

Tilak Venkoba Rao Oration

POST PARTUM PSYCHIATRIC SYNDROMES : ARE THEY BIOLOGICALLY DETERMINED ?

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Mr. Chairman, Distinguished Colleagues Ladies and Gentlemen,

To begin with I would like to extend my grateful thanks to the *Awards Committee of Indian Psychiatric Society* for conferring upon me the *Tilak Venkoba Rao Oration Award* for this year. Many young stalwarts of our society have delivered this oration in the past. I really feel honoured and privileged to stand in their line and to pay my humble tribute to Late Tilak Venkoba Rao in whose memory this oration has been instituted. The topic I have selected for today's oration is "*Post Partum Psychiatric Syndromes : Are they Biologically determined ?*".

Pregnancy and post partum period are generally regarded as maturational crises equal in importance to those of adolescence and the menopause. Varieties of stresses are faced during this period like: endocrinal changes, changes in body image, activation of unconscious psychological conflicts pertaining to pregnancy and intrapsychic reorganisation associated with becoming a mother.

Psychiatric illness following child birth has been an area of concern to medical profession for a long time. My interest in the area of post partum psychiatric illness was aroused about 10 years back while working in the general hospital psychiatric set up. It was a clinical observation which I am sure many colleagues will share that percentage of women suffering from psychiatric illness

following child birth was considerably higher than what was observed in general population. It was then that our initial work on the subject had started and the findings were published in 1982 (Gautam et al., 1982) "Post partum psychiatric syndromes an analysis of 100 consecutive cases". Since then this has been an area of my constant research preoccupation.

Magnitude of the Problem

Mental disorders in puerperium show a well marked variation in their severity. Most are mild and transitory and only a small minority are extremely severe and require admission to a psychiatric service. Estimates of the proportion of puerperal women who develop severe mental disorders necessitating their admissions to hospitals vary. Visle (1956) quotes studies where rates range from 0.8 to 2.5 per 1000 deliveries. In some more recent studies the prevalence of puerperal psychosis per 1000 deliveries has ranged from 1.4 to 4.6.

There is a substantial evidence that at least 10 per cent of women have a depressive illness in the puerperium (Pitt, 1968; Nilsson and Almgren, 1970; Kumar and Robson, 1979) post natal blues (temporary depression or lability of mood in the first 10 days after delivery) is reported by a yet higher proportion upto 50 per cent in some series (Robin, 1962; Yalom et al., 1968; Pit, 1963). Cox et al. (1982) in a series of 100 prospectively studied patients using Standardised Psychiatric

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Table 1

Authors	Place of study	Criterion for duration of puerperium	Prevalence of Puerperal Psychosis for 1000 deliveries
Hemphill (1952)	Bristol (U.K.)	Not stated	1.4
Tetlow (1955)	Warwick (U.K.)	6 months	1.5
Pugh et al (1963)	Massachusetts (U.S.A.)	6 weeks	3.3
Jansson (1964)	Goteborg (Sweden)	1 year	4.6
Paffenbarger (1964)	Ohio (U.S.A.)	6 months	1.9
Kendell et al (1967)	Edinburgh (U.K.)	90 days	2.2

Interview reported post natal depression in 13 per cent of the patients and yet

another 16 per cent had depressive symptoms distinct from the blues of the first 10 days, indicates that psychiatric morbidity is a common and disabling complication of puerperium. In our subsequent work "A prospective study of post partum psychiatric illness in 200 consecutive mothers following childbirth" (Gautam et al., 1987) the incidence of psychiatric illness was found out to be 46% of which 35% were Depressives, 7.5% Anxiety States, 2% Hysteria and 0.5% Schizophrenics. A review of post natal depression in various studies has shown a varied incidence ranging from 3% to 36%.

Nature of the Problem: Distinct features of post partum Psychiatric illness

Puereral Psychosis is no longer recognised as a disease in its own right because psychiatrists have adopted for good reasons a descriptive classification

