Amniotic fluid hormone profiles during normal and abnormal pregnancy

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Summary: Amniotic fluid (AF) and maternal serum (MS) chorionic gonadotropin (HCG), placental lactogen (HPL), pregnancy-specific β_1-glycoprotein (SP_1), total estrogens (ET), alpha-fetoprotein (AFP) and prolactin (PRL) were measured by enzyme-immunoassays, in 50 normal (A) and in 37 abnormal (B) pregnancies, from 16th to 40th weeks. A: the proteins HCG, AFP and PRL showed a similar decreasing trend after the 20th week, while HPL and SP_1 rose progressively throughout the 2nd trimester, thereafter remaining constant. On the contrary ET showed an increasing pattern until term. Chorionic gonadotropin HPL and SP_1 in MS were higher than in AF, while AF values of AFP and PRL were higher than in MS, but the ratio MS/AF of all hormone values increased significantly from the 2nd to the 3rd trimester ($p < 0.005 - p < 0.000001$). Estrogens had about the same concentration in AF and MS during the 2nd trimester, but at term of pregnancy, their AF values were double those of MS. B: in polyhydramnios, elevated AF placental hormones were found, while PRL was very low. In erythroblastosis and diabetes, AFP was very low, but placental hormones, PRL and ET were both high and low. In toxemia, SP_1, hCG and PRL were elevated, while HPL and ET were very low. In anencephaly and hydrocephaly with spina bifida, AFP was markedly elevated and ET were very low, but in simple hydrocephalous, very low AFP was found. In chromosomal anomalies very high placental hormones and very low AFP and ET were found. In conclusion, *a*) with advancing gestation the MS/AF ratio of protein hormones increases, while that of estrogens is reduced, *b*) the AF hormone reference values could be useful to identify normal and/or abnormal pregnancy.

Key words: AFP; Amniotic fluid hormones; Complicated pregnancies, ET; HCG; HPL; Normal pregnancy; PRL; SP_1.

INTRODUCTION

The amniotic fluid (AF) is a remarkably dynamic liquid through which the fetus conveys a great deal of physiologically useful information concerning its health and maturity ([1]). During recent years, advances in methodology of transabdominal amniocentesis, as well as enzyme immunoassays for sensitive and specific hormone measurements have made amniotic fluid (AF) examination a useful tool in biochemical monitoring of fetal well-being.

The purpose of this study was the determination of AF and maternal serum (MS) levels of chorionic gonadotropin (HCG) (against β-hCG), placental lactogen (HPL), pregnancy-specific β_1-glycoprotein (SP_1), total estrogens (ET), alpha-fetoprotein (AFP) and prolactin (PRL) throughout the normal gestation, in an effort a) to establish reference AF hormone values, for identification of normal or abnormal pregnancies, since only scattered results

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on AF hormones have been found in the literature, and b) to understand the physiological role of AF hormones in pregnancy, by evaluating the changes of MS and AF hormone values with advancing gestational age.

MATERIALS AND METHODS

Sixty-six AF and MS samples from 50 pregnancies with normal outcome and healthy neonates, as well as 45 AF and MS samples from 37 abnormal pregnancies were evaluated (Table 1).

Table 1. – *Material.*

Normal pregnancy	n = 50
Abnormal pregnancy	n = 37
– Polyhydramnios	n = 6
– Erythroblastosis	n = 6
– Diabetes	n = 5
– Intrauterine growth retardation (IUGR)	n = 5
– Toxemia	n = 5
– Anencephaly	n = 3
– Hydrocephaly	n = 2
– Hydrocephalous with spina bifida	n = 1
– Down's syndrome	n = 2
– Turner's syndrome	n = 2

Our material consisted of pregnancies between the 16th and the 40th week. The indications for the amniocentesis were prenatal diagnosis, evaluation of IUGR and fetal lung maturity. Blood was drawn 30 min prior to amniocentesis. Amniotic fluid withdrawals were performed by means of ultrasonic guided transabdominal amniocentesis. Serum and AF were frozen at —20° C until the analysis. The newborns of the normal pregnancies studied had a birthweight of 3.300±400 grs and Apgar Scores 9-10.

