

SERUM CYSTINE AMINOPEPTIDASE IN PREGNANCY

by

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Introduction

One of the important problems in obstetric management today is the proper timing of delivery, specially when the life of foetus or the mother is in jeopardy. This involves the difficult choice between prematurity and the high foetal risk of continued intrauterine existence.

Several laboratory methods have been reported for evaluation of placental function. Urinary excretion of pregnanediol and estriol are said to predict foetal viability and distress in pregnancy. Certain disadvantages are present however, in these methods. They are costly procedures and need to be done in 24 hours collected urine specimen and the procedure is too long to be used in an emergency situation. In spite of their proved scientific value they are inconvenient and impractical for routine use.

The human placenta in addition to estrogens and progesterone contains a complex of enzymes most of which are present in the maternal serum. The

studies of this enzyme complex of the maternal serum during pregnancy have established that the levels of glutamic oxaloacetic transaminase, lactic dehydrogenase alkaline phosphatase and creatinine phosphokinase show a progressive increase with maturity in pregnancy while the levels of others like cholinesterase and tributyrinase follow the reverse order. Since many of these enzymes are also produced by certain tissues other than placenta, their levels during pregnancy may not necessarily reflect the true state of placental function. This impasse has been got over with the finding that the enzyme cystine aminopeptidase (oxytocinase) is largely, if not, solely, the product of placenta. Thus the study of this enzyme bears comparatively bright prospects of better accuracy in the investigation of functional capacity of human placenta.

The aim of the present study has been to correlate the relationship between the serum oxytocinase values and placental function and foetal prognosis in normal and abnormal pregnancies.

Material and Methods

The enzyme cystine aminopeptidase can be estimated from the maternal serum or from the placental homogenates. In this study only the serum estimation was taken up.

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The study of cystine aminopeptidase was carried out on non-pregnant women and in women with normal and abnormal pregnancies attending the antenatal outpatient department and also those that were admitted in the ward of obstetrics and Gynaecology department, King George Hospital, Visakhapatnam.

Normal pregnant women were studied as there were no established normal values of the enzyme cystine aminopeptidase with this method of estimation in this area of India, to enable us to compare with the values in toxæmia cases. It was planned to study serial samples from the same woman in different periods of gestation with an interval of two weeks starting from 28 weeks of gestation till term and also at the time of labour and puerperium. After delivery weights of the infant and placenta were noted.

Some patients were reluctant to give serial samples either for fear of losing blood or for fear of prick. Some did not keep up to regular appointments given to them due to ignorance. All were not interested in an institutional delivery. So it was decided to collect and study random samples also along with the cases of serial followup of normal pregnant women.

The number of cases in this study were 97 and the estimations done were 231. Samples were taken at random from 9 healthy non-pregnant nulliparous women. Samples were taken at random from 26 cases of normal pregnancy of varying ages and parity at various period of gestation ranging from 28 weeks to term.

Serial estimations of cystine aminopeptidase were done in 7 cases of normal pregnancy of varying age and parity from 28 weeks of gestation upto labour

at two weeks interval, and on 2nd, 5th and 10th day of puerperium.

In abnormal pregnancies estimations of cystine aminopeptidase were done from 28th week onwards at different intervals depending on the clinical condition of the patient, foetus and cystine aminopeptidase values that were obtained in the prior estimations. The following are the details of cases studied.

- (1) Non-pregnant — 9
- (2) *Normal pregnancy*:
 - Random study — 36
 - Followup study — 7
- (3) *Abnormal*:
 - (A) (i) Post-caesarean pregnancy followup — 3
 - (ii) Intrauterine death — 2
 - (iii) Twin pregnancy with pre-eclampsia — 2
 - (B) Toxaemia of pregnancy—
 - (i) Pre-eclampsia .. 18
 - (ii) Eclampsia .. 10
 - (iii) Hypertension .. 12

The method used for determination of serum cystine aminopeptidase in this study was that described by Babuna and Yenen (1966a).

The values were expressed in terms of optical density (O.D.). For convenience the readings were multiplied by thousand. The results when expressed in optical density give better chances to detect small variations in the enzymes activity because the O.D. values are twenty times larger than the absolute values.

Results and Discussion

The mean serum cystine aminopeptidase value in non-pregnant females was 27.7 units. The enzyme, is said to be present in small traces in sera of non-

pregnant females (Titus *et al* 1960; Page and Titus 1961).

A. Normal pregnancy:

The mean, the maximum and minimum values of cystine aminopeptidase in 44 cases of normal pregnancy at different weeks of gestation are represented in Fig. 1.

