INTRODUCTION

Postpartum Psychosis

Women are vulnerable to mental health problems during pregnancy and postpartum period. 'Postpartum psychosis' is an umbrella term that covers the severe forms of major depression, manic episode, and psychotic disorders occurring during the period after delivery. There is an intense debate on offering a separate nosological status to postpartum psychosis. Suicide and infant harm are both serious consequences of postpartum psychosis (Babu et al., 2008; Chandra et al., 2002; Jones et al., 2014). Postpartum psychosis is reported to occur in about 1–2/1000 childbearing women within the first few weeks after delivery (Kendell et al., 1987; Klompenhouwer and van Hulst, 1991; Meltzer and Kumar, 1985). Some secondary (organic) causes have also been linked to manifestation of postpartum psychosis (Dahale et al., 2014; Fassier et al., 2011). However, in the absence of such obvious secondary causes, an interaction between psychosocial factors and biological factors has been put forth to explain the pathogenesis of postpartum psychosis.

A common hypothesis for postpartum psychiatric disorders is that the estrogen levels fluctuation following delivery triggers an episode in vulnerable women.

Mother-Infant Bonding

Mother-infant bonding refers to the responsive, reciprocal and loving relationship that is recognized and attended by both the mother and infant (Brockington et al., 2001; Spinner, 1978). In a pioneering study, women with history of mental illness described lack of love/affection towards the child and occasional thoughts of harming the child, rejection or hate (Kumar, 1997). This phenomenon was first described by Kumar as 'maternal bonding disorder'. The recent literature has focused on the bio-behavioural aspects of bonding especially on the role of oxytocin in the process of bonding.

OBJECTIVES

Primary

a. To study *ESR1*, *HMCN1*, *METTL13* and *5-HTTLPR* gene polymorphisms in women with postpartum psychosis and unaffected parous women.

b. To study the association of *OXTR* gene polymorphism with bonding process in women with postpartum psychosis and unaffected parous women.

Secondary

a. To study the sociodemographic factors associated with postpartum psychosis and mother-infant bonding in mothers with postpartum psychosis.

b. To study the clinical characteristics of postpartum psychosis and of mother-infant bonding in mothers with postpartum psychosis.

METHODS

Subjects

The study was conducted in Bangalore and subjects with postpartum psychosis formed the cases for the study. The cases were recruited from outpatient, inpatient general psychiatry services and from perinatal psychiatry services of National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, India.

Healthy controls were recruited from general hospitals and community. The study was approved by the Institute Ethics Committee No. NIMH/DO/SUB-COMMITTEE/2012 Sl. No.9 Behavioural Sciences, Dated 12-09-2012.

Inclusion criteria

Cases (N=100)

- Subjects fulfilling ICD-10 (World Health Organization, 1992) criteria for mania, depression, acute transient psychotic disorder, schizoaffective disorder, schizophrenia during postpartum period (defined in the study as illness occurring within 6 months of childbirth).
- Age: 18-45 years.
- Informed consent obtained from the patient or family caregiver.

Controls (N=100)

- Healthy women within 6 months of their postpartum period.

Exclusion criteria

Cases

- If informed consent could not be obtained.
- History of secondary causes contributing to postpartum psychosis.

Controls

- If informed consent could not be obtained.
- History of psychiatric illness during pregnancy and postpartum period in controls.

Procedure

Subjects were recruited according to the inclusion and exclusion criteria. Informed consent was obtained from subjects themselves or from caregivers if the former was not possible. The diagnosis was confirmed by the consultant in charge of the patient. The socio-demographic factors and clinical details were recorded using a semi-structured proforma. Brief Psychiatric Rating Scale was used to rate the clinical condition of the subjects (Overall and Gorham, 1962). Edinburgh Postnatal Depression Scale was used to screen for depressive symptoms in both cases and controls (Cox et al., 1987). Rating of the mother–infant bonding was done using the Postpartum Bonding Questionnaire in both cases and controls (Brockington et al., 2006). Under aseptic precautions, about 10 ml of venous blood was collected from cases and controls after obtaining informed consent. Genomic DNA isolation and all wet lab work were carried out at the Molecular Genetics laboratory, Department of Psychiatry, NIMHANS using standard procedures. The following loci were examined in the present study.

