HISTAMINASE AND HISTAMINE IN NORMAL AND TOXAEMIC PREGNANCY

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Although the blood histamine concentration during normal pregnancy is within the normal range, the serum histaminolytic power is greatly increased (1-3). This remarkable increase in serum histaminolytic power is much more characteristic of pregnancy in man than in any other animals (4). The increase in serum histaminase activity starts as a rule during the second or third month, reaching a maximum in the fifth to the seventh month at which level it remains with modest variations until full term. It then rapidly returns within 3 or 4 days postpartum to the negligible values as found in normal non-pregnant women (2).

The placenta is very rich in histaminase activity (5) and is the principal source of increased serum enzyme activity (6). Pathological changes in the placenta can, therefore, be expected to produce alterations in the normal pattern or sequence of changes in the serum histaminolytic power during pregnancy.

Lindberg (6) recently showed that an intravenous infusion of histamine resulted in a lower concentration of histamine in blood when a woman was pregnant, and that administration of aminoguanidine, an inhibitor of histaminase, to pregnant women raised the concentration of histamine in blood (7).

It has been suggested that deviations from the normal pattern of increase in serum histaminase activity are indicative of an abnormal pregnancy (1), and variable changes in the enzyme activity in cases of pre-eclampsia have been reported (8). Studies on urinary excretion of histamine in cases of pre-eclampsia (9) suggest that there is increased concentration of histamine in circulation under this condition.

Until recently, it has been thought that serum histaminase estimations might possibly serve to indicate indirectly the histamine content of blood, and that the high histaminolytic power of blood could thus be satisfactorily correlated with the common clinical observation of remission of allergic manifestations during pregnancy. Hopes were entertained of throwing light on the significance of tissue and blood histamine via studies of this factor, in the same way that studies of acetylcholinesterase have yielded valuable information on the functions of acetylcholine in the body. The reported similarities between lesions produced by experimental poisoning with histamine in pregnant animals and the clinico-pathological features of pre-eclampsia and eclampsia, and the partly direct and partly indirect evidences that have accumulated pointing toward an excess of circulating histamine...
in pre-eclampsia and eclampsia together with the establishment of the fact that histamine produces definite hypertensive effects under certain conditions have stimulated our interest in the study of the problem of histamine metabolism in normal and toxaemic pregnancy, and have led to the hypothesis that histamine plays a decisive role in the aetiology of pre-eclampsia and eclampsia, which has, hitherto, eluded discovery despite extensive research in the past six decades.

It seemed desirable from the foregone facts to investigate into the possible variations from normal of the serum histaminase and whole blood histamine contents in pre-eclampsia and eclampsia, and also to make an attempt to find out the correlation, if any, between the enzyme activity and blood histamine concentration and the severity of the condition.

MATERIAL AND METHODS

In the work reported here, determinations of serum histaminase and whole blood histamine contents were made simultaneously on the blood of a total of 56 pregnant women, both normal and toxaemic, with a duration of pregnancy ranging from 31 to 40 weeks. The serum histaminase activity was estimated by the microvolumetric method of Kapeller-Adler (2) and expressed in Permanganate Units per one ml of serum (PU/ml). The whole blood histamine equivalent was determined by the biological assay method by a direct comparison of the responses to the test sample with those of the standard solutions on guinea-pig's terminal ileum after its extraction following the chemical method of Schmitterlow (10) and expressed in micrograms per 100 ml of whole blood in terms of histamine base (mcg/100 ml).

RESULTS

The clinical data and the findings of serum histaminase and whole blood histamine contents from 16 normal pregnant women are presented in Table 1.

The relationships among the serum enzyme activity, whole blood histamine concentration and other clinical factors such as age, parity, and blood pressure were analyzed statistically. There was statistically significant positive correlation between the enzyme activity and duration of pregnancy ($r' = +0.994$, $p'<0.001$), implying that, with an increase in the duration of pregnancy, there is an increase in serum histaminase activity. There were no significant correlation between the enzyme activity and whole blood histamine, and age, parity and blood pressure ($P' >0.05$).

The clinical data and the findings of serum histaminase and whole blood histamine contents from 14 cases of mild pre-eclampsia are shown in Table 2.

The clinical data and the mean values of serum histaminase and whole blood histamine contents from mild pre-eclampsia were compared with those from cases of normal pregnancy. Table 3 shows a summary of the comparison between normal pregnancy and mild pre-eclampsia.

