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Plasma alpha-fetoprotein levels in normal and abnormal pregnancy

by
P. GRELLA, A. ROS and F. MANGANELLI

A new variable has recently been added to the biochemical monitoring of pregnancy at risk; the determination of alpha-fetoprotein in the maternal plasma and in the amniotic fluid.

The chemical and physical properties of the substance have been described in a number of reports ([1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12]).

The origin of alpha-fetoprotein in the maternal plasma has not been entirely explained as yet. The most likely hypothesis is that it is produced by the foetus and that it passes to the mother either through the placenta or through the amniotic fluid. As to its production site, autoradiographic tests have shown that in the human foetus it can be synthetised in the liver and in the amniotic sac, but not in the placenta ([19, 20, 21]).

The significant correlation between maternal and fetal levels and the gradient between the two compartments (300 to 600 times) favours the foetal origin ([13]). However, maternal origin, at least in part, is not excluded.

Radio-immunological studies have revealed small quantities of alpha-fetoprotein in the serum of healthy adult subjects ([14, 15, 16]).

It may be that pregnant women produce a greater quantity of alpha-fetoprotein than other women; in other words, an unknown placental factor may weaken the repression of the foetal gene responsible for alpha-fetoprotein synthesis ([17]), as occurs in primary neoplasia of the liver, severe hepatitis and cirrhosis ([19]).

Jacob and Monod ([22]) have suggested that the biosynthesis of alpha-fetoprotein in healthy adults is inhibited by a repressor agent which affects the gene responsible for its production.

The possibility that a large amount of alpha-fetoprotein is produced during pregnancy also appears to be confirmed by the high concentration found in a case of vesicular mola, where fetal production was negligible ([23]).

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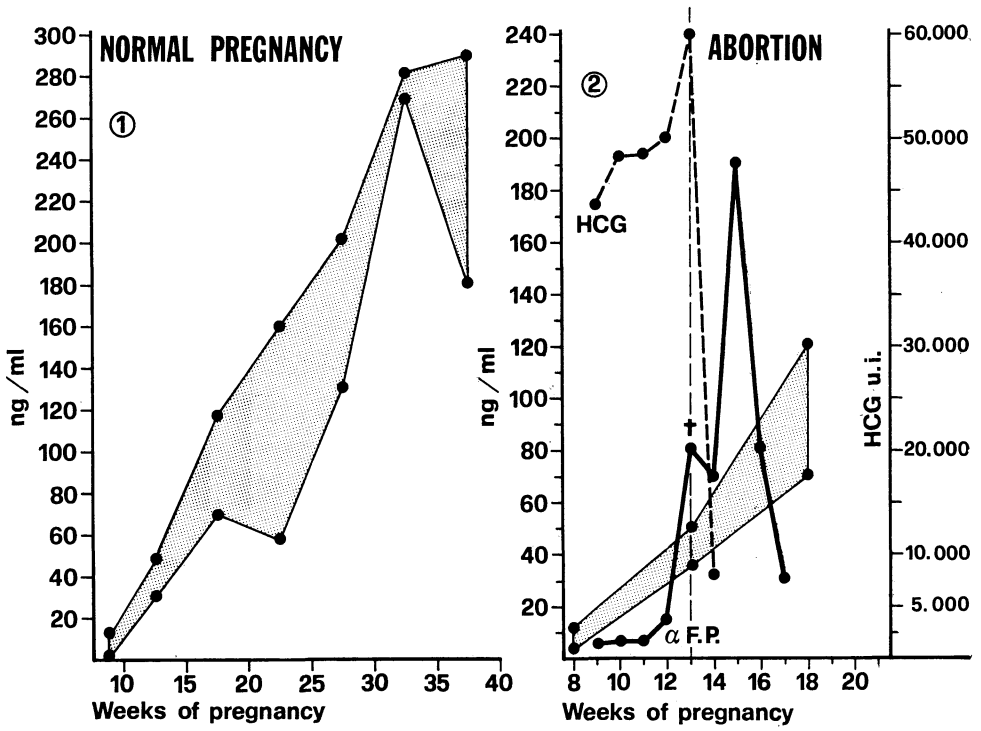

FIG. 1 - Normal pregnancy. The alpha-fetoprotein plasma level tends to decrease during the final weeks of pregnancy.