- Serotonin-Transporter Gene -Linked-Polymorphic-Region *(5-HTTLPR)*
- Estrogen Receptor Alpha Gene *(ESR1)* rs9340799; rs2234693
- Hemicentin Gene *(HMCN 1)* rs2891230
- Methyltransferase like 13 Gene *(METTLI3)* rs12080760
- Oxytocin Receptor Gene *(OXTR)* rs 53576

Statistical Analysis

Chi-square test and *t* test were used to compare the categorical variables and continuous variables across the groups respectively. The tests were two-tailed and the results with $p < 0.05$ were considered as significant. Controls with a family history of psychiatric illness in a first degree relative were excluded from the analysis for genotype and allele frequency differences, as compared to cases. Spearman

correlation was used to find the association between postpartum bonding as measured by PBQ scores and clinical severity as measured by EPDS scores and BPRS scores. In the present study, the internal reliability coefficients were α= 0.79 for Impaired bonding, α= 0.68 for Rejection/Pathological Anger, α= 0.42 for Maternal Anxiety, and α= 0.3 for Risk of Abuse. The subscales of Maternal Anxiety and Risk of Abuse subscales were dichotomized for group comparisons in view of infrequent positive responses and low internal reliability. Any positive response to a question under subscale was coded as 1 and others were coded as 0. Mann-Whitney U test was used to compare the clinical characteristics with the bonding subscale scores. Kruskal-Wallis test was used to compare the scores of the three broad diagnostic groups on bonding subscale scores. Locally weighted regression (Loess), a non-parametric scatter plot smoothing regression technique was used to examine the relationship between mother infant bonding (PBQ scores) and clinical severity (EPDS and BPRS scores). Scatterplot smoothing and fitting a smooth curve helps visual evaluation of the functional dependence of the variables that are included in the analysis. The smooth curve thus fitted will be non-horizontal in shape if the two variables are related to each other (Jacoby, 2000).

Multifactor dimensionality reduction (MDR) approach was used to check for gene-gene interactions i.e. epistasis among the polymorphisms in the causation of postpartum psychosis. MDR is considered as non-parametric alternative to logistic regression. It is a data mining approach to characterize the interaction among independent variables that in turn influence a dependent variable with a binary outcome for e.g. ill and not ill. MDR is based on a constructive induction algorithm that involves conversion of two or more attributes to a single attribute. The formation of the new attribute changes the representation space of the data. A representation thus created facilitates the detection of nonlinear or non-additive interactions among the attributes. The prediction of the class variable improves over that of the original representation of the data. An additive model MDR analysis was done using the open source MDR software package (Computational Genetics Laboratory, www.epistasis.org).

RESULTS

Cases were 105 subjects who had a clinical diagnosis of postpartum psychosis and controls were 102 subjects without any history of psychiatric illness in the past or currently and who were in their postpartum period.

Comparison of Cases and Controls on Sociodemographic Characteristics

There was no significant difference in age between cases and controls **(**25.1±4.4 years and 24.2±3.1 years)

Table Comparison of Sociodemographic Data of Cases and Controls

Variable	**Case N=105**	**Controls N=102**	**t/ chi U**	**P**
Residence			15.1	<0.001
Rural	63 (60%)	86 (84.3%)		
Urban	42 (40%)	16 (15.7%)		
Diet				
Vegetarian	13 (12.4%)	18 (17.6%)	1.12	0.28
Non-vegetarian	92 (87.6%)	84 (82.4%)		

Religion				
Hindu	90 (85.7%)	99 (97.1%)	8.78	0.01 *
Muslim	12 (11.4%)	03 (2.9%)		
Christian	03 (2.9%)	-		
Family type			4.09	0.04 *
Non-nuclear	47 (44.8%)	60 (58.8%)		
Nuclear	58 (55.2%)	42 (41.2%)		
Median Years of Education (IQR)	10 (9 to 12)	7 (5 to 10)	3178	<0.001*
Median Family Income/ Month In rupees (IQR)	2000 (2000 to 5000)	2000 (2000 to 3000)	4261	0.01*
Salaried Employment			0.0	0.79
No	99 (94.3%)	97 (95.1%)		
Yes	06 (05.7%)	05 (04.9%)		

Subjects from the rural area were represented more among controls. The controls were predominantly from non-nuclear family and majority of them belonged to Hindu religion. The cases had relatively better educational status. The income status was significantly higher among cases when compared to controls.