It is evident from the table that the two groups are comparable with respect to age, parity and duration of pregnancy. There was a significant fall in serum histaminase ac-
### Table 1. Serum histaminase and whole blood histamine values in cases of normal pregnancy.

| Case No. | Age (years) | No. of previous parturitions | Duration of pregnancy (weeks) | Blood pressure of Hg | Serum histaminase (PU/ml) | Whole blood histamine (meg/100 ml) |
|----------|-------------|------------------------------|-------------------------------|----------------------|--------------------------|----------------------------------|
| 1        | 24          | 0                            | 36                            | 120                  | 20                       | 23.5                             |
| 2        | 20          | 0                            | 38                            | 112                  | 26                      | 5.26                             |
| 3        | 30          | 3                            | 38                            | 126                  | 21.6                    | 6.04                             |
| 4        | 25          | 1                            | 32                            | 120                  | 18.4                    | 5.64                             |
| 5        | 20          | 0                            | 36                            | 128                  | 19.8                    | 6.04                             |
| 6        | 18          | 0                            | 37                            | 116                  | 24.2                    | 6.91                             |
| 7        | 22          | 1                            | 32                            | 120                  | 16.8                    | 6.47                             |
| 8        | 20          | 0                            | 37                            | 112                  | 26.0                    | 5.90                             |
| 9        | 32          | 2                            | 40                            | 116                  | 25.8                    | 5.14                             |
| 10       | 25          | 1                            | 36                            | 120                  | 23.6                    | 4.38                             |
| 11       | 22          | 0                            | 32                            | 126                  | 14.8                    | 7.43                             |
| 12       | 25          | 2                            | 36                            | 118                  | 19.2                    | 5.26                             |
| 13       | 28          | 2                            | 38                            | 112                  | 27.8                    | 5.51                             |
| 14       | 28          | 1                            | 36                            | 126                  | 28.2                    | 5.38                             |
| 15       | 30          | 3                            | 40                            | 118                  | 22.0                    | 5.64                             |
| 16       | 24          | 0                            | 35                            | 116                  | 21.5                    | 5.14                             |

Mean: 24.56
S.D.: ±4.343
S.E. of mean: ±1.086

### Table 2. Serum histaminase and whole blood histamine values in cases of mild pre-eclampsia.

| Case No. | Age (years) | No. of previous parturitions | Duration of pregnancy (weeks) | Blood pressure of Hg | Serum histaminase (PU/ml) | Whole blood histamine (meg/100 ml) |
|----------|-------------|------------------------------|-------------------------------|----------------------|--------------------------|----------------------------------|
| 1        | 26          | 3                            | 38                            | 148                  | 16.5                    | 6.47                             |
| 2        | 22          | 0                            | 32                            | 156                  | 16.5                    | 7.16                             |
| 3        | 24          | 2                            | 32                            | 150                  | 16.5                    | 5.51                             |
| 4        | 26          | 0                            | 31                            | 146                  | 14.2                    | 4.91                             |
| 5        | 24          | 2                            | 36                            | 150                  | 20.5                    | 5.38                             |
| 6        | 24          | 0                            | 35                            | 148                  | 10.8                    | 6.88                             |
| 7        | 26          | 2                            | 35                            | 148                  | 26.5                    | 5.90                             |
| 8        | 24          | 0                            | 36                            | 152                  | 23.5                    | 5.77                             |
| 9        | 25          | 2                            | 34                            | 146                  | 24.8                    | 5.90                             |
| 10       | 18          | 0                            | 34                            | 152                  | 25.5                    | 5.51                             |
| 11       | 25          | 1                            | 40                            | 152                  | 18.0                    | 4.91                             |
| 12       | 25          | 2                            | 38                            | 146                  | 17.3                    | 4.91                             |
| 13       | 24          | 2                            | 37                            | 154                  | 18.6                    | 5.77                             |
| 14       | 20          | 0                            | 36                            | 154                  | 14.7                    | 6.02                             |

Mean: 23.79
S.D.: ±2.342
S.E. of mean: ±0.625
TABLE 3. Comparison between normal pregnancy and mild pre-eclampsia.

| Clinical data                      | Normal pregnancy 16 cases | Mild pre-eclampsia 14 cases | Difference between means ± error of diff. | 't' (28 d.f.) |
|-----------------------------------|---------------------------|-----------------------------|------------------------------------------|-------------|
| Age (years)                       | 24.56 ± 1.086 (4.343)     | 23.79 ± 0.625 (2.342)       | -0.77 ± 1.253 0.616                      | P > 0.5     |
| No. of previous parturitions      | 1.00 ± 0.274 (1.095)       | 1.14 ± 0.294 (1.100)        | 0.14 ± 0.402 0.345                      | P > 0.5     |
| Duration of pregnancy (weeks)     | 36.20 ± 0.628 (2.510)      | 35.29 ± 0.684 (2.558)       | -0.91 ± 0.928 0.957                      | P > 0.2     |
| Serum histaminase (PU/ml)         | 22.45 ± 0.978 (3.912)      | 18.85 ± 1.253 (4.688)       | -3.60 ± 1.591 2.265                      | P < 0.01    |
| Whole blood histamine (mcg/100 ml)| 5.566 ± 0.179 (0.717)      | 5.786 ± 0.185 (0.693)       | ±0.22 ± 0.257 0.855                      | P = 0.4     |