The method used for the determination of proteins and estrogens were enzyme-immunoas- (EIA) (Table 2).

Statistical analysis was performed using paired t-test.

RESULTS

A) *Normal pregnancies*

In Table 3 the AF hormone values are presented ($\bar{x}\pm SD$) and in figures 1-6 the AF hormone ($\bar{x}\pm SD$) profiles from the 16th week to the 40th in normal pregnancy are depicted.

The proteins HCG (Fig. 1), AFP (Fig. 5) and PRL (Fig. 6) showed similar decreasing trends in their patterns after the 20th week, reaching the lowest levels during the last month of pregnancy, while HPL (Fig. 2) and SP_1 (Fig. 3) rose progressively after the 20th week and remai-

Table 2. – *Type of assays, their specific performance characteristics and trade names.*

Hormone	Type of assays	Sensitivity	Precision inter-assay (V%)	Accuracy recovery	Trade names
β-hCG	Sandwich	0.76 mIU/ml	6.4	84-116	Abbott β-hCG 15/15 Abbott Lab. Diagnostics
HPL	Competitive	32 ng/ml	7.26	85-122	HPL-nosticon Organon Technika
SP_1	Sandwich	0.30 ng/ml	3.5-6.5	95-104	Enzygnost-SP_1 Behring
ET	Competitive	0.60 ng/ml	8.4	82.5-120	Estronosticon Organon Technika
AFP	Sandwich	2.0 ng/ml	4.45	96-104	Abbott AFP Monoclonal Abbott Laboratories
PRL	Sandwich	1.5 ng/ml	6.0	92-100	Tandem E PRL Monoclonal Hybritech

Table 3. – *Hormone levels ($\bar{x}\pm SD$) in amniotic fluid during normal pregnancy.*

Weeks Hormone	16th-18th	19th-21st	26th-31st	35th-40th
β-hCG mIU/ml	4330±1875 n = 19	3144±1331 n = 15	1073±597 n = 6	455±284 n = 6
HPL ng/ml	463±197 n = 19	402±129 n = 17	491±178 n = 6	593±244 n = 7
SP_1 ng/ml	1324±672 n = 23	1545±757 n = 17	2083±524 n = 8	2096±890 n = 8
ET ng/ml	72±23 n = 18	112±66 n = 15	422±304 n = 6	1133±773 n = 8
AFP ng/ml	15963±3907 n = 19	10880±4886 n = 17	1940±1697 n = 6	300±180 n = 6
PRL ng/ml	3012±2169 n = 14	3496±2294 n = 15	1449±727 n = 7	528±204 n = 6

ned relatively constant in the 3rd trimester. On the contrary, ET (Fig. 4) showed a continuously increasing pattern until term, with a sharp increase after the 36th week of pregnancy.

Maternal serum concentrations of placental hormones HCG, HPL and SP_1 were higher than those in AF concentrations (Fig. 7, on the left) and this relationship increased significantly from early second (A) to the third trimester (B) ($p<0.005$–$p<0.000001$). On the contrary, AFP and PRL showed much higher values in AF than in MS (Fig. 7, on the right) and the ratio MS/AF increased also with the progress of gestation ($p < 0.005$–$p < 0.000001$).

Estrogens had about the same concentration in both biological fluids during the second trimester (Fig. 7) but with advancing gestational age, AF estrogen values increased rapidly so that at the end of gestation they were almost double that of MS estrogens.

B) *Abnormal pregnancies*

Individual AF hormone values in abnormal pregnancies, in relation to $\bar{x}\pm SD$ range in normal pregnancy are presented in Figures 1-6.

a) The six cases with polyhydramnios (PH) and healthy fetuses showed elevated placental hormones HCG, HPL and SP_1, while PRL values were very low and ET

