VILLOUS FIBRINOID NECROSIS AND BASEMENT MEMBRANE THICKENING IN TOXAEMIA OF PREGNANCY AND IN INTRA-UTERINE GROWTH RETARDATION*

by

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Hyaline eosinophilic deposits staining with periodic acid schiff, are found at various sites in placenta and are labelled as 'Fibrinoid deposits'. In the villous, it initially appears within the substance of trophoblast and gradually involves whole thickness of the villous and this lesion is labelled as "Fibrinoid Necrosis" of villous and is found with increasing frequency in placentae of toxaemia of pregnancy by Fox (1968) who considered this lesion to be possibly an immune reaction (Fox; 1975).

Thickening of basement membrane is another villous lesion which is found to be increased in diabetes mellitus and Rh incompatibility and is considered to be either due to ischaemia or antibody reactions.

Immunological factors are not only implicated in maintainance of pregnancy but also in intrauterine development of fetus. It is with this in mind that the two lesions are proposed to be studied in placentae of toxaemia and IUGR. As placenta shows marked histological variations in different areas, it is important that sections are taken in a manner to be well representative.

Material and Method

Placenta was studied in 100 term parturients admitted to labor ward of Lady Hardinge Medical College & Hospital, New Delhi. These parturients included:

(a) Control: Normal term parturients—25.

(b) Toxaemia of pregnancy with B.P. 130/90 mm of Hg. and above with or without edema and/or proteinurea—25.

(c) Intrauterine growth retardation birth weight less than 2,500 gms.—25.

(d) Anaemia of pregnancy; Hb. less than 8.0 gms.—25.

From each placenta, 8 whole thickness tissue blocks, 2.5 cms. x 0.5 cms. in size were taken from definite representative sites along an S-shaped area so as to include all areas of placentae under study (Fig. 1).

Formol fixation was followed by processing and embedding the tissues in the paraffin. Tissue section, 5-7 μ. in thickness, were cut from each block and stained with conventional haemotoxylin and eosin stain and with periodic acid schiff

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reagent (P.A.S.) as a special staining procedure in order to study the villous fibrinoid material and the thickening of the villous basement membrane which tookup a homogenous pink stain with P.A.S.

Random microscopic fields were selected from 8 slides and 100 villi were counted and studied for the presence of the following in each slide:

1. Intravillous fibrin or fibrinoid change of whole villi.
2. Basement membrane thickening.

The number of villi showing these changes were counted in 8 sections and expressed as percentage of total 800 villis.

Observations

Fibrinoid Necrosis

Significantly high percentage of villi showed fibrinoid necrosis in placentae of toxaemia groups, the difference in the incidence of fibrinoid necrosis in placentae of I.U.G.R. and anaemia group compared to control group was not significant (Table Ia).

TABLE Ia

Percentage of Villi Showing Fibrinoid Necrosis in Placentae with 25 in Each Group

Groups	Mean	Range	S.D.
Control	3.40	1.5-8.5	1.78
Toxaemia	7.80	4.15	2.33
I.U.G.R.	4.78	0.5-11.5	2.91
Anaemia	4.16	1-9.2	2.19

No. of villi counted—800.

Of control placentae 84% had fibrinoid necrosis in less than 5% of villi, this incidence if considered normal was exceeded in 80% (20/25) of toxaemia cases and 36% (9/25) of IUGR cases (Table Ib).

Thickened basement membrane (Table II a and b)

TABLE Ib

Percentage of Villi Showing Fibrinoid Necrosis in Various Groups

Fibrinoid Necrosis	Control		Toxaemia		I.U.G.R.		Anaemia	
	No.	%	No.	%	No.	%	No.	%
0—5%	21	84	5	20	16	64	20	80
6—10%	4	16	18	72	8	32	5	20
Above 10%	—	—	2	8	1	4	—	—
Villi counted (800)	25	100	25	100	25	100	25	100

F = 11.52 for degree of freedom 3 + 96. Significant difference between mean values of normal and toxaemia at p = 0.05.

TABLE II a

Mean Percentage of Villi Showing Thickened Basement Membrane

Groups	No.	Mean	Range	S.D.
Control	25	0.22	0-1.5	0.37
Toxaemia	25	0.84	0-3	0.89
I.U.G.R.	25	0.72	0-3	0.89
Anaemia	25	0.15	0-2.2	0.44

Total number of villi counted — 800.

TABLE II b

Incidence of Villi Showing Thickened Basement Membrane (T.B.N.) in Various Group— (N-25 each)

T.B.N. %age Villi	Control		Toxaemia		I.U.G.R.		Anaemia	
	No.	%	No.	%	No.	%	No.	%
Absent	6	24	5	20	6	24	11	44
0-2.0%	19	76	15	60	17	68	13	52
Above 2.0%	—	—	5	20	2	8	1	4

F = 6.19 for of 3 x 96.
at P = 0.015 Significant between control and IUGR and between Control and Toxaemia.
Not significant difference between control and anaemia.

The mean incidence of thickened basement membrane in the 2 groups toxaemia and I.U.G.R. was found to be statistically significantly raised.

Its incidence was less than 2% of villi in term control placentae. It was higher than this in 5 (20%) of toxaemia and 2 (8%) of I.U.G.R. placentae.

