SERUM PROLACTIN LEVELS IN TOXAEMIA OF PREGNANCY

(A Study by Radio Immuno Assay)

by

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SUMMARY

Forty-eight cases of 32-40 weeks of gestation were studied. Fifteen cases were taken as control group while study group comprised of 15 cases of pre-eclampsia and 18 cases of eclampsia including 3 cases of post-natal eclampsia. Antenatal and postnatal serum prolactin levels were estimated by radio immuno assay technique. Mean antenatal serum prolactin levels were significantly raised in both the study groups as compared to control group. The severity of diastolic pressure, oedema and proteinurea showed positive correlation with the serum prolactin levels. However, this correlation was not significant statistically. Serum prolactin levels showed a definite rise with the rise in serum uric acid levels. In cases of pre-eclampsia this correlation was statistically significant. Mean postnatal serum prolactin levels were lower than the antenatal levels in all the three groups. A further study including larger group of patients with serial estimations of serum prolactin levels is suggested.

Introduction

Toxaemia of pregnancy is a disease having an age old identification which continues to be responsible for maternal and perinatal mortality in large number of pregnancies especially in developing countries. This condition is peculiar to the late pregnancy and puerperium. The levels of prolactin hormone in blood rises progressively during pregnancy and fall during puerperum (Tyson *et al* 1972). The possible correlation between these two seems to promise a better understanding of the fundamental pathology alongwith the earliest possible warning for timely management of mother and fetus in peril.

However, the reports of serum prolactin levels during hypertension of pregnancy are conflicting. Raised levels have been reported by Redman *et al* (1975), Jenkins and Perry (1978) and Elibschitz *et al* (1979). Ho Yuen *et al* (1978) reported

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low levels while Dubowitz *et al* (1975) Sadovsky *et al* (1977) and Ranta *et al* (1980) noted no significant correlation. In view of the existing controversy in this field and recognition of increasing importance of prolactin in toxaemia it was considered relevant to carry out the present study.

Material and Methods

The present study was conducted in the Department of Obstetrics and Gynaecology and Nuclear Medicine Unit of the Postgraduate Department of Medicine, S. N. Medical College, Agra. The series included 48 cases of 32-40 weeks gestation comprising of following groups:

1. *Control Group*: Fifteen normotensive cases without any evidence of oedema or proteinurea.

2. *Pre-eclamptic Group*: Fifteen cases with blood pressure more than 150/90 mm of Hg and proteinurea or oedema.

3. *Eclamptic Group*: Eighteen cases with blood pressure more than 140/90 mm of Hg and proteinurea or oedema with convulsions. Out of them 3 cases were of postnatal eclampsia.

The cases showing evidence or past history of hypertension, chronic renal disease, diabetes, breast cancer or schizophrenia were eliminated from this study. Patients taking antihypertensive or antidepressant drugs were also excluded. The cases thus selected, were subjected to routine examination, renal function tests and fundoscopy. Blood samples for serum prolactin estimation were taken before starting any antihypertensive treatment. Second sample was taken after delivery when the blood pressure reverted back to normal in cases of toxaemia and within 24 hours of delivery in control group. Three cases of eclamptic group expired undelivered so second sample could not be taken. In cases of postnatal eclampsia 1st and 2nd samples were taken in hypertensive and normotensive stages respectively.

The amount of prolactin in a sample is determined by measuring the distribution of prolactin between its free and bound moitcis when exposed to a limited quantity of binding reagent i.e. antibody. This distribution is measured by using a radiolabelled prolactin whose distribution is inverse to the distribution of prolactin to be estimated. For this prolactin labelled with I^{125} at Swiss federal Institute for reaction research was used. The prolactin standard had code No. 75/504 and antisera used was provided by Dr. A. F. Parlow (Los Angles U.S.A.) to W.H.O. and was used in a final dilution of 1 : 400,000. The second antibody used was donkey antirabbit gamma globulin in a final dilution of 1 : 40. A typical 100 tube assay designed for prolactin is shown in Table I. The tubes containing the double antibody precipitate were counted. A standard curve (Fig. 1)