TABLE II

Authors and date	Sample	Measure	Time after birth	Criteria for diagnosis of 'postnatal depression'	Prevalence
Gordon et al (1959)	98 primiparae	Physician rating	4 months	Emotional Adjustment ('much upset')	13%
Ryle (1961)	137 women on register of one GP (345 pregnancies)	Records of GP consultation	Up to 1 year	Diagnosis as 'endogenous depression'	3%
Tod (1964)	700 pregnancies at one GP practice	GP consultation	Up to 1 year	Diagnosis as 'puerperal depression'	2.9%
Gorden et al (1965)	306 primiparae	Obstetrician rating	6 weeks	Emotional problems	30%
Jacobsen et al (1965)	404 Swedish women	Checklist of physical and emotional symptoms	—	6 or more symptoms	25%
Pitt (1968)	330 at one antenatal clinic	Pitt's depression questionnaire and interview	6 weeks	Increase of 6 points in score (pre-/ post-natal) + 2 week duration of distress + onset of birth	10.8%
Dalton (1971)	189 at one GP obstetric unit	GP consultation	6 weeks	Psychiatric intervention Rated as transiently or mildly depressed	7% 34%

Rees & Lutkins (1971)	67 attending one GP obstetrician	Beck depression inventory	Up to 1 year	Cut-off score 10.....30% 14.....17% 17.....10% 25.....3%	
Breen (1975)	50 volunteers responding to clinic advert.	Pitt's depression questionnaire	10 weeks	Increase of 6 points	34%
Kumar & Robson (1978)	190 married primiparae from one antenatal clinic	Goldberg standardised psychiatric interview	3 months	Severity rating of 2 or more	16% overall (14% affective)
Wolkind et al (1980)	131 primiparae	Psychiatric interview	4 months	Psychiatric disorder (level of symptoms and impairment)	10%
Oakley (1980)	58 married primiparae	Interviewer	Up to 5 months	Depression (level of symptoms and impairment)	24%
			3 weeks-5 months	Depressed mood	33%
Paykel et al (1980)	120 at postnatal clinic	Raskin 3 area depression scale	6 weeks	Score \geq 7	20%
Cox et al (1982)	103 from antenatal clinics	Goldberg standardised psychiatric interview	3-5 months	Pitt's criteria (see above)	13%
Gautam et al (1987)	200 consecutive mothers at obstetric unit	Indian psychiatric interview schedule	6 weeks	IPIS Depressive	36%
Nott (1987)	212 mothers	G.H.Q. semistructured Psychiatric Interview	3 months	—	18.5%

and have not accepted the claim that puerperal psychosis has its own specific clinical features. In the Ninth revision of the international classification of diseases (WHO, 1978) this condition has been classified under "Complication of pregnancy child birth and the puerperium". According to DSM. III this disorder is classified as atypical psychosis and is used only when no other psychotic disorder can be diagnosed. Many psychiatrists believe that the puerperium is not associated with any particular type of mental illness but that almost any psychiatric state may be precipitated by childbirth. This is because the research studies (Foundeuer et al., 1957) have failed to find differences in

symptoms between post partum and comparison group. These studies have used diagnosis as the method of comparison.

Recent studies (Kadrmaz et al., 1980; Brockington et al., 1981; Gautam et al., 1986) have looked at the phenomena of the illness in a controlled investigation using accepted disciplines of clinical research such as standardised interviews and operationally defined diagnosis. The debate over a specific aetiological link between parturition and psychosis (Hamilton, 1962, 1982; Brockington et al., 1982) has been revived by recent reports showing that there is a very short time-lag (upto two weeks) between birth and the onset of most cases of post partum

psychosis. The characteristic clinical features may perhaps be additional (Brockington et al., 1981; Dean and Kendell, 1981).

We should remind ourselves of the clinical characteristics of patients with puerperal psychoses because they bear directly on the entry criteria we might use. The first point to note is that great majority of psychotic illness have their onset in first three weeks (Dean and Kendell, 1981; Brockington, 1982; Gautam et al., 1982; Meltzer and Kumar, 1985) after child birth. Kendell et al. (1987) have reported extremely high risk of admission to psychiatric hospital within first 30 days after child birth.

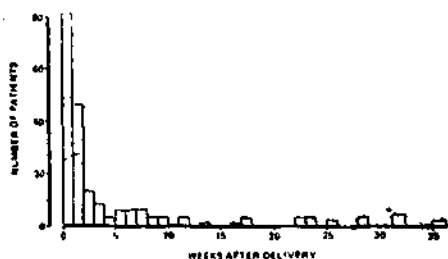


Figure 1. Onset of illness in patients admitted to the Manchester Mother and Baby Unit

The clinical characteristics of patients are illustrated by Edinburgh study of Dean and Kendell (1981; Figure 2). The great majority of patients suffered from some form of Affective disorder according to RDC applied to patients admitted within few weeks of delivery.