Table Comparison of Cases and Controls Regarding the Details of Marriage

Variable	Case N=105	Controls N=102	t/ chi U	P
Marital history				
Married	105 (100%)	102 (100%)	-	-
Unmarried/widowed/separated	-	-		
Consanguinity in Subjects				
Yes	19 (18.1%)	38 (37.3%)	9.51	0.002 *
No	86 (81.9%)	64 (62.7%)		
Mean age at marriage in yrs. (s.d)	21.4 (4.2)	18.9 (2.5)	5.1	<0.001*
Marriage duration in months(s.d)	45.3 (35.1)	63.4 (26.9)	-4.1	<0.001*
Discord in family				
Yes	29 (27.6%)	11 (10.9%)	9.21	0.002*
No	76 (72.4%)	90 (89.1%)		

All subjects were married. The consanguinity rates were higher among controls. The controls had married earlier and had a longer duration of married life. Discord in the family was higher among cases.

Table Clinical Presentation of Postpartum Psychosis

Type	Frequency	Percentage
Acute polymorphic psychosis	39	37.1
Bipolar episode	37	35.2
(Bipolar Illness-Manic Episode)	*(22)*	*(21.0)*
(Bipolar Illness-Depressive Episode)	*(9)*	*(8.6)*
(Bipolar Illness-Mixed Episode)	*(6)*	*(5.7)*
Depressive episode	20	19.0
Other Psychosis	09	08.6

Acute polymorphic psychosis was the most common clinical presentation. Acute psychosis and other psychosis presentation were seen in nearly half of the study subjects. The rest of the subjects presented either with a depression or with mania/mixed affective episode.

Table Details of Past History of Psychiatric Illness

Variable	Frequency	Percentage
Past history of psychiatric illness (including postpartum illnesses)		
Yes	48	45.7
No	57	54.3
Diagnostic details of past History		
Bipolar Illness	27	56.2
Acute and Transient Polymorphic Psychotic Disorder	13	27.1
Other Psychosis	6	12.5
Unipolar Depression	2	04.1
Past history in relation to postpartum (n=48)		
With a postpartum course	22	45.8
Without any postpartum course	26	54.2

Nearly half (45.7%) of the study subjects had a past history of psychiatric illness. Bipolar illness disorder was the most common illness (56.2%) among those who had past history of illness, followed by acute and transient psychotic disorder. A postpartum onset of illness was seen in nearly half (45.8%) of the number of subjects who had past history of psychiatric illness.

Table Details of the Presenting Episode of Postpartum Psychosis

Variable	Details
Mean age at onset of illness (s.d)	22.5 (4.5)
Median total duration of illness in days (IQR)	30 (15-105)
Median postpartum day of onset illness (IQR)	30 (4.5-90)
Onset within 6 weeks following delivery	65 (62%)
Median duration of illness in days during postpartum period (IQR)	28 (15-71)
Mean EPDS score (s.d)	12.9 (7.5)
Mean BPRS Score (s.d)	50.7 (17.1)
Total number of subjects with EPDS score >11	60 (57.1%)
s.d=Standard Deviation *IQR=Inter-quartile Range*	

The onset of illness was in the early twenties. Most subjects had an onset of illness by 90 days of postpartum period. Nearly 62% of subjects had an onset within 6 week of delivery. More than half of the study subjects scored above cut-off on EPDS scale (depression rating scores).

Table Comparison among Study Subjects on Medical and Obstetric Variables

Variable	Case N=105	Controls N=102	chi	P
History of Medical Problems during Pregnancy				
Yes	15 (14.3%)	01 (1.0%)	12.84	<0.001*
No	90 (85.7%)	101 (99.0%)		
Thyroxine Supplementation				
Yes	7 (6.7%)	1 (1.0%)	4.50	0.03*
No	98 (93.3%)	101 (99.0%)		
Parity				
Primiparae	54 (51.4%)	09 (8.8%)	44.36	<0.001*
Multiparae	51 (48.6%)	93 (91.2%)		
Planned Pregnancy				
Yes	54 (51.4%)	20 (19.8%)	22.37	<0.001*
No	51 (48.6%)	81 (80.2%)		
Antenatal Visits				
< 3 Visits	05 (4.9%)	02 (02.0%)	1.24	0.26
≥ 3 Visits	100 (95.2%)	100 (98.0%)		
History of Abortion				
Yes	23 (21.9%)	11 (10.8%)	4.66	0.03*
No	82 (78.1%)	91 (89.2%)		
Total EPDS Scores	12.95 (7.5)	.21 (0.8)	16.94	<0.001*

Cases had higher rates of medical problems. The rates of planned pregnancy and abortions were higher among cases as compared to controls. Primiparae and multiparae were almost equally represented among cases as compared to controls where multipara were the majority. The cases scored higher on EPDS (depression rating scale) as compared to controls.