The slight rise in the mean whole blood histamine content seen in mild pre-eclampsia, however, was found to be statistically insignificant.

The clinical data and the findings of serum histaminase activity and whole blood histamine content in mild pre-eclampsia are presented in Table 4.

Table 5 gives a summary of the comparison of the clinical data and the mean figures for serum histaminases and whole blood histamine in normal pregnancy and severe pre-eclampsia.

It becomes obvious from the table that the two groups are comparable as regards to age, parity and duration of pregnancy. There was a marked diminution of serum histaminase activity with statistically significant rise in whole blood histamine concentration.
TABLE 5. Comparison between normal pregnancy and severe pre-eclampsia.

| Clinical data | Normal pregnancy 16 cases | Severe pre-eclampsia 12 cases | Difference | 't' | 'P' |
|---------------|---------------------------|-------------------------------|------------|-----|-----|
| Age (years)   | 24.56 ± 1.086 (4.343)     | 22.67 ± 1.614 (5.583)         | -1.890 ± 1.944 0.975 | 0.4>P>0.2 |
| No. of previous parturitions | 1.00 ± 0.274 (1.095)     | 0.83 ± 0.271 (0.938)         | -0.170 ± 0.386 0.434 | P>0.5 |
| Duration of pregnancy (weeks) | 36.20 ± 0.628 (2.510)     | 34.75 ± 0.618 (2.140)        | -1.450 ± 0.881 1.644 | 0.2>P>0.1 |
| Serum histaminase (PU/ml) | 22.45 ± 0.978 (3.912)     | 12.20 ± 0.914 (3.160)        | 10.25 ± 1.338 7.691 | P<0.001 |
| Whole blood histamine (mcg/100 ml) | 5.56 ± 0.179 (0.717)     | 6.580 ± 0.333 (1.145)        | +1.014 ± 0.378 2.673 | 0.05>P |

in severe pre-eclampsia when compared to normal pregnancy.

The clinical data and the results of serum histaminase and whole blood histamine contents from 14 cases of eclampsia are shown in Table 6.

The clinical data and the mean values of serum histaminase and whole blood histamine contents obtained from severe pre-eclampsia cases were compared with those of normal pregnancy cases and the results are summarized in Table 7.

From the above table, it can be seen that the two groups are comparable with regards to age, parity and duration of pregnancy and that the reduction of serum histaminase and the rise in the whole blood histamine level are more than the corresponding values

TABLE 6. Serum histaminase and whole blood histamine values in cases of eclampsia.

| Case No. | Age (years) | No. of previous parturitions | Duration of pregnancy (weeks) | Blood pressure (mm of Hg) | Serum histaminase (PU/ml) | Whole blood histamine (mcg/100 ml) |
|----------|-------------|-------------------------------|-------------------------------|---------------------------|--------------------------|------------------------------------|
|          |             |                               |                               | Syst. | Diast. |                      |                                    |
| 1        | 25          | 1                             | 34                             | 186  | 120   | 6.2                  | 8.73                              |
| 2        | 23          | 1                             | 36                             | 178  | 126   | 2.5                  | 6.94                              |
| 3        | 22          |                               | 32                             | 180  | 118   | 8.0                  | 7.98                              |
| 4        | 24          | 0                             | 38                             | 176  | 120   | 11.6                 | 6.78                              |
| 5        | 20          | 0                             | 35                             | 170  | 116   | 8.5                  | 7.43                              |
| 6        | 23          | 1                             | 32                             | 180  | 126   | 12.8                 | 7.10                              |
| 7        | 18          | 0                             | 36                             | 166  | 116   | 5.6                  | 6.78                              |
| 8        | 25          | 1                             | 32                             | 176  | 120   | 9.5                  | 6.47                              |
| 9        | 20          | 0                             | 38                             | 168  | 120   | 10.6                 | 8.34                              |
| 10       | 24          | 1                             | 35                             | 180  | 130   | 6.2                  | 5.42                              |
| 11       | 20          | 0                             | 34                             | 172  | 126   | 11.8                 | 7.81                              |
| 12       | 25          | 2                             | 37                             | 156  | 118   | 19.2                 | 5.93                              |
| 13       | 24          | 1                             | 39                             | 164  | 124   | 3.4                  | 6.16                              |
| 14       | 18          | 0                             | 34                             | 178  | 130   | 12.2                 | 5.67                              |