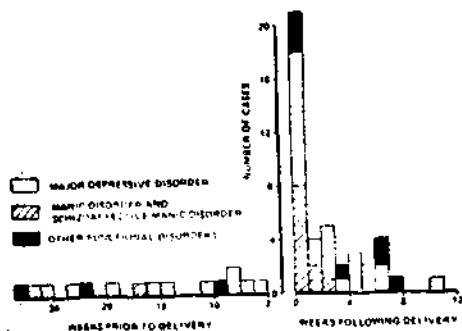


Figure 2. Onset of major functional disorders in the puerperal group

The Manchester series (Brockington, 1982) show essentially the same picture. In a prospective series of 58 admissions to mother and baby unit most presented with a predominantly affective disorder (Table III). Twenty five women met criteria for mania or schizophrenia and this is rather a higher proportion than in a comparable series of 52 consecutively admitted nonpuerperal patients. There was a similar proportion of depressed people in two groups but a smaller number of women with schizoaffective disorder, depressed type in the puerperal group. Therefore the findings are similar in the two centres. Most of the patients are affective, a good proportion of them manic and only a few schizophrenics in the puerperal population.

Table III-RDC Diagnosis in Psychotic Patients (Brockington, 1982)

	Puerperals N=56	Controls N=52
Mania or Hypomania	17	10
Schizoaffective Manic	8	1
Major or Episodic Minor depressive disorder	22	13
Schizodepressed	4	12
Schizophrenic	5	16

One way of trying to study what is special about puerperal psychosis is to see whether there are particular patterns of symptoms in puerperal psychotic patients.

Brockington (1982) studied this in great detail applying 217 scales or factors to a series of 58 consecutive admissions to mother and baby unit and to 52 controls. There were many significant differences but most significant ones (Table IV) show that puerperal cases are significantly more confused, in need for supervision and seeking reassurance. In addition they

have an organic type picture with prominent affective symptoms particularly lability and presence of elation but rather fewer hallucinations.

Table IV-Symptom Patterns (Brockington, 1982)

Non Puerperals greater	Puerperals greater
Systemization	Confusion
Persecution	Incompetence
Auditory hallucinations	Needing supervision
Autism	Seeking assurance
	Elation euphoria
	Lability
	Thought disorder
	Distractibility
	Overactivity

Brockington also compared puerperal with nonpuerperal manics, 11 out of 180 ratings being significantly different. There was generally a picture of disorganisation with confusion being significantly more prominent in the puerperal patients and may be this should be one criteria for diagnosis i.e. presence of so called characteristic symptoms of puerperal psychosis, the presence of clouding, disorientation perplexity and confusion.

Comparison of puerperal depression with non puerperal depression both groups meeting criteria for major depressive disorder (RDC) in the Edinburgh study showed that puerperals were significantly more psychotic and more clouded compared with non puerperal patients and again there was evidence of disorientation and perplexity (Table V) (Dean and Kendell, 1981).

Comparison of Puerperal with non puerperal schizophrenic patients matched on age of onset, socioeconomic

Table V-Puerperal depression versus Psychotic Depression (Dean and Kendell, 1981)

	Puerperals (in %)	Controls (in %)
42 PSE items significant differences		
Psychotic	45	15
Lability	27	3
Agitation	49	21
Disorientation	18	0
Perplexity	39	18
Organic Imp.	12	0
Depressive Del.	39	12

All patients meet RDC major dep. disorder. Differences more marked with onset 2 weeks delivery.

status, literacy status, occupation, domicile and type of family in Jaipur study (Gautam et al., 1986) revealed significant difference in symptoms measured by Indian Psychiatric Interview Schedule (Kapur et al., 1971). The puerperal schizophrenics had marked irrelevant speech, incongruent affect, distractibility, disorientation and forgetfulness (Table VI) while non puerperal schizophrenics showed significantly higher, bizzare behaviour, violence, hallu-

Table VI-Puerperal Vs. Non Puerperal Schizophrenic (Gautam et al., 1986)

IPIS Items Sign. different	Puerperal N=67 %	Nonpuerperal N=67 %
Irrelevant Speech	76	52
Disorientation	51	18
Incongruent Affect	42	7
Forgetfulness	33	13
Distractibility	21	5

Diagnosis of Schizophrenia according to ICD-9.

cinations, suspiciousness, blunted affect and delusions (Table VII).