Table Presence of Family History of (F/h/o) Psychiatric Illness among Subjects

Variable	Case N=105	Controls N=102	t/chi	P
F/h/o psychiatric illness (including first degree relatives)				
Yes	37 (35.2%)	01 (1.0%)	40.51	<0.001*
No	68 (64.8%)	101 (99.0%)		
F/h/o Psychiatric Illness in First Degree Relative				
Yes	8 (7.6%)	1 (1 %)	5.48	0.01*
No	97 (92.4%)	101 (99%)		
F/h/o postpartum mental illness (including first degree relatives)				
Yes	13 (12.4%)	0	13.47	<0.001*
No	92 (87.6%)	102 (100%)		
F/h/o postpartum mental illness in first degree relatives				
Yes	5 (4.8%)	0	4.97	0.02*
No	100 (95.2%)	102 (100%)		

The percentages of family history of psychiatric illness and postpartum mental illness were higher among cases as compared to health controls indicating that those women with a family history of psychiatric illness or family history postpartum mental illness may be at a higher risk for developing postpartum psychosis.

Table Anthropometric Details of Study Subjects

Variable	**Case N=105**	**Controls N=102**	**t/ chi**	**P**
Weight	52.85 (10.04)	48.67 (7.34)	3.42	0.001*
Height	153.28 (5.75)	153.62 (5.34)	-.45	0.65
Body-Mass Index (BMI)	22.47 (3.95)	20.62 (2.92)	3.84	<0.001*
Sitting Height	76.80 (4.08)	76.85 (3.21)	-.10	0.92
Sitting Height-Height Ratio	0.50 (0.02)	0.50 (0.01)	0.30	0.76
Leg Length	76.47 (4.60)	76.77 (3.96)	-.49	0.62
Sitting Height-Leg Length Ratio	1.00 (0.08)	1.00 (0.06)	0.44	0.66

The body weight and BMI were higher among cases as compared to controls

Table Comparison of Cases and Controls on Infant Related Variables

Variable	**Case N=105**	**Controls N=102**	**chi**	**P**
Mode of delivery				
Normal	71 (67.6%)	93 (92.1%)	18.97	<0.001*
Instrumental	34 (32.4%)	08 (07.9%)		
Term baby				
Yes	98 (93.3%)	97 (96.0%)	0.74	0.38
No	07 (06.7%)	04 (04.0%)		
Gender of the baby				
Male	49 (46.7%)	65 (64.4%)	6.51	0.01*
Female	56 (53.3%)	36 (35.6%)		
History of NICU care				
Yes	22 (21.0%)	03 (3.0%)	15.61	<0.001*
No	83 (79.0%)	98 (97.0%)		
Serious infant physical illness #				
Yes	13 (12.4%)	01 (01.0%)	10.54	0.001*
No	92 (87.6%)	100 (99.0%)		

The rates of instrumental deliveries, Neonatal Intensive Care Unit (NICU) care, and serious infant physical illness were higher among cases. The percentage of male babies was higher among controls. # Serious illness included medical problems requiring admission and specialist paediatric care.

Table Comparison of Cases and Controls on Mother-Infant Bonding Assessments

PBQ Factors	Case N=105	Controls N=102	Chi	P
General factor – F1				
Normal	66 (62.9%)	101 (99.0%)	43.4	<0.001*
High	39 (37.1%)	01 (1.0%)		
Rejection and pathological anger -F2				
Normal	93 (88.6%)	102 (100%)		
High	12 (11.4%)	0	12.3	<0.001*
Infant focused anxiety – F3				
Normal	96 (91.4%)	102 (100%)	9.1	0.003*
High	09 (8.6%)	0		
F4 Incipient abuse – F4				
Normal	93 (88.6%)	102 (100%)	12.3	<0.001*
High	12 (11.4%)	0		

Cases scored high on all the four PBQ factors

Table Correlations between EPDS, BPRS Scores and PBQ Factor Scores

Measure	F1 Impaired Bonding	F2 Rejection & Anger	F3 Infant Focused Anxiety	F4 Risk of Abuse	Total Scores
BPRS	0.01	0.04	0.06	0.21*	0.10
EPDS	0.18	0.18	0.25**	0.08	0.16
*p<0.05 **p=0.01					

BPRS total scores correlated positively with F4 subscale scores and EPDS scores correlated positively with F3 subscale scores.