Fig. 1 – STANDARD CURVE OF PROLACTIN

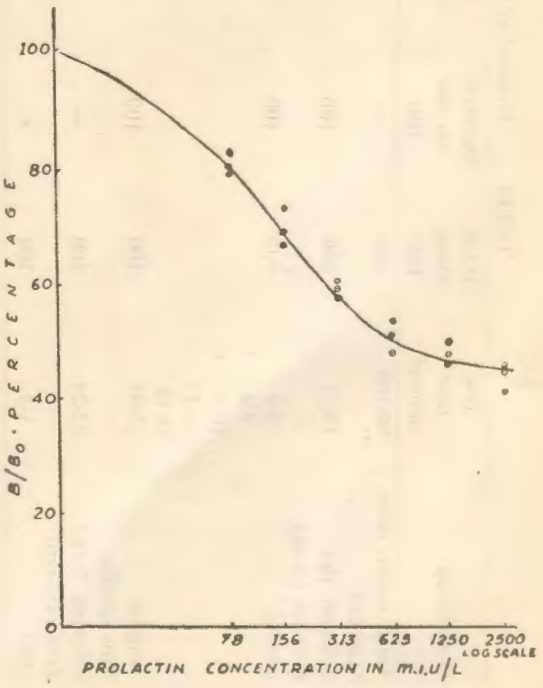

TABLE I *Protocol of Radio-Immuno-Assay of Prolactin*

Description	Test tube number	Traces alone (ul)	Standard solution (ul)	Anti-serum (ul)	Assay buffer (ul)	Incubation at 4°C for 48 hours	Second antibody (ul)	Incubation at 4°C for 20 hours centrifugation for 30 minutes
Total count tubes	99-100	100	—	—	—	—	—	
Standard Solution (b)	19-21	100	100	100	100		100	
Internal quality control	4-6	100	100	100	400		100	
	7-9							
	10-12							
	13-15							
	16-18							
Samples	25-98	100	100	100	400		100	
Non specific (binding NSB)	22-24	100	—	—	600		100	
Zero standard (Bo)	1-3	100	—	100	500		100	

was plotted comparing hormones concentrations versus the bound free ratio of labelled hormone existing in bound and free fractions respectively, the concentration of prolactin was read from this standard curve by inter polation.

Observations

In the control group the mean antenatal serum prolactin level was 3790.37 ± 2775.75 mIu/L. In the eclamptic group the mean value was 15074.58 ± 10397.23 mIu/L while in the pre-eclamptic group the value was 14295.35 ± 952083 mIu/L. The postnatal values in all groups were lower as compared to antenatal values (Table II).

Serum prolactin values increased with the duration of pregnancy (Table III). Prolactin levels had a positive correlation with the untreated level of diastolic pressure in study group as well as control group. However, the correlation was not statistically significant ($p > 0.5$) Table IV). Similarly, the severity of oedema and proteinurea also had a protective correlation with serum prolactin levels but again without any statistical significance (Tables V and VI). There was a positive correlation between serum uric acid levels and serum prolactin levels in all the three groups but the significance was noted only in pre-eclamptic group (Table VII(.

Discussion

The antenatal serum prolactin levels had a big range. In control group it was from 1312.5 to 12125 mIu/L (Table II) which is comparable with that reported by Tyson *et al* (1972) who also observed range of 35-600 ng/ml at 38-40 weeks of gestation. The wide range was also observed by Ho

TABLE II

Antenatal and Post Natal Serum Prolactin Levels (mIu/L) in Different Groups

	Study Group				Control Group	
	Eclampsia		Pre-Eclampsia		Ante-natal	Post-natal
	Antenatal	Post-natal	Antenatal	Post-natal		
Number	15	12	15	15	15	15
Mean	15074.58	7334.22	14295.35	4919.52	3790.37	2670.18
S.D.	10397.23	7052.38	9520.83	2881.13	2775.75	2158.02
Range	6325 to 37500	344.4 to 27562.5	2062.5 to 27500	1800 to 11062.5	1312.5 to 10125	834.5 to 8482.5

Statistical Correlation	t value	p value
Antenatal control V/s		
Eclampsia	4.0616	< 0.001
Pre-eclampsia	4.1030	< 0.001
Antenatal V/s Postnatal		
Eclampsia	2.4854	< 0.05
Pre-eclampsia	3.6509	< 0.005
Control	1.2341	> 0.05

Yuen *et al* (1978).