FIG. 2 - Miscarriage. In this case the death of the embryo, established ultrasonically, was preceded by a sudden increase of alpha-fetoprotein in the maternal plasma; the HCG values remained high for a further week.

During pregnancy alpha-fetoprotein increases up to the 32nd week, and then remains more or less constant; after birth it decreases gradually, with an average half-life of about 5 days ([13, 20, 23]). The fetal plasma concentration already begins to diminish after the 13th week, as a result of variation in the synthesis/circulating mass ratio, although fetal synthesis actually only begins to diminish during the 32nd week ([18]).

In the light of findings reported in the literature, the determination of the alpha-fetoprotein plasma level may represent a useful prognostic element in fetal condition.

In regard to the HPL and progesterone levels (placental indicators only) and to urinary oestrogens (indicator of feto-placental unit), it would be useful to have a variable of predominantly fetal origin, such as alpha-fetoprotein promise to be.

MATERIALS AND METHODS

We studied 59 women in various stages of pregnancy, and with varying degrees of risk; a total of 174 radio-immunological estimations were carried out by the double-antibody method.

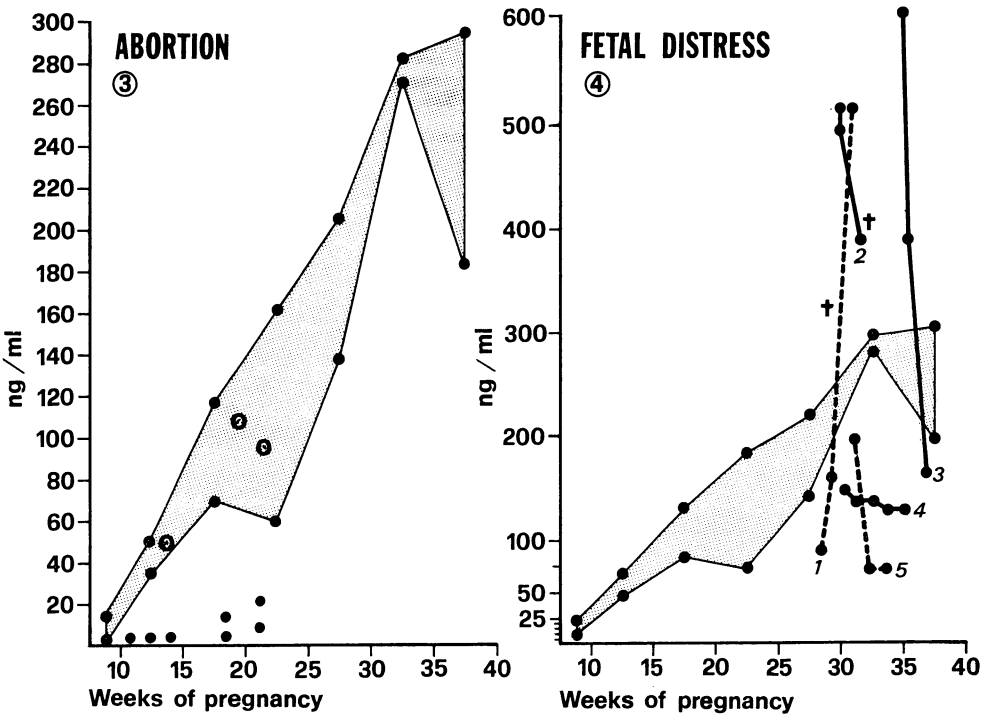

FIG. 3 - Threatend Miscarriage. The very low values were obtained from cases which terminated in miscarriage; the values within the normal range relate to pregnancies with a normal outcome.

FIG. 4 - Fetal Distress. Case 1: Rh isoimmunisation with intra-uterine death. Case 2: Intra-uterine death due to severe placental insufficiency. Case 3: Severe placental insufficiency, terminating with caesarian section because of acute fetal distress. Cases 4 and 5: Placental insufficiency, terminating with the birth of a low-weight infant.

The Dianabot Laboratories (Tokyo) provided the reagents and the Kit method used.

