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Maternal serum α_1-antitrypsin concentrations in normotensive and hypertensive pregnancies

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SUMMARY Maternal serum α_1-antitrypsin concentrations were measured serially in pregnant women who were normotensive and those with mild, moderate, and severe hypertension of pregnancy from 27 weeks' gestation to term. α_1-antitrypsin concentrations increased with advancing gestation in all four groups. In addition, the hypertensive pregnancies showed higher than normal concentrations at each stage of pregnancy, with values in the severe hypertension group being higher than values in the other two hypertensive groups. At 35–36 weeks' gestation to term the increase in α_1-antitrypsin in the severe hypertension group was significant ($p < 0.05$) when compared with the normotensive group. Although plasma oestriol and progesterone concentrations increased with advancing gestation in all groups, there was no direct relation between their concentrations and the increase in α_1-antitrypsin concentration in the hypertensive groups.

Human plasma proteinase inhibitors are a group of proteins with the specific property of neutralising proteinase activity in either plasma or tissue. Of the eight known plasma proteinase inhibitors, α_1-antitrypsin and α_2-macroglobulin appear to be the most important.[1] Both these proteinase inhibitors neutralise the elastolytic leucocyte proteinases. Of the two, α_1-antitrypsin is responsible for at least 70% of the total inhibitory activity in non-pregnancy[2] and up to 96% during pregnancy.[3]

α_1-antitrypsin is an acute phase protein; its function is to protect tissues from released proteolytic enzymes, in particular the elastic tissues of the lung. Since the work of Ganrot and Bjerre,[4] who showed that α_1-antitrypsin values increase by about 100% in the third trimester, other workers have failed to find a specific function for the increased concentrations during pregnancy. It is assumed that they are the result of the increased oestrogen concentrations inducing α_1-antitrypsin synthesis by the liver.[4–6] We have examined the relation between α_1-antitrypsin in pregnancy and hypertension and postulate a possible role for α_1-antitrypsin during pregnancy.

Patients and methods

Venous blood was collected at planned intervals from patients attending the university department's antenatal clinics. The serum was separated and stored at −20°C until required for analysis. α_1-antitrypsin concentrations were assayed by electroimmunophoresis using 1% antisera (Dakopatts, Denmark) in agarose gel.[7] The standards were obtained from Behringwerke (Hoescht, NZ Ltd). The intra-assay coefficient of variation was 3·4%, and the inter-assay coefficient of variation was 6·0%. Plasma oestriol and progesterone were assayed by radioimmunoassay,[8] and the normal ranges were those previously described.

All patients in this series had their dates previously established by ultrasound during early pregnancy. Blood pressure measurements were taken at each clinic visit and the patients were classified as follows on the basis of their diastolic blood pressures: ≤85 mmHg (11·3 kPa) normotensive; 90–100 mmHg (12·0–13·3 kPa) mild hypertension; 105–115 mmHg (14·0–15·3 kPa) moderate hypertension; ≥120 mmHg (≥16·0 kPa) severe hypertension.

For statistical analysis the mean and standard deviation were calculated and each of the hypertensive groups was tested for significance using Student's *t* test for unpaired data. The normotensive patients were the reference group.

Results

The concentrations of α_1-antitrypsin in all four groups increased with advancing gestation (Table). No significant difference was found between the normotensive pregnancies and those with mild or

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moderate hypertension ($p > 0.05$). In the severe hypertension group no significant difference could be shown up to 35–36 weeks' gestation. From this gestation period to term the severe hypertension group showed significantly higher values when compared with the corresponding normal group ($p < 0.05$). In all three hypertension groups the concentration of α_1-antitrypsin increased in relation to the severity of the hypertension.

Although plasma α_1-antitrypsin, oestriol, and progesterone concentrations showed similar trends, no direct relation was found between either of the steroid concentrations and α_1-antitrypsin concentrations—in other words, patients with α_1-antitrypsin concentrations above the normal pregnancy values did not have correspondingly increased plasma oestriol or progesterone concentrations.

Discussion

α_1-antitrypsin is an acute phase protein, the primary function of which is believed to be protection of tissues against the release of proteolytic enzymes by the formation of molar 1:1 complexes.[10] As an acute phase protein, the plasma α_1-antitrypsin concentration can increase in response to stimuli such as infection, tissue trauma,[11] and oestrogens.[6] It is synthesised in the liver.[12] In addition to its acute phase protein role, α_1-antitrypsin is also considered to be a plasmin inhibitor.[13] It is to one or all of these roles that the increase in α_1-antitrypsin concentration during pregnancy has been attributed. But there is no conclusive evidence to associate the raised α_1-antitrypsin values with these roles.

Laurell *et al*[6] showed a 51% increase in plasma α_1-antitrypsin concentrations in women taking contraceptive pills containing oestrogen; however, Kueppers *et al*[14] failed to find any change in plasma α_1-antitrypsin concentration during the menstrual cycle. If a direct relation exists between pregnancy plasma oestriol or progesterone concentrations and the α_1-antitrypsin concentrations then the progressive increase in α_1-antitrypsin concentration with the increasing severity of hypertension should be accompanied by a similar increase in the plasma oestriol or progesterone concentration. We did not find any such relation.

Recent work has shown that the functional role of α_1-antitrypsin in the coagulation and fibrinolytic system during pregnancy is doubtful.[15] These findings would question the role of α_1-antitrypsin as a plasmin inhibitor.

