BLOOD GROUPING IN TOXAEMIA OF PREGNANCY

by

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Introduction

Landsteiner's discovery of blood groups in 1900 opened up a new horizon in many fields of study, particularly in medicine and genetics. For more than half a century, attempts have been made to understand the importance of host factors in diseases, as to why a particular individual gets a particular disease whereas another drawn from the same environmental, nutritional and physical background is immune to it. Aird's study of blood groups in relation to gastric carcinoma in 1953 made vast impact and had wide implications in this respect. Blood groups are inherited and thus it is possible to correlate heredity and host factors to disease through them. The blood group of a person is not only genetically determined but also remains essentially unchanged throughout life. It is thus exceedingly valuable genetically, and it has been postulated that disease may be genetically linked with blood groups, or caused by direct immunological effects of the antigen, or the susceptibility to disease may be related to blood groups.

A number of authors have claimed to show that an association exists between ABO blood groups and certain diseases such as carcinoma of stomach, duodenal and gastric ulcers and pernicious anaemia. Proof of the existence of this association would open up a new horizon, both in pathology and anthropology. It would appear that this association although vigorously claimed and apparently widely accepted by clinicians has not yet been established. Most investigations have led to contradictory results and are open to objection on methodological grounds.

The discovery that there is a higher incidence of pregnancy toxaemia with certain blood groups of ABO system is comparatively recent. In 1954, Pike and Dickins examined the frequencies of ABO groups in toxaemic and non-toxaemic women and showed that group O was significantly more frequent in toxaemic mothers than in the remainder. From time to time, beginning with Dienst in 1905, it has been suggested that toxaemia of pregnancy is due to ABO incompatibility between foetus and mother, isoimmunisation of the mother taking place because the red cells of the foetus bear an antigen which is

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absent from the mother. The published results have not, however, convincingly supported this hypothesis. For example, although Hurst *et al.* (1946) found a greater number of incompatible blood groups between infants and mothers in cases of toxaemia of pregnancy than in normal cases, the difference was not statistically significant. They also found that some mothers showed a significant rise in isoagglutinin titre and that these formed a greater proportion of the toxaemic group than in normal cases, but the series was too small for any definite conclusions to be reached.

Material and Method

In view of the above mentioned hypothesis, an attempt has been made in the present study to find out the relationship, if any, between blood groups and toxaemia of pregnancy. The cases studied comprised of mild, moderate and severe pre-eclamptic toxaemia and eclampsia in all age groups. Besides the classical ABO system, Rh-D grouping was also done in all cases and antibody titre determination carried out, except in women belonging to group AB, as they do not possess any antibodies in their blood.

For the present study, 224 women from Queen Mary's Hospital, Lucknow, were investigated. Of these, 130 were non-toxaemic pregnant women and 94 were cases of toxaemia. The 94 toxaemic patients included 89 cases of pre-eclampsia (43 mild, 28 moderate and 18 severe) and 5 cases of eclampsia. For the ABO and Rh-D frequencies in the general population the readings of 2011 subjects who were grouped in the State Blood Bank of Lucknow, were taken.

ABO and Rh grouping was done by slide technique according to the standard procedure. Proof grouping was done by testing the serum of individuals against known A and B cells. Antibody dilution determination was done by titration method. The study of test cases was done under the following headings:-

1. Clinical study including detailed history and complete physical examination.
2. Investigations:-

(a) Routine; blood and urine examination.

(b) Special; such as blood sugar, blood urea estimations and fundus examination, where needed.

3. ABO and Rh blood grouping of mother, father and baby.
4. Antibody titre determination in antepartum and postpartum periods.

ABO and Rh-D group frequency in toxaemic cases has been compared with obstetrical controls and the general population, and incidence of homospecific and heterospecific pregnancies in toxaemic cases has also been compared with obstetrical control cases. (A heterospecific pregnancy is a pregnancy in which the foetus carries an ABO group antigen, absent from the maternal blood cells.)

Observations

ABO and Rh-D group frequency of general population, non-toxaemic and toxaemic cases.