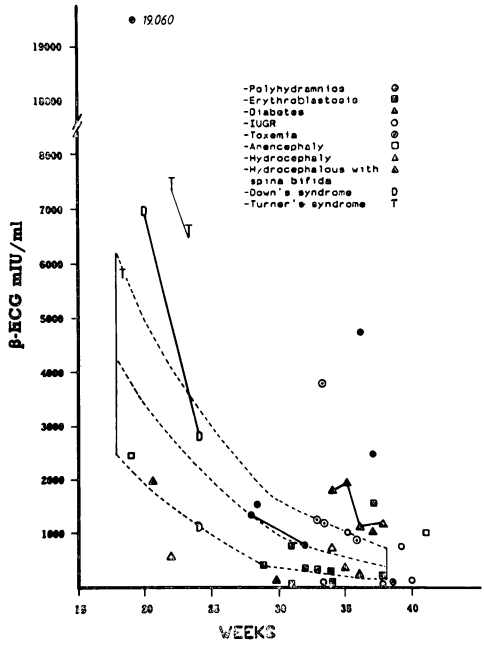

Fig. 1. — Amniotic fluid HCG (as β-hCG) profile ($\bar{x}\pm SD$) in normal pregnancy and individual values in cases of abnormal gestation.

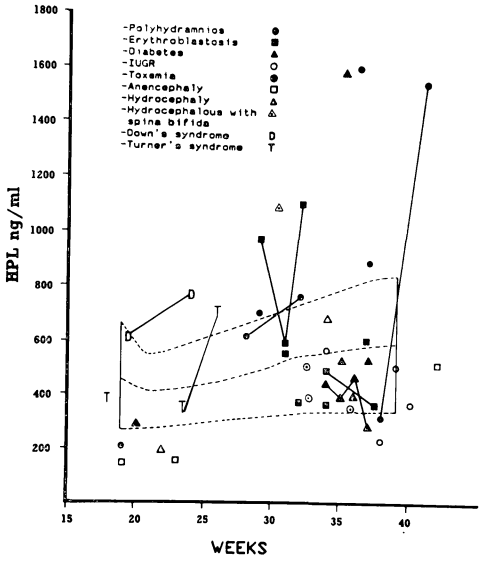

Fig. 2. — Amniotic fluid HPL profile ($\bar{x} \pm SD$) in normal pregnancy and individual values in cases of abnormal gestation.

showed a tendency towards lower normal values. Alpha-fetoprotein values were within the normal range.

b) In erythroblastosis (ER) and diabetes (DB), AFP values were very low, while ET were high in DB and low in ER. Placental hormones and PRL showed both very high and very low values.

c) In pregnancies complicated with IUGR, the AFP, HPL and SP_1 values were very low. Total estrogens were found usually in low normal values, while PRL and HCG showed high and low values.

d) In pregnancies with toxemia and low birth weight neonates, SP_1, HCG and PRL were elevated, while HPL was low but ET and AFP showed both high or low values.

e) In the pregnancy with anencephaly and in the case of the embryo with hydrocephaly and spina bifida, AFP values were markedly elevated, while ET were very low. On the contrary, the cases with simple hydrocephalous presented very low AFP values.

f) In chromosomal anomalies (Down's and Turner's syndrome), very high placental hormones and low ET were found. Alpha-fetoprotein was very low in the cases with Down's syndrome and in one case with Turner's, while in the second case (18 weeks) with twins – normal and Turner – a highly elevated value was found Prolactin was within normal range.

DISCUSSION

Amniotic fluid as well as amnion, chorion laeve, decidua and myometrium are the paracrine arm of fetal maternal communication and play an important role in pregnancy maintenance and parturition [2]. A variety of protein and steroid hormones

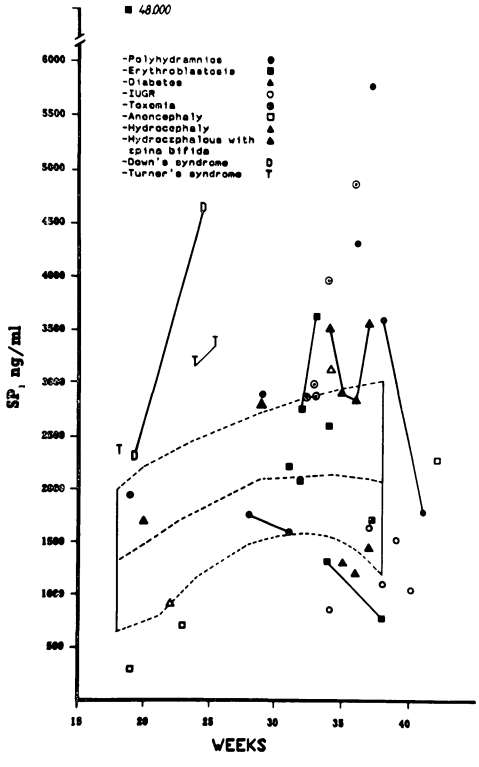

Fig. 3. — Amniotic fluid SP_1 profile ($\bar{x} \pm SD$) in normal pregnancy and individual values in cases of anormal gestation.