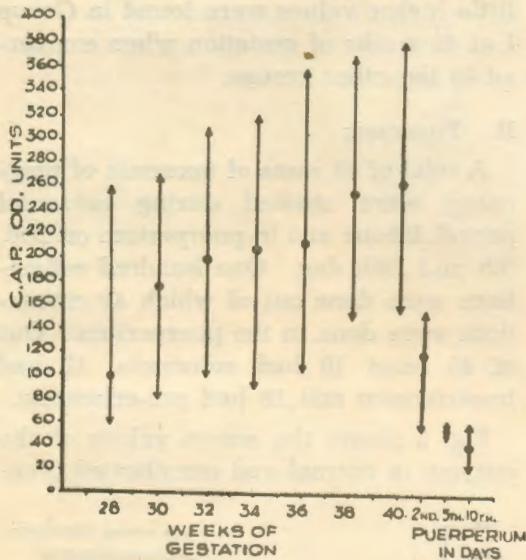


Fig. 1

The mean, maximum and minimum values of cystine aminopeptidase (O.D. x 1000) at different periods of gestation in normal pregnancy.

There is a progressive increase in cystine aminopeptidase values, the maximum value being reached at term. It also shows the wide range of normal values at different weeks of gestation.

Serial estimation of cystine aminopeptidase was done in 7 cases of normal pregnancy during antenatal period and puerperium and the weights of infants were noted in all. Fig. 2 shows the progressive rise of oxytocinase values from early pregnancy till term and a steep fall by second day and near non-pregnant values by 10th day.

FOLLOW-UP OF NORMAL PREGNANCY CASES

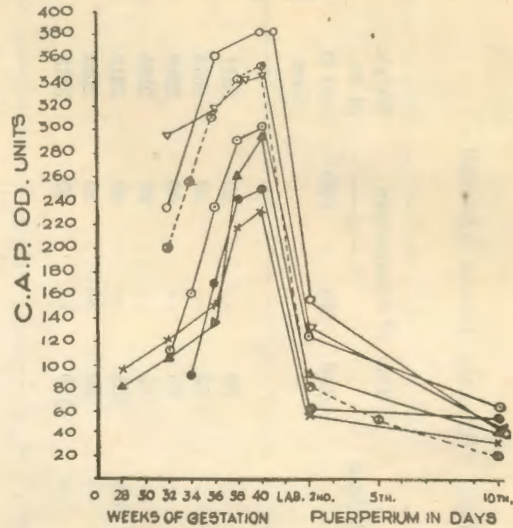


Fig. 2

Serial values of cystine aminopeptidase in seven cases normal pregnancy.

Titus *et al* (1960) Raid (1962), Melander (1965) and Babuna and Yenen (1966) have found a steep curvilinear rise in plasma cystine aminopeptidase in normal pregnancy starting from the fourth month and reaching its highest value around term.

No correlation was found between cystine aminopeptidase value at term and weight of the infant (Table I).

There is a drop of cystine aminopeptidase concentration by 65.09% on 2nd day, 81.58% by 5th day and 85.9% by 10th day of puerperium from the level of enzyme during labour. In this study 14.1% of the enzyme content of sera during labour is recoverable ten days postpartum. According to Riad (1962), on an average, 40% of the enzyme content of term sera is still recoverable one week postpartum. 38.06%, 20.08%, 15.30% of the enzyme content of sera at

TABLE I
Serum C.A.P. Values (O.D. x 1000) in Seven Cases of Normal Pregnancy During Antenatal and Postnatal Periods

S. No.	T. No.	Weeks of Gestation							Labour			Day of Puerperium			Weight of infant in Gms.
		28	30	32	34	36	38	40	—	—	—	2nd	5th	10th	
1	2	—	—	—	90	170	240	250	—	—	—	60	—	50	3181
2	27	98	—	120	—	150	255	230	—	—	55	—	30	2613	
3	28	80	—	105	—	135	260	295	—	—	90	—	40	2500	
4	35	—	110	110	160	225	290	300	—	—	125	—	60	2386	
5	44	—	—	235	—	360	200	380	380	—	155	—	40	2812	
6	15	—	—	200	255	310	340	350	—	—	80	50	20	2954	
7	54	—	—	295	—	315	340	345	—	—	130	—	40	2613	

40 weeks is recoverable on second day, fifth day and tenth day of the puerperium respectively.

Cystine aminopeptidase values were compiled in Table II under four groups according to age and parity. From this Table it is seen that not much of correlation was found between cystine aminopeptidase values and age and parity. A little higher values were found in Group I at 40 weeks of gestation when compared to the other groups.

B. Toxaemia

A total of 40 cases of toxæmia of pregnancy were studied during antenatal period, labour and in puerperium on 2nd, 5th and 10th day. One hundred estimations were done out of which 40 estimations were done in the puerperium. Out of 40 cases 10 had eclampsia, 12 had hypertension and 18 had pre-eclampsia.