The ABO and Rh-D group frequency of 2011 subjects from the general population, 130 non-toxae-

mic obstetric controls and 94 cases of toxaemia were studied. It was found that groups O and B were almost equally distributed in the general population and obstetric controls, in contrast to which there was a marked preponderance of group O in the toxaemic study group, 47.83% as opposed to 36.15% in the non-toxaemic controls Table 1.

TABLE I

ABO and Rh-D group frequency in general population, non-toxaemic and toxaemic cases

Blood group.	General population	Non-toxaemic obstetric controls.	Toxaemic cases.	% increase or decrease of toxaemia over non-toxaemic.
O	695(34.55%)	47 (36.15%)	45 (47.83%)	+32.0
B	670(33.31%)	40 (30.76%)	25 (26.50%)	—13.0
A	477(23.71%)	27 (20.76%)	14 (14.89%)	—28.0
AB	169(8.40%)	16 (12.30%)	10 (10.63%)	—13.0
Rh-D neg.	46 (2.23%)	4 (3.07%)	1 (1.06%)	..
Total Cases	2011	130	94	

Incidence of Homospecific and Heterospecific pregnancy.

Out of 224 obstetric cases studied, the blood group of the baby was determined in 178 only, as it was not possible to determine the blood group where the baby was still-born or too premature to survive, or when the patients did not return to hospital for delivery. These 178 cases included 109 non-toxaemic subjects and 69 cases of toxaemia. The incidence of heterospecific pregnancies in these 178 cases was 40.4% (72 out of 178). In the non-toxaemic subjects, 27.58% (30 out of 109) pregnancies were heterospecific, while in the toxaemic subjects the incidence of heterospecific pregnancy was as high as 60.86% (42 out of 69). Some cases of toxaemia were also found in homospecific pregnancies but in this group the incidence of toxaemia was only 25.47% (27 out of 106) whereas it was as high as 56.33% (42 out of 72) when the pregnancy was heterospecific Table 2.

The 72 heterospecific pregnancies were further analysed to determine the commonest ABO group frequency. The highest number of heterospecific pregnancies, 55.55% (40 out of 72) was encountered in group O mothers and the incidence of toxae-

TABLE II

Incidence of homospecific and heterospecific pregnancy in non-toxaemic and toxaemic subjects

	Number of cases.	Non-toxaemic cases	Toxaemic cases.	Incidence of toxaemia
Total pregnancies	178	109	69	38.76
Homospecific pregnancy	106 (59.6%)	79 (72.47%)	27 (39.13%)	25.47
Heterospecific pregnancy	72 (40.4%)	30 (27.52%)	42 (60.86%)	58.33%)

mia was also somewhat higher in this group. Table 3.

Analysis of blood group of mother and baby was possible in 69 out of 94 cases of toxaemia. The various combinations are shown in Tabe 4 from which it will be seen that the frequency of toxaemia was highest in group O mothers who had group A babies.

Severity of toxaemia in relation to blood groups

The study of 69 cases of toxaemia where baby's blood group was known, showed that in 11 out of 12 cases of severe pre-eclampsia the pregnancies were heterospecific, whereas there was no difference in the incidence of homospecific and heterospecific pregnancies in cases

TABLE III

Blood group frequency and incidence of toxaemia in 72 cases of heterospecific pregnancy

Blood Group Mother.	baby.	No. of cases.	Total No.	Number of cases with toxaemia.	Increase of toxaemia.
O	A	16		11	
O	B	18	40	9 } 24	60.0%
O	AB	6	(55.55%)	24	
B	A	11	17	6 } 10	58.8%
B	AB	6	(23.6%)	4	
A	B	11	15	5 } 8	53.3%
A	AB	4	(20.8%)	3	
Total			72	42	

TABLE IV

Blood groups of mother and baby in cases of toxaemia

Blood Group Mother	baby	Number of cases with toxaemia.	Percentage toxaemia in each ABO group.
O	A	11	
O	B	9 } 32	(46.3%)
O	AB	4	
O*	O*	8	
B	A	6	
B	AB	4 } 18	(26.8%)
B*	B*	5	
B*	O*	3	
A	B	5	
A	AB	3 } 13	(18.8%)
A*	A*	1	
A*	O*	4	
AB*	A*	1	
AB*	B*	.. } 6	(8.6%)
AB*	AB*	2	
AB*	O*	3	
Total		69	

* Denotes homospecific pregnancy.

with mild toxaemia. Out of 5 cases of eclampsia, in 4 the babies were still-born, hence the blood group could be done in only one case, and in this pregnancy was found to be heterospecific (mother of group O and baby of group B). Table 5.