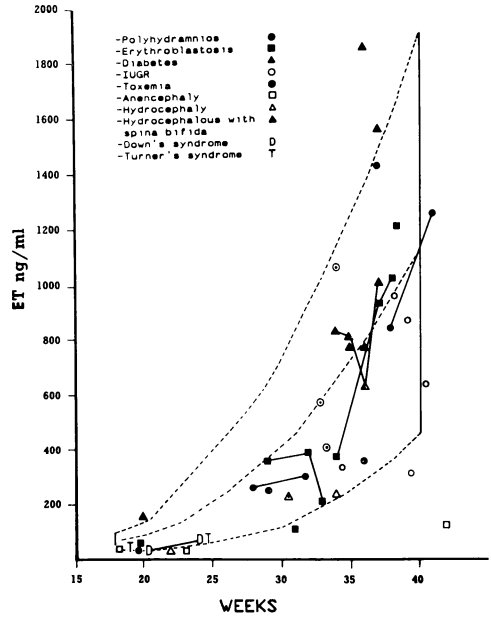

Fig. 4. — Amniotic fluid ET profile ($\bar{x} \pm SD$) in normal pregnancy and individual values in cases of abnormal gestation.

are found in AF, but caution should be exercised in interpreting any change in the hormone concentration, because it is a function of hormone inflow and outflow as well as the volume of AF [1]. With advancing gestation, both origin and composition of AF change gradually, because the features of one source are superimposed on the other [4]. In early pregnancy, AF might show the change from maternal to fetal interstitial fluid, while in the second trimester it might show the appearance of an element of fetal urine and in the last third period the composition of AF is dominated by fetal urine [3, 4].

Moreover, the facility with which any material passes through AF and other fetal or maternal compartments may change during pregnancy. The fetal skin which in early pregnancy is a site of active transfer of water and solutes becomes impenetrable by 17-20 weeks. Thus the movements of each molecular species must be considered separately because in many instances entry or exit must be active transfer or at least passively impeded [4].

Amniotic fluid hormone levels are representative of source and entry of each hormone as well as of possible physiological role in pregnancy. Maternal blood bathes the villous trophoblast [5], so the protein hormones HCG, HPL, SP_1 originating from the placenta, circulate predominantly in maternal serum and are found in AF in small amounts [1] and, as the placental function and permeability decrease during the third trimester, the ratio MS/AF in hormone concentration increases, just as was demonstrated in this study.

Our data on amniotic fluid HCG concentration and pattern during normal pregnancy are in agreement with previous stu-

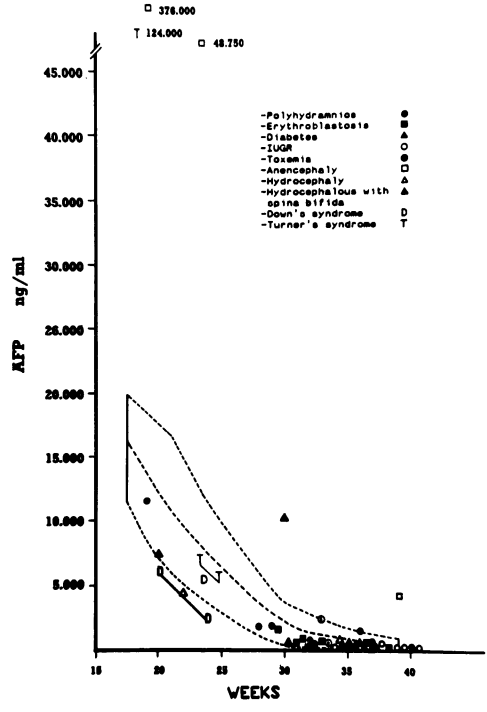

Fig. 5. — Amniotic fluid AFP profile ($\bar{x} \pm SD$) in normal pregnancy and individual values in cases of abnormal gestation.