McKay *et al*[16] noted that the trophoblast becomes thinner as pregnancy progresses. In the normal placenta this change affects only 10–40% of the villi, but in toxaemia 90–100% are affected. Previous workers[17] had shown that the transfer of radioactive sodium across the placenta increased with advancing gestation and that the rate of transfer was related to thickness of trophoblast covering the villi. Later work[18–20] showed that trophoblast cells may be detected in the maternal blood during pregnancy and were a consistent finding in toxaemic patients. Attwood *et al*[18] found that 81% of eclamptic and pre-eclamptic patients in their series had significant numbers of trophoblast cells in the maternal lungs, and these were also frequently present in the

Serial measurements of plasma α_1-antitrypsin, oestriol, and progesterone in gestational groups from normal pregnancies and those complicated by severe, moderate, and mild hypertension of pregnancy

	Gestation (wk)						
	27–28	*29–30*	*31–32*	*33–34*	*35–36*	*37–38*	*39–40*
Normotensive (n = 52)							
α_1-antitrypsin	400 (108·7)	400 (95·9)	426 (115·8)	418 (75·9)	452 (116·6)	461 (125·2)	466 (117·3)
Oestriol	5·0 (1·29)	5·4 (1·58)	6·4 (2·0)	7·7 (2·56)	9·6 (3·0)	12·3 (4·04)	13·4 (4·69)
Progesterone	78·5 (26·40)	83·3 (27·10)	104·5 (35·65)	119·5 (40·35)	132·1 (44·75)	146·8 (43·0)	136·0 (55·40)
Mild hypertension (n = 28)							
α_1-antitrypsin	413 (94·8)	456 (88·7)	454 (110·2)	465 (110·1)	466 (96·3)	474 (91·6)	462 (93·0)
Oestriol	5·0 (1·52)	5·3 (1·59)	5·8 (1·08)	6·8 (2·44)	9·2 (3·07)	11·0 (4·16)	11·9 (3·76)
Progesterone	67·3 (17·02)	89·2 (18·31)	105·3 (23·71)	114·4 (48·6)	127·7 (42·7)	148·9 (42·6)	141·9 (39·16)
Moderate hypertension (n = 10)							
α_1-antitrypsin	478 (41·07)	508 (91·4)	498 (68·3)	506 (75·0)	511 (98·5)	514 (111·7)	563 (83·3)
Oestriol	5·0 (1·45)	5·4 (2·16)	7·2 (2·53)	7·9 (2·18)	10·7 (3·36)	13·3 (3·0)	13·1 (4·62)
Progesterone	77·5 (14·34)	95·6 (21·4)	137·4 (47·38)	126·7 (32·87)	147·8 (54·61)	141·5 (29·34)	130·2 (37·05)
Severe hypertension (n = 6)							
α_1-antitrypsin	501 (23·0)	512 (73·2)	518 (74·7)	523 (93·1)	535 (46·4)	543 (30·6)	575 (35·36)
Oestriol	3·8 (0·75)	7·1 (2·13)	7·4 (1·55)	7·8 (1·76)	10·19 (2·31)	13·2 (3·79)	13·1 (3·72)
Progesterone	77·0 (5·50)	77·5 (15·39)	86·5 (24·14)	135·7 (50·02)	139·4 (38·42)	160·0 (59·79)	139·8 (69·71)

n = number of patients in each group.
Values given as mean (SD).

kidneys. Previous studies[21] have shown that the trophoblast is highly invasive, destroying tissue either by phagocytosis or by lysis; the lung is particularly susceptible. Earlier work[22] showed that deported trophoblast is destroyed in the lungs without cellular reaction and that the trophoblast was also lysed in vitro by serum from pregnant women. From this work it was proposed that a "syncytiolysin" existed, which was capable of destroying trophoblasts in the blood and lungs.

We believe that α_1-antitrypsin may have an important role in the inhibition of highly invasive deported trophoblast[21] and may form part of a "syncytiolysin" system, possibly in the same way that it inhibits leucocyte proteinases from damaging lung tissue and basement membranes—in other words it moves into the extravascular space, complexes proteinases, and removes them to be complexed by α_2-macroglobulin in the intravascular compartment before removal by the reticuloendothelial system. The increase in serum α_1-antitrypsin concentrations during pregnancy could therefore be in response to the presence of trophoblast in the maternal blood, in particular in the lungs. Failure to inhibit the proteolytic activity of the deported trophoblast could produce many of the principal symptoms of severe hypertension during pregnancy—namely pulmonary oedema, glomerular basement membrane changes, and coagulation defects. Such complications of pregnancy could be mediated through strong proteinase activity of the deported trophoblast,[21] although the exact mechanism of such a reaction remains to be elucidated. It may follow, therefore, that a patient with a pathological variant of α_1-antitrypsin could be more susceptible to hypertension of pregnancy and its sequelae because the serum α_1-antitrypsin concentration is normally lower and there is variable proteinase activity. As hypertension of pregnancy is predominant in populations of European origin it is interesting to note that the genetic differences of α_1-antitrypsin are virtually confined to the same population.[23] This may well provide some basis for the apparent genetic link of severe hypertension of pregnancy in families. Further investigations are required to determine the relation of the genetic polymorphism of α_1-antitrypsin and the susceptibility of individuals to hypertension of pregnancy.

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