Fig. 3 shows the serum values of the enzyme in normal and complicated preg-

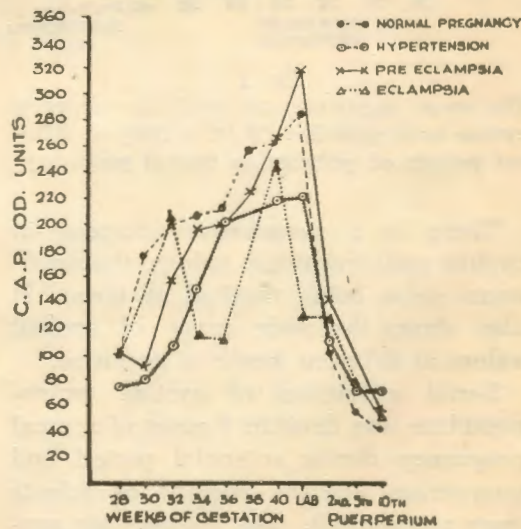


Fig. 3

The mean values of serum cystine aminopeptidase at different periods of gestation in normal and complicated pregnancies.

TABLE II
Mean Values of C.A.P. (O.D. x 1000) at Different Weeks of Gestation in Different Groups

Group	Age	Gravida	Weeks of Gestation				Labour	Day of Puerperium			
			28 to 32	34 to 38	40	2nd		5th	10th		
I	15-25 Yrs.	Primi	160	223.21	295	380	117.5	50	47.5		
II	15-25 Yrs.	Second	125	218.12	257.0	—	91.66	—	36.66		
III	15-25 Yrs.	Multi	170	220.71	155	190	—	—	—		
IV	26-35 Yrs.	Multi	193.33	242.0	260	—	95	55	20		

nancies at different weeks of gestation at two weeks interval, during labour and puerperium.

The average mean values at 36 and 40 weeks in eclampsia are lower than those in normal pregnancy showing the impaired function of the placenta. The relatively high serum cystine aminopeptidase levels in the puerperium can be explained as due to diminution in inactivation of enzyme due to the impaired renal function in eclampsia (Masao Koida *et al* 1971). Masao Koida *et al* (1971) showed that the kidney homogenates have the highest degree of inactivating property indicating that the kidneys are the major organs involved in the inactivation of this enzyme.

The mean cystine aminopeptidase values in pre-eclampsia were lower than those of the normal pregnancy except on 40th week and during labour and puerperium.

In pre-eclampsia and eclampsia the plasma levels are scattered on both sides of the normal range indicating that an enzymatic disturbance is associated with this disease. The same findings have been observed by Page (1946), Babuna and Yenen (1966) and Josepides and Turkington (1967). But the levels of oxytocinase in toxæmic patients were found to be lower than those of the normal cases by (Riad 1962; Ichaliotis 1964; Ichaliotis Lambrinopoulos and 1965).

The enzyme levels in hypertension were found to be increased by Hurry *et al* (1972). The mean values of cystine aminopeptidase in hypertension associated with pregnancy were lower than in normal pregnancy except during puerperium in our cases.

Since cystine aminopeptidase is said to be an index of placental function, an attempt was made to compare the cystine

aminopeptidase values in sera collected at term with placental and foetal weights in cases where follow up was possible. The results are given in Table III. It

confirmation with those of Ichaliotis and Lambrinopoulos (1965), Ichaliotis (1964), Thompson *et al* (1969) and Alant Blunt (1971). Thomson *et al*

TABLE III

Correlation Between Cystine Aminopeptidase at Term, Weight of Placenta and Weight of Infant

S. No.	Case	Cystine aminopep- tidase Units at term (O.D. x 1000)	Weight of placenta in Grams.	Weight of Infant in Grams.
1.		250	454.5	3181
2.		230	568.2	2613
3.	Normal	295	482.9	2500
4.	Pregnancy	300	482.9	2386
5.		380	482.9	2812
6.		350	454.5	2954
7.		345	454.5	2613
8.		200	454.5	2500
9.	Post Ceasarean	215	454.5	2727
10.	Pregnancy	200	454.5	3181
11.		160	454.5	2215
12.	Hypertension	290	454.5	2613
13.		250	454.5	2556
14.		175	454.5	2272
15.		200	454.5	2386
16.	Eclampsia	170	454.5	2556
17.		360	454.5	2727
18.		420	511.3	2556
19.		250	454.5	3068
20.	Pre-eclampsia	150	454.5	3693
21.		400	482.9	2443
22.		220	454.5	2500
23.		150	454.5	2982
24.	Twins with pre-eclampsia	530	568.1	1818 1363
25.		290	455.5	2329 1960

is clear from the Table that there is no positive correlation between placental or foetal weight and the enzyme levels. This is so in normal as well as in abnormal pregnancies. These results are

(1969) stated that placental weight is not a good indicator of placental adequacy and that placental insufficiency on account of small size is probably rare. Mathur and Walker (1970) found that

there was very little difference between placenta whether from normal subjects or from patients with toxæmia when cystine aminopeptidase activity was expressed per unit volume of trophoblast.