Table VII-Puerperal Versus Nonpuerperal Schizophrenia (Gautam et al., 1986)

IPIS Item Sign. different	Puerperal N=67 %	Nonpuerperal N=67 %
Bizzare Behaviour	63	85
Blunted Affect	46	64
Violence	42	64
Hallucinations	30	49
Suspiciousness	25	51
Delusions	22	39

Diagnosis of schizophrenia according to ICD-9

Review of the literature suggests that affective disturbances are prominent in most post partum illnesses and have early onset after child birth. However some studies have reported an almost equivalent incidence of schizophrenia and affective disorders (Da Silva and Johnstone, 1981) in their sample and most of the schizophrenic illnesses had an onset within a fortnight after child birth as well.

Postnatal depression is yet another common finding apart from post partum blues. One prominent feature common to all studies of phenomenology of post-partum illnesses is a constant finding of "confusion" or "disorientation".

The element 'confusion' has been mentioned in the literature quite often. In the days before antibiotic it is possible that some of these patients had toxic confusional states but this is no longer a plausible explanation. It is possible that grandiosity, misinterpretation and attentional deficits account for the phenomenon. The confusional component in puerperal psychosis has never been properly investigated but there is much evidence that these patients are more disorganised than other psychotics.

Risk of Puerperal Psychoses in Subsequent Childbirth and Prognosis

Most of the studies indicate that primipara have a high risk of postpartum Psychiatric illness. In our series 66% (Gautam et al., 1982) had with first child birth which was subsequently confirmed in our later work also (Gautam et al., 1987). Proportion of women having further postpartum psychosis shows that the risk of puerperal psychosis in subsequent deliveries is 32% in our study which is higher than what has been reported in the West (Table VIII).

Hays' recent study using cluster analysis (Hays, 1978), observations made by Savage (1896) long ago that puerperal psychosis has an unusually good prognosis and more recent work by Platz and Kendell (1988) report good outcome of puerperal psychosis.

Table VIII-Proportion of Women having further Post-Partum Psychosis

Study	No. of Women with subsequent pregnancies	Proportion of women with subsequent puerperal psychosis (%)
Fondeur et al. (1957)	22	13.6
Jansson (1964)	74	9.5
Vislie (1956)	63	23.9
Arentsen (1968)	72	15.4
Protheros (1969)	53	26.4
Gautam et al. (1982)	50	32.0

Platz and Kendell in a follow up study of matched groups of 72 pairs of puerperal and nonpuerperal psychiatric patients for a mean interval of nine years found out that puerperal women had significantly fewer relapses in the followup period, fewer committed suicide and the

psychiatric morbidity of their relative tended to be lower. Their better outcome was most marked in puerperal subjects with major depression. It has been suggested that child birth is a uniquely potent precipitant of affective illness.

Factors Related to Post Partum Psychiatric Syndromes

Number of factors are reportedly associated with psychiatric illness following childbirth which include biological factors like genetic factors, endocrinal factors, age, parity and menstrual cycle and biochemical factors, Psychological factors like previous psychiatric status, premorbid personality, psychodynamic factors, and social factors like marital relationship, family type, social support and stressful life events.

Biological Factors

The relative risk of admission to a psychiatric hospital with psychotic illness found to be extremely high in the first 30 days of childbirth particularly in primipara suggests that metabolic factors are involved in genesis of puerperal psychosis. Most of the contributors in this area have focussed on the possible interaction of the thyroid and adrenal function with the high oestrogen and progesterone level of pregnancy and the abrupt termination of these high levels of sex hormones at parturation.

Genetic Factors : Nearly all authors who have concerned themselves with puerperal psychosis have discussed the occurrences of mental illness in the families of the patients. Thuwe (1974) while studying genetic factors in puerperal psychosis studied 120 children over 15 years of 43 women with puerperal psychosis and 173 grand children of 34 women with puerperal psychosis and controls of these probands and found that record of mental illness or psychiatric treatment is

significantly more common among children of women who have been treated for puerperal psychosis. The same tendency is evident in the grandchild generation but the differences here are not statistically significant.

This work therefore provides strong evidence of genetically operating factors in the general category of puerperal psychosis. It is not possible to indicate any particular pattern of major genes but the fairly high risk of mental illness in the first filial generation suggests that dominant transmission plays some part in the operation of genetic factors.