TABLE V

Severity of toxaemia in relation to homospecific and heterospecific pregnancies

Pregnancy.	Total cases.	Pre-eclamatic toxaemia			Eclampsia
		Mild.	Moderat.	Severe.	
Homospecific	27	17	9	1	..
Heterospecific	42	17	13	11	1
Total	69	34	22	12	1

Anti-A and Anti-B titre

Out of 224 subjects of this study, the antibody titre determination with proper follow-up was done in 192 cases, (6 cases did not come for follow up while in 26 cases the question of antibody titre determination did not arise as the mothers belonged to group AB). Of these 192 cases, 109 were non-toxaemic obstetric control cases and 83 belonged to the toxaemic study group. The results are shown in Table 6.

It will be seen that the majority in the non-toxaemic group did not show any change in titre, whereas 36 out of the 47 cases showing a rise in antibody titre belonged to the toxaemic group, and in 87.8% of these the pregnancies were heterospecific. A significant fall in titre occurred in 4 cases of eclampsia following the birth of still-born babies.

It was further seen that there was a definite relationship between the severity of toxaemia and the antibody titre.

In the majority of the non-toxaemic controls, the titre ranged from weakly positive to 1/320 (in a small number of cases the range was between 1/320-1/640). In contrast to this in the toxaemic group, no case of severe toxaemia was recorded with a titre of less than 1/640 and in one case of eclampsia the titre was as high as 1/1280.

TABLE VI

Antibody titre in non-toxaemic and toxaemic subjects

Antibody titre.	Total cases.	Non-toxaemic subjects.	Toxaemic Subjects.				
			Total	Mild	Moderate	Severe	Eclampsia
Unchanged titre	132	91	41	23	9	9	..
Rise in titre in antenatal or postnatal period or both ..	47	11	36	18	10	8	..
Fall in titre in first post-natal week ..	13	7	6	1	..	1	4
Total ..	192	109	83				

TABLE VII

Antibody titre in relation to homospecific and heterospecific pregnancy

Antibody Titre.	Total cases.	Total		Non-toxaemic 94.		Toxaemic 63.	
		Hetero-specific.	Homo-specific.	Homo-specific.	Hetero-specific.	Homo-specific.	Hetero-specific.
Unchanged titre ..	105	35	72	55	23	17	10
Rise in ant body titre in antenatal, postnatal or both	42	35	7	3	6	4	29
Fall in titre in first post-natal week ..	10	4	6	1	6	..	3
Total	157						

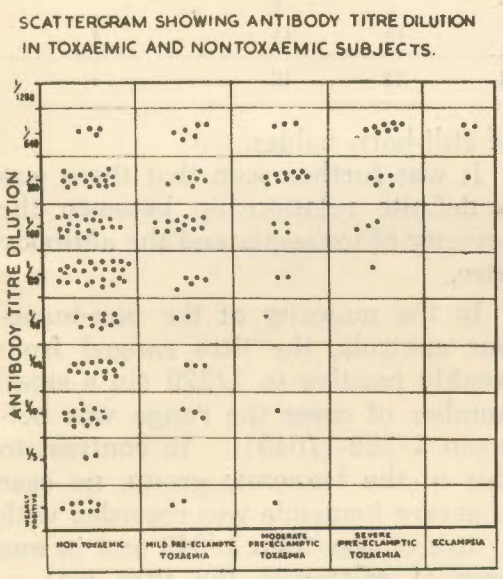

Fig. 1.

Discussion

It is by no means implied that all cases of toxaemia can be explained on a basis of ABO iso-immunisation, for many cases of toxaemia certainly do occur in A and B mothers with O foetus and AB mothers whose foetus cannot be heterospecific, but the preponderance of group O mothers developing toxaemia is very striking. Toxaemia is stated to be rare in natives of the Dutch East Indies, Siam, Hawai and Alaska and the frequency of group O is definitely low in the inhabitants of these countries.