The blood samples were taken with heparinised syringes; the plasma was separated by centrifuging and kept at −20 °C until the test. All measurements were carried out twice.

RESULTS

In normal pregnancy terminating with the birth of a healthy infant alpha-fetoprotein levels gradually increase up to the 34th week. Our results agreed with those reported by other investigators ([23, 17, 24]). In seven cases of pregnancy terminated by miscarriage the alpha-fetoprotein levels were markedly lower, while the plasma and urinary HCG levels were normal. In contrast, in as many cases of threatened miscarriage which had a favourable outcome, the alpha-fetoprotein values always returned to normal (fig. 1 and 2).

As described by Seppälä and Rouslahti ([17]), in some cases which were observed over a long period a sudden and marked increase in the maternal plasma level of alpha-fetoprotein was found immediately before the death of the foetus, with a subsequent fall in the level.

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It should be noted that in our cases this alpha-fetoprotein peak in the maternal circulation preceded by a week, on average, the fall of the chorionic gonadotropin levels.

In chronic placental insufficiency of a nutritional type the alpha-fetoprotein levels are lower than normal, and is observed the birth of relatively small infants.

In fetal distress due to severe placental insufficiency or to Rh isoimmunisation we consistently found an increase in the maternal alpha-fetoprotein levels, and fetal death is certain if the levels rise beyond 1000 nanograms/ml.

CONCLUSIONS

In view of the foregoing and the results obtained in our cases it can be said that, as alpha-fetoprotein is of predominantly (although not exclusively) fetal origin, its maternal plasma level reflects fairly faithfully the rate of synthesis of the fetal tissues.

The occurrence of sub-normal values thus indicates embryofetal distress which is also evidenced by reduced biosynthetic activity of the proteins and which can result, clinically, in miscarriage or in limited bodily development of the fetus.

The sudden and marked increase of alpha-fetoprotein in the maternal plasma may be due to an increased production by the « distressed » foetal tissues, but it is more likely to be due to the release of large quantities of protein by fetal cytolysis processes.

The alpha-fetoprotein contained in the fetal and amniotic compartment would then move, in massive quantity, into the maternal circulation.

Although they are only preliminary, our results indicate that the determination of alpha-fetoprotein in the maternal plasma provides valuable information on the state of health of the foetus.

SUMMARY

In 59 pregnant women the determination of the alpha-fetoprotein plasma levels indicated that by this method it is possible to establish a prognosis of threatened miscarriage, assess the nutritional condition of the foetus and foresee imminent intrauterine death.

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Morphological and functional changes in the gonads of the albino rat following administration of an alkylating cytostatic agent during intra-uterine life

by
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Even though the administration of radiomimetic cytostatic drugs to animals during gestation may not always bring about obvious somatic injury in the offspring, it may induce profound changes in the gonads, with more or less serious involvement of the functions of reproduction.

There is unanimous agreement concerning the cause of the action produced by cytostatics in the primary germ cells at the time when the gonadal primordia are being colonized ([1-9]). It is well know, in fact, that the mammalian gonads develop on the wall that forms the posterior border of the intra-embryonic coelomic cavity, from the genital tubercles which are situated longitudinally on each side, between the root of the mesentery and the mesonephric folds, and extending beyond the mesonephros or Wolffian body either upwards or downwards. At a stage of development which is predetermined for each animal species, the primitive germ cells, originating from the site where the yolk-sac is first formed in the dorsal endoderm, and later from the dorsal wall of the small intestine, arrive at the genital tubercles. The cells migrate by putting out pseudopodia along the root of the mesentery as far as the gonadal primordia; and as they develop, they undergo intensive multiplication ([10-11]). Although the amoeboid movements and the numerical growth of the gonocytes are in any case blocked, a more or less complete reversal takes place at the primordium for which they were destined, in that the gonocytes develop a process of induction upon the genital tubercles.

Since, in consulting the relevant literature, it was found that sometimes the morphological aspect of the injuries produced in the treated animals was taken into consideration, and sometimes only the functional aspect, and that the observations were often limited to one sex only, I tested groups of albino rats of both sexes, which had been exposed during embryonic and fetal development to the action of a radiomimetic antiblastic agent, which was administered to the mothers, during gestation, with the object of checking the short and long term effect.

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