C. *Post-caesarean Pregnancy*

Serial estimation of enzyme activity was done in 3 cases of post-caesarean pregnancies during antenatal and postnatal period (Fig. 4).

explained that relatively less amount of enzymes is liberated into the circulation from the placenta, thus indirectly favouring the quick disappearance of the enzyme from the circulation in the puerperal period.

D. *Twins*

High levels of serum oxytocinase were noted in 2 cases of twins at term. The values were 530 and 590 units. Both

FOLLOW-UP OF POST-CAESAREAN PREGNANCY CASES

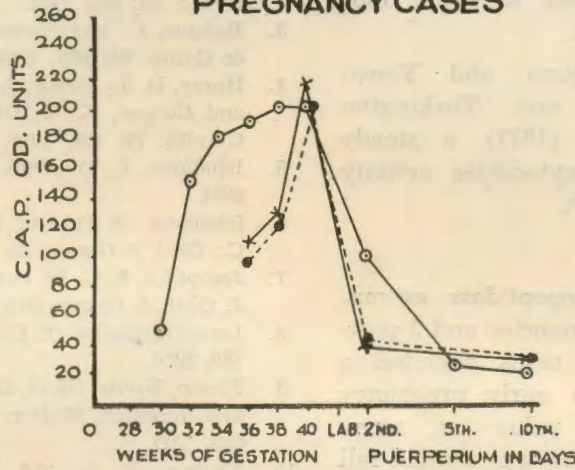


Fig. 4
Serum aminopeptidase activity in 3 cases of postcaesarean pregnancies during antenatal and

A progressive increase was observed in the cystine aminopeptidase values in all the 3 cases. Caesarean section was done for all three cases and live foetus was delivered in all.

29.27% and 12.98% of the enzyme content of sera at 40 weeks is recoverable on second day and tenth day of the puerperium respectively. In normal pregnancy the values in the similar period are 38.06% and 15.30%. It shows the quick disappearance of cystine aminopeptidase values in cases of pregnancy terminated by elective caesarean section. It can be

cases were associated with mild pre-eclampsia. The high value of cystine aminopeptidase in these cases could be due to associated pre-eclampsia. The mean value of cystine aminopeptidase in cases of pre-eclampsia with single foetus is 265 units. Both delivered live foetuses each with Apgar 10. The high level of enzyme cystine aminopeptidase in cases of twins could be due to increase in active or functional placental trophoblastic tissues.

High values of enzyme in twin pregnancy were found by Ichaliotis and

Lambrinopoulos (1965) and Alan Blunt (1971).

E. Intrauterine Death

Serial estimation of oxytocinase at intervals of two days was done in 2 cases of severe pre-eclampsia. Sudden fall in oxytocinase value from 170 to 110 units and from 240 to 160 units was noted with the disappearance of foetal heart beat. Progressive fall in oxytocinase levels was observed and subsequently labour was induced with syntocinon drip and they delivered dead foetuses weighing 1363 grams and 1818 grams.

According to Babuna and Yenen (1966), Josephides and Turkington (1967), Alan Blunt (1971) a steady decrease in serum oxytocinase activity resulted in foetal death.

Summary

Serial cystine aminopeptidase estimations in 7 normal pregnancies and 3 post-caesarean pregnancy cases depicted a progressive rise from early pregnancy reaching maximum value at term. Following delivery there was a rapid fall of cystine aminopeptidase value. The fall of cystine aminopeptidase value in cases of toxaeimias of pregnancy was slow when compared to that in normal pregnancy.

In 2 cases of intra-uterine foetal death, there was a marked and sudden fall in cystine aminopeptidase levels, even before actual foetal death occurred. The observations indicate that determination of cystine aminopeptidase in maternal serum might be a valuable parameter in judging the condition of the placenta. Serial estimation of serum cystine aminopeptidase levels is found to be of value in the diagnosis of impending foetal

death in certain pathological pregnancies. Whenever such a decrease is found the pregnancy should be terminated if the foetal size is estimated to be adequate for viability.

No correlation was found between the weight of the placenta and serum cystine aminopeptidase level.

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