Combined lesion of fibrinoid necrosis and thickened membrane Table III (a and b)

The combined lesion was found only in 20% of control placentae compared to 48% of toxaemia and 36% of IUGR. However statistically significant difference was found only in mean values of toxaemia group.

Discussion

Immunological dysparity, as suggested by the higher transformation index of lymphocytes in mixed lymphocytic cul-

TABLE III a

Percentage of Villi Showing Fibrinoid Necrosis in Association with Thickened Basement Membrane

Groups	No.	Mean	Range	S.D.
Control	25	0.09	0-1	0.24
Toxaemia	25	0.48	0-3	0.80
I.U.G.R.	25	0.33	0-2.5	0.59
Anaemia	25	0.09	0-1	0.24

Total No. of villi counted — 800.

TABLE III b

Percentage of Villi Showing Fibrinoid Necrosis in Association with Thickened Basement Membrane in Various Group (n = 25 each)

%age Villi	Control		Toxaemia		I.U.G.R.		Anaemia	
	No.	%	No.	%	No.	%	No.	%
Absent	20	80	13	52	16	64	20	80
0-2%	5	20	9	36	8	32	5	20
Above 2%	—	—	3	12	1	4	—	—

F = 4.62 for 3 x 96 difference. Significant difference of mean values between control and toxaemia at P = 0.05.
No significant difference between Control and I.U.G.R. or between Control and anaemia.

ture, increased immunosuppressive agents such as seromucoproteins, is considered to be etiological factor in toxaemia of pregnancy (Jenkins *et al* 1973). Stevenson *et al* 1971 considered it to be genetic dysparity as he found consanguity less in toxaemia patients as compared to the general population. Das Gupta (1975) from Jamshedpur considered it may be a disease of multiple etiology, in some it may be due to maternal antigens provoking foetal lymphocytic system as he found seromucoprotein higher in cord blood than in serum of toxaemia cases. Recently even fibrinoid deposits in placenta have been considered as manifestation of immune reaction as immune fluorescent studies have demonstrated deposits of IgG, IgM, fibrinogen and complement in areas of fibrinoid deposits by Kitzmiller (1977), in decidual vessels by Kitzmiller and Benirshke (1973) and in glomeruli of Kidney by Pettruco *et al* (1974).

Fibrinoid necrosis in less than 6% of villi was found in normal term placenta by Mathews, *et al* (1973) and Sen and Langley (1974). In the present study also fibrinoid change was found in 5% of villi or less in placentae from control cases. Significant increase in fibrinoid change in villi was found in toxaemia of pregnancy in present study (Table I).

Nine out of 25 placentae of IUGR also had fibrinoid change in more than 5% of villi, this was not found to be statistically significant, though Sen and Langley (1974) and Goeffrey *et al* (1975) found it increased in IUGR. This may be due to parameter of 2,500 Gms. weight used in present study for definition of IUGR which may be high for India.

The villous trophoblastic basement membrane, which appears at about the time of sixth week of pregnancy, gets gradually thicker with age of placenta. A certain proportion of villi show abnormal thickening of trophoblastic basement membrane in the whole of their circumstance and stand out from neighbouring normal villi in sections stained with periodic-acid-schiff stain.

Increased basement membrane thickening has been observed in prematurity and hypertension (Fox 1968) in pre-eclamptic toxaemia (Mehrotra *et al* 1972) and in diabetes mellitus and Rh incompatibility (Burstein *et al* 1963). In the present study statistically significant increase was found in number of villi showing thickened basement membrane in toxaemia and in I.U.G.R. group as compared to control group. Increased frequency of thickened basement membrane of villous in toxaemia has also been observed by Sayeed *et al* (1976) who found it markedly increased also in anaemia group and considered it to be due to ischaemia. No significant increase was found in anaemia group in present study.

The association of the two histological lesions, thickened basement membrane and fibrinoid necrosis in diabetes mellitus (Burstein *et al* 1963) and demonstration of IgG in placental elutes which reacts with fibrinoid deposits and thickened basement membrane (McCormick *et al* 1971) suggest these two lesions to be associated with antigen and antibody reaction. Sen and Langley (1973) proposed immunological etiology for both toxaemia and I.U.G.R. as these changes of villi were found increased in both conditions. In the present study however, these two histological changes together in a villous were found significantly increased in toxaemia but not in I.U.G.R. group. This could probably be due to rather high parameter of weight taken for I.U.G.R. as previously mentioned.

These changes in placentae of I.U.G.R.

group suggest that immunological dysparity may significantly contribute to growth retardation of the foetus.

Summary and Conclusions

Placentae from term normal pregnancy, toxaemia and IUGR were studied Eight sections from each placenta were taken in view of normal geographic variations. Histological changes in 800 villi were observed and recorded as percentages.

Following observations were made:

(i) Fibrinoid necrosis was significantly increased in toxaemia of pregnancy.

(ii) Basement membrane thickening was significantly increased in toxaemia and I.U.G.R. group.

(iii) The two lesions combined were significantly increased in toxaemia and suggest immunological basis.

In India if lower birth weight is taken as a parameter for I.U.G.R; an association of thickened basement membrane and fibrinoid necrosis may also be found in I.U.G.R. group.

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See Fig. on Art Paper VIII