DILEMMAS IN INTRAUTERINE FETAL GROWTH RETARDATION

The significance of anticomplement and heparin-like activities of placenta at term and the prognostic value of HCS and E_3 maternal plasma concentrations during pregnancy

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Summary: The Authors studied the behaviour of anticomplement and heparin-like activities in human term placentas in relation to intrauterine fetal growth retardation. These two biological activities might be involved in regolatory mechanisms of great importance for the fetal growth. The anticomplement activity was significantly lower in IUGR placentas than in controls, while no change was found in heparin-like activity. The decrease of anticomplement activity might be associated to immunological mechanisms, possibly related to a placental microcirculation damage, with consequent fetal growth retardation.

For what concerns HCS and E_3 plasma levels during pregnancy, a significant reduction of HCS in IUGR subjects was observed, confirming a decreased functional activity of placenta. The E_3 levels, on the contrary, were slightly, but not significantly lower in IUGR patients.

The presence of anticomplement and heparin-like activities in human term placentas have been previously reported ([4,6]). These two biological activities might be involved in regulatory mechanisms of great importance for the fetal life, such as the opening of the vascular bed (heparin-like activity) and the effectiveness of the resolution system of syncitiotrophoblast in inhibiting adverse transplant reactions (anticomplement activity).

Concerning anticoagulant heparin-like activity, by means of discontinuous electrophoresis on agrose gel of two different human placenta preparations (PLA and PLA_1), as compared to a reference standard, a slow-moving heparin and two condroitinsulphates (AC and B) were identified; the presence of heparinsulphate and of a fast-moving heparin was dubious ([4]).

The anticomplement and heparin-like activities in different pathophysiological situations, such as EPH-Gestosis and Diabetes Mellitus were previously reported: the anticomplement activity was significantly lower than in controls, while no change was found in heparinlike activity ([7]). A decrease of anticomplement activity might then be associated with immunological mechanisms, possibly related to a placental microcirculation damage.

The aim of the present study was therefore the investigate these two biological activities in Intrauterine Growth Retardation, in which abnormalities of placental function are thought to be present.

SUBJECTS AND METHODS

70 pregnant women, aged 19 to 38 years, were studied. The subjects, all of whom had term deliveries, were divided into two groups according to neonatal birth weight: 40 normal controls, with birth weight ranging from 2500 to 4000 gr (mean ± S.E.: 3237 ± 50) and 30 women with intrauterine fetal growth retardation: birth weight wass less than 2500 gr (2181 ± 58).

Placental weight was evaluated without umbilical cord, membranes and blood.

Heparin-like activity of placental extracts was evaluated as anticoagulant activity and expressed

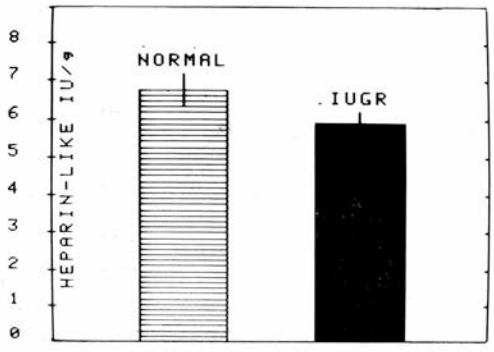

Fig. 1. — Heparin-like activity in IUGR and normal placentas (mean ± SE).

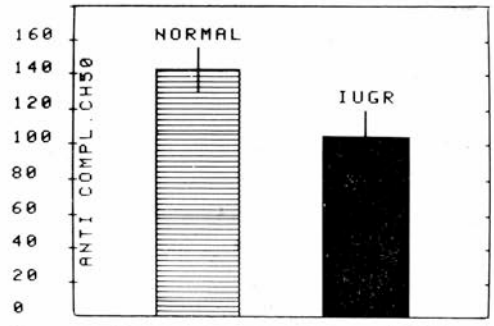

Fig. 2. — Anticomplement activity in IUGR and normal placentas (mean ± SE).

as international in vitro Units with reference to the III International WHO Standard (I.U./gm) [4].

Anticomplement activity was determined by finding the dose capable of inhibiting by 50% the immune hemolisis induced by specific antibodies on ram red cells in the presence of complement: as reference a so called « house standard » (=109 A.C.U./ampoule) was used (A.C.U./gm) [1].