Endocrinal Factors : Nott et al. (1976) studied hormonal changes and mood in the puerperium, measures of clinical status and mood were completed before and after delivery and corresponding plasma levels of lutinising hormone (LH) follicle stimulating hormone (FSH) total oestrogen and progesterone were estimated and prolactin assay was also done. They attempted to test three hypothesis concerned with progesterone and its metabolism during pregnancy (1) that the levels of progesterone before delivery are excessively high in women who develop affective disturbance (2) that the rate of fall is too fast and (3) there is an abnormal ratio of oestrogens to progesterone. The results showed that predelivery oestrogen levels tend to be higher in those who are more irritable; greater the progesterone drop the more likely are subjects to rate themselves depressed within 10 days but the less likely they are to report sleep disturbance. Lower the post partum oestrogen levels more is sleep disturbance reported. Other hormone levels showed no correlation to any other symptoms. The authors felt that future enquiries might be better directed at trying to relate hormone changes to specific symptoms rather than the whole syndrome known as maternity blues. Progesterone had been reported to

be related to causation of post partum illness earlier too (Malleon, 1953).

Ballarchy et al. (1958) reported response to L-triiodothyronine of post partum psychiatric symptoms. Hamilton (1962) postulated long lasting depression of thyroxin production after child birth. Hamilton's study using desiccated thyroid and triiodothyronine gave good results but study was uncontrolled.

Prolactin has traditionally been thought to be involved only in lactation. Prolactin in physiological concentrations has been shown to stimulate progesterone synthesis. It has been reported to restore adrenal sensitivity to ACTH in patients on high dose steroid therapy (McNatty et al., 1974; Ingvansson, 1969). Harrobin concluded that Prolactin has action which could be implied in mental illness (Harrobin et al., 1976). Nott et al. (1976) did not find any difference in prolactin levels in relation to mood changes.

Bower (1956) reported that low levels of corticosteroids are related to affective disorder (Depression) in puerperium. Hamilton postulated disorders of adrenal metabolism as being related to post partum mental disorders because of similarity of syndromes associated with the use of exogenous corticoids but no study exists to that demonstrate that corticoid levels in post partum psychosis (Manic or Schizophrenic or Schizomanic) are higher than in those of other psychoses. Plasma 17OH steroid levels are higher during pregnancy due to oestrogen induced elevation of proteins that bind these hormones.

BIOCHEMICAL FACTORS : The Biochemical studies of plasma aminoacids levels (Stein et al., 1976; Gard et al., 1986; Handley et al., 1977) have mainly revealed low tryptophan levels in puerperium in those women who suffer from post partum blues. Lindstorm et al. (1984) found that certain cases of post partum psychoses are associated with occurrence in plasma and

CSF of an unique opioid peptide related to Bovine B. Casmomorphine. Endorphines have also been implicated in mood changes (Koob and Bloom, 1983) and have been shown to increase during pregnancy and labour (Thoms et al., 1982). Newham et al. (1984) however found no correlation between post partum blues and endorphine levels.

Treadway et al. (1969) reported decreased excretion of normetanephrine in conjunction with increased neuroticism and depression scores in normal pregnant women as compared with controls. They postulated that this represented increased utilisation of norepinephrine due to a reduction in receptor sensitivity by gonadal hormone changes associated with pregnancy and may result in an increased biological susceptibility to affective disorders.

SLEEP STUDIES : Research into the biology of sleep of pregnant and post partum women have reported sleep pattern disturbances (Karacan et al., 1968). Just before delivery stage 8 sleep was markedly reduced returning to normal by the second partum week. Studies from early pregnancy to post partum period revealed that sleep system is profoundly affected throughout pregnancy and sometimes for several months after delivery, during the third trimester subnormal levels and by parturition there was marked suppression of total sleep time which did not reach normal levels until several weeks post partum. These investigators raised a question whether excessive drop in level of stage 4 sleep in late pregnancy or failure or delay in rebound of this stage in the early post partum period contributes to increasing one's susceptibility to emotional disturbance.

AGE AND PARITY : Paykel et al. (1980) reported younger age as predisposing factor. Enomotos et al. (1986) found

common age group 25-29 years. In our earlier study (Gautam et al., 1982) 71% of the post partum patients had onset of illness in less than 25 years of age against 31% of the clinical OPD population of females in the same age group while others (Tod, 1964; Jacobsen et al., 1965; Pitt, 1968) did not find association between age and post partum psychiatric illness.

Most of the studies have reported higher percentage of their patients being primipara (Gordon et al., 1953; Nott et al., 1976; Gautam et al., 1982; Meltzer and Kumar, 1985; Gard and Handley, 1986 and Enomotos, 1936). This may be one reason that younger age is positively correlated with Postpartum Psychiatric illnesses. However, some authors (Grossman, 1971; Paykel et al., 1980) have found no association between parity and PPPS.