Mean 22.90 0.57 35.14 173.57 122.14 9.15 6.967
S.D. ±3.410 ±0.647 ±2.324 ±8.010 ±4.806 ±4.376 ±0.832
S.E. of mean ±0.912 ±0.173 ±0.621 ±2.143 ±1.288 ±1.172 ±0.222
TABLE 7. Comparison between normal pregnancy and eclampsia.

| Clinical data | Normal pregnancy 16 cases | Eclampsia 14 cases | Difference between means ± error of diff. | 't' | 'P' (28 d.f.) |
|---------------|---------------------------|-------------------|------------------------------------------|-----|-----------|
| Age (years)   | 24.56±1.086 (4.343)       | 22.90±0.912 (3.410) | -1.66±1.418                              | 1.169 | 0.4> P> 0.2 |
| No. of previous parturitions | 1.00±0.274 (1.095)       | 0.57±0.173 (0.647)   | -0.43±0.324                              | 1.324 | 0.2>P>0.1  |
| Duration of pregnancy (weeks) | 36.20±0.628 (2.510)     | 35.14±0.621 (2.324)  | -1.06±0.883                              | 1.200 | P>0.5      |
| Serum histaminase (PU/ml) | 22.45±0.978 (3.912)     | 9.15±1.172 (4.376)   | -13.3±1.526                              | 11.967 | P<0.001   |
| Whole blood histamine (meg/100 ml) | 5.566±0.179 (0.717)   | 6.967±0.222 (0.832)  | +1.401±0.225                              | 4.909 | P<0.001   |

DISCUSSION

Our results of serum histaminase and whole blood histamine in cases of normal pregnancy in the last 10 weeks are in accordance with the well known observation that despite the remarkable increase in serum histaminolytic power, the blood histamine concentration remains within the normal range found in non-pregnant women. There is a significant positive correlation between serum enzyme level and duration of pregnancy. Other clinical factors such as age, parity and blood pressure showed no significant relation with serum enzyme activity.

In cases of pre-eclampsia and eclampsia the fall in serum enzyme activity appears to be related to the severity of the condition and there is a significant negative correlation between the enzyme activity and whole blood histamine concentration and hypertension.

There has been general agreement that maternal placenta is the principal source of histaminase in circulating plasma during pregnancy and the degenerative lesions observed in this organ in toxemic pregnancy might be responsible for the decreased production of the enzyme and the infacted placental tissue might well be thought of as the source of
increased histamine liberation into the circulation where it accumulates as a result of impaired inactivating mechanism and starts exerting its untoward effects on the mother.

Our findings suggest that the increased serum histaminase activity might be protective in nature to the mother against potential intoxication with histamine. It can also be reasonably adduced that the estimation of serum histaminase may be useful to indicate indirectly the blood histamine concentration which shows definite increase in severe pre-eclampsia and eclampsia, serial determinations of the serum enzyme activity in later weeks of pregnancy may be of diagnostic value in detecting pre-eclampsia in its pre-clinical stages and thus helpful in its prevention by prompt institution of suitable treatment.

**SUMMARY**

1. Simultaneous determinations of serum histaminase and whole blood histamine contents were made on the blood of a total of 56 pregnant women in the last 10 weeks of pregnancy. These cases included 16 normal pregnant women and 40 cases of pre-eclampsia and eclampsia.

2. The average serum histaminase activity was found to be 22.45 ± 3.912 (S.D) PU/ml and the average whole blood histamine content was 5.56 ± 0.717 (S.D) mcg/100 ml.

3. There was significant reduction of serum histaminase activity accompanied by an increase in whole blood histamine in pre-eclampsia and eclampsia the extent of the changes being related to the severity of the condition. There was a significant correlation between the fall of serum histaminase and the increase in whole blood histamine and the extent of hypertension.

4. It is suggested that the pathological lesions in placenta commonly observed in pre-eclampsia and eclampsia might be responsible for the decreased production of histaminase and increased liberation of histamine into the circulation and that determinations of serum histaminase activity might possibly serve to indirectly indicate the blood histamine concentration and hence the severity of the condition.

5. Serial determinations of serum histaminase activity in the second half of pregnancy might be useful to detect pre-eclampsia in its pre-clinical stages and prevent it by institution of suitable treatment promptly.

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