Kletzky*et al* (1980) reported that mean prolactin levels were 27 ± 4 ng/ml in first trimester, 67 ± 10 ng/ml in second trimester and 157 ± 15 ng/ml in third trimester. In the present series these levels were 2113.75 ± 539.61 mIu/L at 32-34 weeks, 2158.88 ± 1109.38 mIu/L at 35-37 weeks and 7170.50 ± 2249.56 mIu/L at 38-40 weeks of gestation (Table III). Thus serum prolactin levels showed a positive correlation with gestational age ($r = .6917$) which was statistically high significant ($p < 0.005$). Ho Yuen *et al* (1978) has also shown positive correlation with gestational age.

In cases of pre-eclampsia the mean antenatal prolactin level was 14295.35 ± 9520.93 mIu/L while in cases of eclampsia it was 15074.78 ± 10397.23 mIu/L. When compared with the control group these levels were very much raised and the difference was statistically highly significant with p value < 0.001 (Table II).

Raised prolactin levels were reported by Redman *et al* (1975) in hypertensive pregnancies. Elibschitz *et al* (1979) also reported raised levels. Jenkins and Perry (1978) studied prolactin levels in primigravid patients of pregnancy induced hypertension, higher levels were noted both at the beginning and at the end of third trimester significantly so at the end ($p < 0.02$). Biswas and Rodeck (1976) also noted raised levels in some cases but the difference was statistically not significant. Dubowitz *et al* (1975) noted no significant difference in maternal prolactin level between 12 women with pre-eclampsia and 5 normotensive pregnant cases. The variability in the prolactin levels and small number of cases studied might explain the lack of difference. The levels reported by Ranta *et al* (1980) showed no significant

TABLE III

Antenatal Serum Prolactin Concentrations (mIu/L) According to Period of Gestation

Period of Gestation (Weeks)	Eclampsia			Pre-Eclampsia			Control		
	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.
32 to 34	12	13280.73	9146.58	5	8668.05	10410.84	6	2113.75	539.61
35 to 37	2	14625.00	7159.46	4	11631.88	7750.56	4	2158.88	1109.38
38 to 40	1	37500.00		6	20760.42	5600.00	5	7170.50	2249.56
Total	15	15074.58	10397.23	15	14295.35	9520.83	15	3790.37	2775.75

TABLE IV

Serum Prolactin Levels (mIu/L) According to Severity of Hypertension

Diastolic B.P. (mm. of Hg)	Eclampsia			Pre-Eclampsia			Total		
	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.
Mild (90-99)	3	14854.17	9629.94	3	12208.33	11179.00	6	13531.25	10433.25
Moderate (100-109)	2	16781.25	10208.85	4	12639.75	9890.48	6	14020.25	9182.48
Severe (110 & above)	13	18076.44	12219.79	8	15905.84	9862.37	21	17249.54	11408.08
Total	18	17395.49	11134.81	15	14295.35	9520.83	33	15986.34	10436.87

(Eclampsia ($r = 2486 + = 1.02266$, $p > .05$).
Pre-Eclampsia ($r = .1342 + = .4822$, $p > .05$).

TABLE V

Mean Serum Prolactin Levels (mIu/L) According to Severity of Oedema

Oedema	Eclampsia			Pre-Eclampsia			Total		
	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.
Absent	3	18937.50	6967.84	3	19916.68	8804.59	6	19427.09	7939.51
Mild	11	11096.02	5968.00	6	6457.12	3440.73	17	9458.76	5262.21
Moderate	3	32250.00	9093.27	3	16666.67	13131.29	6	24458.33	11294.21
Massive	1	37500.00	—	3	21979.16	5026.62	*4	25859.38	3554.35
Total	18	17395.49	11134.81	15	14295.35	9520.83	33	15986.34	10436.87

Eclampsia ($r = .3507$ $t = 1.4979$ $p > .05$).
Pre-eclampsia ($r = .1977$ $t = .7272$ $p > .05$).

TABLE VI

Serum Prolactin Levels (mIu/L) According to Proteinurea

Protei-nurea	Eclampsia			Pre-Eclampsia			Total		
	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.
Absent	0	—	—	1	4312.5	—	1	4312.5	—
Mild	7	14113.29	8120.09	6	10749.42	10042.44	13	12560.73	9044.68
Moderate	7	19250.00	13698.04	3	17843.75	10814.00	10	18828.13	13036.98
Severe	4	19893.63	12407.79	5	18843.00	8133.91	9	19309.95	10187.54
Total	18	17395.49	11134.81	15	14295.35	9520.83	33	15986.34	10436.87

Eclampsia ($r = .3114$, $t = 1.2691$; $p > .05$).
Pre-eclampsia ($r = .4275$; $t = 1.7050$; $p > .05$).