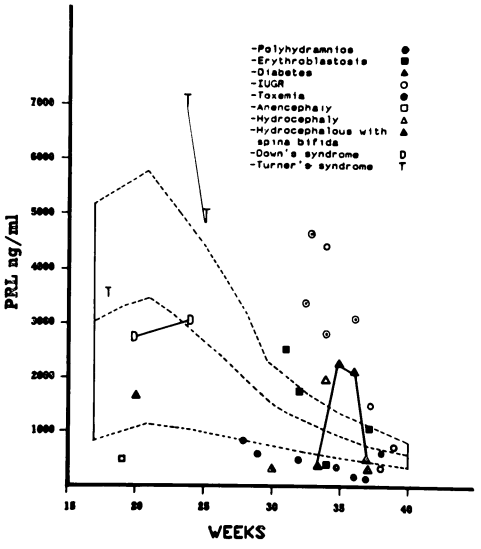

Fig. 6. — Amniotic fluid PRL profile ($\bar{x} \pm SD$) in normal pregnancy and individual values in cases of abnormal gestation.

dies ([6, 7]). The elevated values in PH may be caused by over-production of HCG by the placenta, or its increasing permeability in these cases, while in chromosomal anomalies the high HCG values seem to be an alarm signal from malformed fetuses. Both the very high and the very low values found in ER and DB have also been reported, probably according to the severity of the diseases ([7, 8]).

In the case of HPL, in vitro studies on fetal membranes at term showed bidirectional transfer of hormone by simple diffusion without any evidence of asymmetric transfer or cell-mediated process ([9]). Although the AF concentration has shown a tendency to parallel MS concentration ([10]), the latter rises more rapidly and thus the ratio MS/AF increases significantly from 4.2 in the second to 11.1 in the third trimester ($p < 0.005$). Probably increasing metabolism of HPL by AF or a decreasing transfer through the amnionic chorion from the outset to the end of pregnancy could account for the increasing ratio of HPL ([11, 12]). Our data also reconfirm the hormone concentration and the HPL pattern during pregnancy, as has been reported by others ([9, 13]). The amniotic fluid HPL values in abnormal pregnancies PH, ER, and DB showed a quite analogous profile with HCG. In general, HPL values in AF, cannot assist in the assessment of other pathological disorders, except in cases of IUGR and PH.

Our findings on amniotic fluid SP_1 showed some similarities with the interesting study of Wurz *et al.* ([14]), mainly in the distribution of AF hormone values throughout normal pregnancy, while our finding on the difference in the MS/AF ratio between second and third trimester (37.5 and 85 respectively, compared to 100 of later study) is probably due to antibodies of RIA techniques. Amniotic fluid SP_1 concentration also reflects the placental function and correlates well with fetal size, so in the cases of IUGR and

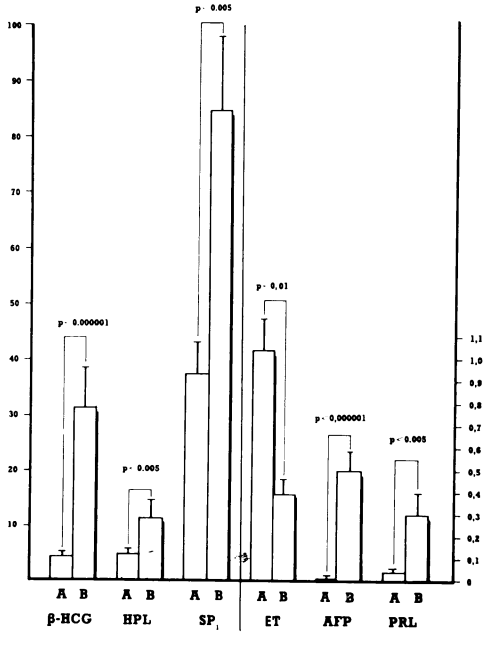

Fig. 7. — Maternal serum/amniotic fluid hormone ratios in early second (A) and in third (B) trimester.

anencephaly it showed a tendency towards very low values because of placental dystrophy. In contrast, the markedly elevated values in pregnancies with Turner's and Down's syndrome and toxemia, seem to reflect the fetal distress ([15]) in these cases, rather than the placental dysfunction. The hormone values in ER, DB, PH, although showing a tendency towards steep increase, because of enlarged placental mass, are not of value for the diagnosis and the management of these disorders.