Menstrual Disturbances: Menstrual irregularity has been frequently reported in patients of PPPS (Malleon, 1953; Dalton, 1971; Hamilton, 1962; Nott et al., 1976). Recurrence of symptoms at the time of menses (Blumberg and Billig, 1942) also seems to implicate the sex steroid alterations as being related to the precipitation of the illness. Delay et al. (1953) have reported transient endometrial changes during psychiatric illness.

Psychosocial Factors: Earlier studies have stressed on *Psychodynamic factors* like conflicting feelings within the mother with regard to her mothering experience. Zilboorg (1929) described the patients as ambivalent with a castration complex, failure of resolution of oedipal stage of psychosexual development and sadistic tendencies towards men. Anderson (1933) and Smalldon (1940) confirmed these observations but did not find evidence of increased frigidity, homosexuality, eroticism or masturbation. Several writers (Brew and Scidenberg, 1950; Ostwald and Regan, 1957) have

found atleast implicit evidence of some of these characteristics. Some authors have reported *higher neuroticism score* in premordid personality of patients with PPPS (Pit, 1968; John et al., 1977 and Enomotos et al., 1986) while Kumar and Robson (1978) have not supported this view.

A significant association has been found between *poor marital relationship* and PPPS (Kumar and Robson, 1978; Paykel et al., 1980; Cox et al., 1982 and Watson et al., 1984). The literature is scanty in relation to studies of social support system and family interaction. Paykel et al. (1980) have reported the women whose *social system is poor or inadequate* are more prone to develop psychiatric illness in post partum. Discrepancy between expected and born sex of child and its psychological impact on the mother is not clear from the available literature though John et al. (1977) have reported that women who are more particular about sex of the born child are more prone to develop psychiatric illness. However this view was not supported by Grossman (1971). In our study (Gautam et al., 1982) also it was observed than discrepancy in expected and born sex of the child existed among 20% of the patients suffering from PPPS. A strong association has been reported between occurrence of recent stressful life events and PPPS (Paykel, 1980; Dutt et al., 1983 and Watson, 1984).

CONCLUSIONS

Having reviewed the available literature on post partum psychiatric syndromes it is possible to arrive at some fair conclusions at this stage.—

- (1) PPPS have specific and strong precipitating factor i.e. child birth and most PPPS occur within 30 days of child birth i.e. short time lag between child birth and occurrence of PPPS.

- (2) PPPS are having convincingly higher rate of prevalence in the puerperal subjects in comparison to non puerperal female population.
- (3) PPPS may be diagnosed according to the contemporary nosology (DSM-III, ICD-9 etc) but they have certain distinct clinical features when phenomenology is compared with nonpuerperal patients of similar diagnosis.
- (4) Course and outcome of PPPS differs with comparable non puerperal patients of similar diagnosis. PPPS seem to have better outcome.
- (5) Certain psychosocial factors like premorbid personality, poor marital relationship and poor social support system seems to be related to occurrence of PPPS.
- (6) Many biological factors appear to be contributing to PPPS. The biological changes seem to be specific to pregnancy and puerperium they include
 - (a) Strong evidence of genetic operating factors? dominant transmission plays some part.
 - (b) Endocrinal factors have correlation to specific symptoms of PPPS rather than the syndromes.
 - Higher pre-delivery oestrogen—more irritability
 - Greater progesterone drop in puerperium—more likelihood of subjects to rate themselves depressed.
 - Lower postpartum oestrogen levels—more sleep disturbances
 - Low thyroxin levels postpartum seem to be associated with post partum depression.
 - Role of ACTH, PROLACTIN AND GROWTH HORMONE is not clear.
 - (c) Biochemical factors Low tryptophan levels in plasma associated with post partum blues
 - Increased utilisation of Norepinephrine may lead to increa-

sed biological susceptibility to affective disorder.

- (d) Sleep studies need more research to be conclusive.
- (7) Early age primipara and Menstrual Irregularity seem to be predisposing factors.

The complex interaction of predisposing psychological and biological factors need to be clearly understood and further research in understanding the causation of post partum psychiatric syndromes is needed to be more biologically oriented. There is a need for prospective well designed studies beginning from the early pregnancy to post partum period to look for specific measurable predictors psychosocial as well as biological. The neuroendocrinal response to challenge doses of Apomorphine or clonidine could be one indicator among other possible biological predictors.

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