The findings of the present study show a definite preponderance of group O in toxaemic subjects (47.8%). Since the percentage of heterospecific pregnancy was also higher in this group, it seems logical to explain this preponderance of toxaemia in group O mothers on the basis of incompatibility between mother and foetus, as iso-immunisation of mothers can occur during heterospecific pregnancy. The incidence of toxaemia in the present study was almost double when the pregnancy was heterospecific as compared to when it was homospecific. This is an attractive hypothesis as the pathological features of the disease may possibly be explained by an antigen-antibody reaction in the blood or the walls of the smaller blood vessels of mother. Dienst, as early as 1905, had stated that "Eclampsia is nothing but a transfusion of incompatible blood of the foetus into mother's circulation as a result of communication between two". He also pointed out that necropsy find-

ings in animals transfused with foreign blood very closely resembled those of eclampsia (Ottenberg, 1923). Most of the toxaemic phenomena are essentially vascular—oedema, albuminuria, anuria, oliguria, hepatic and cerebral changes have been thought to be associated with vascular damage and toxaemic hypertension is humoral and not neurogenic in mechanism (Kellar and Sutherland, 1941). No existing theory of the aetiology of toxaemia can explain the appearance of post-partum eclampsia or a continued rise in blood pressure in the puerperium, but Dienst (1905) has found that in such cases the rise in antibody titre persisted untill the fourth day of the puerperium.

This hypothesis of the allergic origin of pregnancy toxaemia has many supporters (Corizontova Nikoiskaya, 1952; Petrov-Maslakov and Coll, 1955). According to this theory the antigen of toxaemia is the placental protein. Petrov-Maslakov and Coll (1955) have confirmed that repeated introduction of not only foreign but also homospecific protein leads to sensitisation of the animal, producing an allergic state. To the allergic theory we could relate also the theory of heterospecific pregnancy as the reason of eclampsia. The work of Ado (1952) has shown that allergen has a stimulating action on various sensory nerve endings. It has been suggested by Ado that the mechanism of development of sensitisation can be represented as a process of summation of weak subminimal irritation produced on the organism which causes excitation of the central nervous system with its subsequent depression. The placental protein and the erythrocytes of the foetus which penetrate into the blood channels of the mother in heterospecific pregnancy are apparently allergens. At a definite stage when the compensator forces of the organism are exhausted the summation of subminimal action of this allergen has a decisive action —excitation of the central nervous system, manifested by the fit of eclampsia, which is then often followed by its abrupt depression—coma.

The results of the present work show definite evidence of iso-immunisation of the maternal circulation in heterospecific pregnancies. A higher incidence of heterospecific pregnancy was encountered in toxaemic cases, 60.86% as against 27.52% in the non-toxaemic group. It is difficult to explain the few cases of toxaemia (25.47%) encountered in cases of homospecific pregnancies on the basis of transfusion of incompatible blood of the foetus. One explaination is provided by the work of Petrov-Maslakov (1955), already referred to, that repeated introduction of not only foreign, but also homospecific protein, leads to sensitisation of the animal. This theory too does not explain the occurrence of toxaemia in mothers with O foetus. Of 27 cases of toxaemia with homospecific pregnancy in this study, in 8, although the pregnancy was homospecific, it was found that the blood groups of the mother and father were different, so one cannot say if the baby genetically inherited some antigenic subgroup of A or B from the father which remained undetected in the baby but had antigenic activity.

It was further found that out of 192 cases where antibody titre deter-

mination was done, 47 cases showed a significant rise in isoagglutinin titre. Of these 76.5% were cases of toxaemia thus showing evidence of iso-immunisation of maternal circulation. It is difficult to explain why the remaining 11 cases showing rise in antibody titre remained non-toxaemic. The explanation may be that in these 11 cases the rise in titre may not have been high enough for the particular case to result in toxaemia, as each individual reacts differently to the same stimuli. Forty-one cases of toxaemic group did not show any change in antibody titre. It may be assumed that in such cases the foetus is a non-secretor.

The routine determination of parental blood groups early in pregnancy, particularly during the first pregnancy is therefore advocated, for one may by this means pick up "toxaemia prone" subjects early and by careful supervision prevent the occurrence of the severe forms of this serious complication of pregnancy.

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