We preferred to measure the total estrogens in AF as more representative of the conjugated and unconjugated fraction, by an available EIA kit with antiserum, which reacts to the same extent with both the free and the conjugated estrogens. The ET pattern is comparable with that of estriol (E_3) in previous studies ([16, 17, 18]). The sharp increase after the 32nd week reflects the great contribution of conjugated E_3 after the onset of the fetal kidney with advanced biochemical maturation of the conceptus ([19]). So the MS/AF ratio from 1 becomes 0.4.

A fairly good correlation between ET values and birthweight has been reported ([20]), as was found in this study with the low ET values in IUGR infants, especially when the measurements of AF estrogens were made on the day of delivery. In erythroblastosis, a drop in E_3 concentration has been found ([21, 22]) as is also observed in our study, though in two cases with mild rhesus immunization ET did not decrease significantly, as has been also reported ([20]). The tendency to low values in PH were in agreement with the findings in other studies ([22]). Extremely low ET levels were found, as expected, in cases with anencephalous as well as in Down's syndrome ([23, 24]) and this is of predictive value for these malformations.

AFP is an oncodevelopmental protein detectable as early as the fourth week after conception in the human embryo, initially produced in the yolk sac and then by the fetal liver ([25]). Normally AFP enters AF via fetal urination ([26]) and subsequently appears in the maternal circulation partly by direct transfer across fetal membranes ([27]). The value of measurements of AFP in AF between week 16-20 to detect fetal abnormalities is now established as a diagnostic rather than a screening test ([28]). Since fetal serum and AF levels decrease sharply after the 13th week, correct interpretation of its concentration requires precise knowledge of gestational age. The AFP levels may be elevated in abnormalities in which fetal integriment is not intact, and the protein leaks from the capillaries into the AF mainly in open neural tube defect, anencephaly and spina bifida, as was found in our study.

Elevated AF values of AFP in cases of PH are associated with congenital abnormalities of the fetus as we have already reported ([29]), while in the present study, in all PH cases with healthy neonates, normal AFP vaues were found. Thus, AFP values in AF seem to be of value in the diagnosis of fetal abnormalities in PH ([30]). The low values in Down's syndrome may be due to maturation delay in fetal liver development, just as AFP synthesis could be lacking in trisomic fetuses ([31]).

High concentration of PRL in AF results from the transport of human decidua prolactin across reflected amniochorion ([32]). Neither amnion, nor chorion is able to synthesize PRL, suggesting a decidual origin of AF prolactin ([33, 34]). Further evidence of a decidual source of PRL is found in cases of suppression of maternal and fetal pituitary prolactin by bromocryptine, without any associated alteration in AF prolactin ([35]).

Amniotic fluid PRL may play a role in the maintenance of AF homeostasis. The lack of PRL receptors in chorion causes diminution of AF prolactin and thus osmoregulatory action is impeded, resulting in the accumulation of AF i.e. polyhydram-

nios ([36]). Almost all PRL values in our cases of idiopathic PH are very low, in agreement with previous studies ([29, 37, 38]). In toxemia low PRL values in AF have been reported ([39]), while in our study markedly elevated values were observed, in agreement with McCoshen and Tyson ([40]), probably as a direct risk signal for the fetus. The elevated values found in pregnancies with IUGR as has been also found by others ([39]) could also be attributed the same reason.

In conclusion, a) with advancing normal gestation, from the early second to the third trimester, the ratio of maternal serum/amniotic fluid protein hormone concentrations increases significantly, while that of estrogens is diminished; b) the amniotic fluid hormone reference values could be useful in the evaluation of complicated pregnancies, especially in the cases of PH, IUGR and fetal abnormalities.

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