TABLE VII

Mean Serum Prolactin Levels (mIu/L) According to Serum Uric Acid Level

Serum Uric Acid (mg%)	Eclampsia			Pre-Eclampsia			Control		
	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D.
2-4	4	13085.94	7657.60	3	4165.50	240.89	15	3790.37	2775.75
4-6	10	17265.00	12807.07	6	16114.59	9330.44	0	—	—
Above 6	4	22031.25	10961.4	6	17541.04	9229.35	0	—	—
Total	18	17395.49	11134.81	15	14295.35	4520.83	15	3790.37	2775.75

Statistical correlation:
Eclampsia ($r = .1791$; $t = .7057$; $p>0.05$).
Pre-eclampsia ($r = .6086$; $t = 2.8128$; $p>0.05$).
Control ($r = .4658$; $t = 1.8979$; $p>0.05$).

difference from those reported in normal controls. The observations in the present series are in contradiction to the findings of Ho Yuen *et al* (1978) who reported diminished levels.

Mean postnatal serum prolactin level in the control group was 2670.18 ± 2158.02 mIu/L which was lower than the antenatal values. The difference, however, was statistically not significant ($p > 0.05$). This is comparable with the reports of Gregoriou *et al* (1979) who observed fall in serum prolactin level after delivery but the difference was not significant. In both the study groups the statistical difference between antenatal and postnatal samples was highly significant ($p < 0.005$ in pre-eclamptic group and $p < 0.05$ in eclamptic group (Table II).

The prolactin levels were correlated with the initial diastolic pressure. A positive correlation was observed in both the study group (Table IV). However, statistically it was not significant ($p > 0.05$). Redman *et al* (1975) and Jenkins and Perry (1978) also could not find any significant correlation between prolactin concentration and diastolic pressure.

When compared with the severity of oedema, the prolactin levels had a weak positive correlation having no statistiical significance (Table V). Proteinurea was present in all the cases of study groups except one, who had low prolactin levels 4312.5 mIu/L. Redman *et al* (1975) also found significant difference according to presence of proteinurea. The mean value in total study group with mild proteinurea was 12560.73 ± 9044.68 mIu/L while with severe proteinurea it was 19309.95 ± 10187.54 mIu/L however, statistically the correlation was not significant ($p > 0.05$).

In the present series, mean serum uric acid levels were raised in cases of eclampsia and pre-eclampsia and had positive cor-

relation with the prolactin levels in both the groups. It was significant in pre-eclamptic group ($p < 0.05$). Redman *et al* (1975) have also reported that the cases having rising urate levels have considerably higher prolactin levels.

Raised prolactin levels observed in the present series indicate that prolactin is in some way involved in these conditions, possibly as a marker of some other underlying causal change. Renal tubular dysfunction may also be contributing to a rise in prolactin level. Horrobin (1971-75) reviewed many relevant studies and showed role of prolactin in vascular reactivity, impaired renal function and fluid and electrolyte balance by various animal experiments and human observations. Prolactin like other peptide hormones might be cleared by kidney and early involvement of kidney in pre-eclampsia could interfere with prolactin. Whether it is culprit of victim of the disease is yet not clear.

Burstyn *et al* (1972) suggested that prolactin could modulate the effect of aldosterone leading to sodium and water retention. This may furher lead to a change in arteriolar wall sodium concentration causing an increased vascular sensitivity to angiotensin II, which is reported to be present even in the patients destined to develop pregnancy hypertension (Gant and Worley, 1977). It has also been suggested that prolactin stimulates synthesis of prostaglandins in vascular tissues (Horrobin *et al* 1974). Jenkins and Perry (1978) have also suggested that altered renal prostaglandin may influence blood pressure and be under prolactin control.

If a direct or indirect causal relationship between prolactin and hypertensive changes in pregnancy is established then effective prophylaxis might be possible by controlling the prolactin level. It's possible role can be (a) in the elucidation of the etiopathogenesis of pre-eclampsia (b) as screening test for early diagnosis of pre-eclampsia (c) in the prognosis of toxaemia of pregnancy. As there is a big range of serum prolactin levels in later months of pregnancy serial estimations in a larger group of patients is required in order to reach a more definite conclusion.

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