Serial Human Chorionic Somatomammotropin (HCS) and Estriol (E_3) plasma levels, determined by radioimmunoassay and expressed respectively in mcg/ml and ng/ml, were evaluated during pregnancy between the 20th and the 40th week of gestation in 28 subjects.

RESULTS

The difference between placental weights was significant, with values of 263.42 gm ± 10.22 (S.E.) in Intrauterine Growth Retardation (IUGR), vs. 325.71 ± 10.73 in controls ($p < 0.01$).

Heparin-like activity (fig. 1) showed no significantly different values between the two groups, while statistically significant was, at the 0.05 level, the difference between anticomplement activity of IUGR and normal placentas (fig. 2). Moreover, the distribution of values within the control group showed two peaks (from 77 to 127 A.C.U./gm and from 152 to 202 A.C.U./gm): it is of interest to note that all the values from patients with IUGR were in the same range of the lower peak.

HCS was consistently and significantly (from the 0.05 to the 0.01 level) lower in IUGR, starting from the 33rd week of pregnancy (fig. 3), but not before (fig. 4),

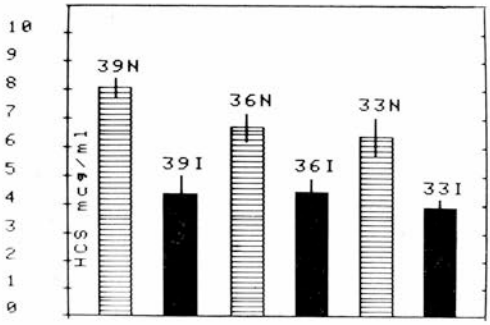

Fig. 3. — HCS levels (mean ± SE) in IUGR (I) and normal (N) pregnancies from 33rd to 39th week of gestation.

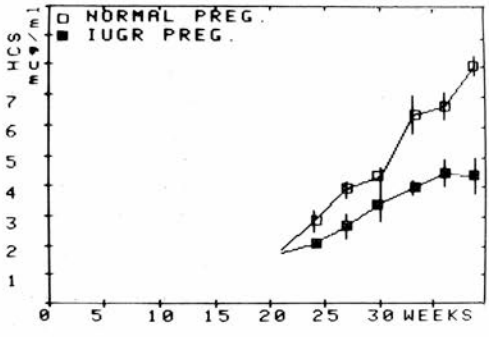

Fig. 4. — HCS levels (mean ± SE) in IUGR and normal pregnancies.

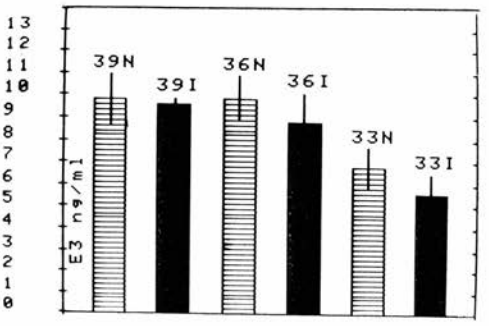

Fig. 5. — E_3 levels (mean ± SE) in IUGR (I) and normal (N) pregnancies from 33rd to 39th week of gestation.

while E_3 levels were slightly, but not significantly, lower in IUGR patients (fig. 5). Neither hormone showed any correlation with heparin-like and anticomplement activities.

DISCUSSION

The observed reduction of E_3 and most of all of HCS stand for a reduced functional activity of placenta in IUGR subjects, in accordance with literature data ([3, 5, 8]). However, our results showed a significant decrease of anticomplement activity in placentas of patients, as compared to controls, similar to what previously observed in placentas of women affected by Diabetes Mellitus and E.P.H. Gestosis ([7]). Since the above mentioned pathologies seem to be associated to immunological mechanisms, the following hypothesis might be formulated: a decrease in anticomplement activity might lead to increased platelets aggregation by immune complexes, with consequent PF4 liberation, heparin activity inhibition and intravascular coagulation. Although metabolic and/or genetic factors cannot be excluded, the same etiopathogenetic hypothesis could be used also in IUGR, to explain the so-called placental insufficiency.

Finally, no abnormality of heparin-like activity was found in the present, as well as in previous investigations on Diabetes and E.P.H. Gestosis, despite the well documented antithrombotic activity of placental extracts, as shown by a more marked capability to inhibit activated X factor than activated partial thromboplastine time ([2]). The reason for this apparent discrepancy may lie in possible deficiencies of extraction methods.

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