP levels have been described in fetuses with immature organs such as the liver (Doran *et al.*, 1986). Nevertheless, our data show that fetuses trisomic for chromosomes 13 and 18 do not exhibit this variation in AFP concentration in the AF, but are even more severely affected in development than fetuses with Down syndrome.

In our study, AFP levels in the two AF of fetuses with unbalanced chromosome aberrations other than trisomy 21 did not differ from those observed in the AF of fetuses with normal karyotypes. Thus, the low AFP concentration seems to be associated with the presence of an extra chromosome 21 in Down syndrome patients. We suggest that chromosome 21 may have one or more genes responsible for the regulation of AFP synthesis or elimination, even though the AFP and albumin genes have been mapped on chromosome 4 (McKusick, 1986).

A low AFP concentration is not sufficient for the diagnosis of Down syndrome *in utero*, but the AF sample must also be submitted to karyotype analysis. However, AFP studies can significantly contribute to the prenatal detection of Down syndrome and to the identification of high-risk groups in the general population.

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RESUMO

A concentração da alfa-fetoproteína foi determinada pela imunoeletróforese tipo "rocket" no líquido amniótico obtido de gestações do segundo trimestre de vários fetos com cariótipo alterado. Os fetos com síndrome de Down (trisomia do cromossomo 21) apresentaram baixos níveis de alfa-fetoproteína, enquanto que os fetos com outras aberrações cromossômicas que não a trissomia 21 apresentaram níveis semelhantes aos observados nos líquidos amnióticos de fetos cromossomicamente normais.

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