Table Association of PBQ Factors with Socio-Demographic and Clinical Characteristics among Cases

Variable	N	F1 Impaired Bonding Median	IQR	U	p	F2 Rejection and anger Median	IQR	U	p	F3 Infant focused anxiety Median	IQR	U	p	F4 Risk of Abuse Median	IQR	U	p
Education				1004.5	0.08			978.5	0.05			968	0.04*			1137.5	0.29
Up to Matric	68	6.0	2-15			4.0	0-8.75			1.0	0-4			0.0	0		
Above Matric	37	8.0	4.5-22.5			7.0	1.5-12.50			3.0	0-7			0.0	0-1		
Discord				944.5	0.25			1054.0	0.72			1001	0.45			1026.5	0.48
No	76	6.0	2-15			5.0	0-10			2.0	0-5			0	0-1		
Yes	29	8.0	2-20			5.0	0-12.5			2.0	0-8			0	0-0.5		
Planned Pregnancy				1332.0	0.77			1179.0	0.19			1177.5	0.18			1331.50	0.70
No	51	7.0	2-15			4.0	0-9			1.0	0-4			0.0	0		
Yes	54	6.5	2-17.5			5.5	1-12			3.0	0-5.5			0.0	0-1		
Parity				1329.5	0.76			1236.5	0.36			1336.0	0.78			1279.5	0.41
Primiparae	54	7.0	2-15.5			4.0	0-10.25			2.0	0-5			0.0	0		
Multiparae	51	6.0	2-17			5.0	2-10			3.0	0-5			0.0	0-1		
Gender				1244.0	0.41			1324.5	0.75			1259.5	0.45			1358.5	0.91
Male	49	7.0	3.5-17.5			4.0	0-9.5			3.0	0-5			0.0	0-1		
Female	56	6.0	2-15			5.0	0-11.5			1.0	0-5			0.0	0-0.75		
Preterm Delivery				210.0	0.08			223.5	0.12			257	0.25			248.5	0.11
No	98	6.0	2-15			4.5	0-10			2.0	0-5			0.0	0-1		
Yes	07	14.0	7-19			10.0	3-12			4.0	2-4			0.0	0		

*P Value < 0.05 IQR= Inter Quartile Range

Educations levels were found to be associated with F2 subscale and F3 subscale of PBQ

Table Association of PBQ Factors with Clinical and Obstetric Characteristics

Variable	N	F1 Impaired Bonding				F2 Rejection & anger				F3 Maternal Anxiety				F4 Risk of Abuse			
		Median	IQR	U	p	Median	IQR	U	p	Median	IQR	U	p	Median	IQR	U	p
Suicidality (clinician rated)				1249.5	0.41			1248.5	0.40			1260	0.43			1353	0.84
No	54	6.0	2-15			4.5	0-9			2.0	0-5			0.0	0-1		
Yes	51	7.0	2-17			5	0-12			3.0	0-7			0.0	0-1		
Suicidality (self-report)				1071.0	0.09			1040.0	0.05			976	0.01*			1185.5	0.23
No	49	6.0	2-14			4.0	0-7			1-0	0-3			1.0	0		
Yes	54	8.5	3-20			5.5	1-12			4.0	0-7			0.0	0-1		
Depression – EPDS				982.0	0.01*			989.0	0.01*			1061.5	0.05			1153.50	0.09
Scores ≤11	45	6.0	2-8			3.0	0-7			1.0	0-3			0.0	0		
Scores >11	60	9.5	3-20			5.5	1-13			3.5	0-7			0.0	0-1		
Psychotic Symptoms				1304.0	0.9			1254.5	0.65			1117.5	0.16			1167	0.18
No	42	7.0	2-15			4.0	0-10			2.0	0-5			0.0	0		
Yes	63	6.0	2-19			5.5	0-10			2.0	0-2			0.0	0-1		
Parity				1329.5	0.76			1236.5	0.36			1235.5	0.34			1278	0.40
Primiparae	54	7.0	2-15.5			4.0	0-10.25			1.0	0-2.25			0.0	0		
Multiparae	51	6.0	2-17			5.0	2-10			1.0	0-2			0.0	0-1		
Mode of Delivery				1072.0	0.42			921.0	0.06			1082	0.44			1099.5	0.42
Vaginal	72	6.5	2-15			4.0	0-10			1.0	0-2			0.0	0		
Caesarean	33	7.0	3-21			7.0	2-12.5			1.0	0-2			0.0	0-1		
Infant Serious Illness #				565.5	0.75			588.5	0.92			394	0.04*			518.5	0.31
No	92	7.0	2-17			5.0	0-11			2.0	0-5			0.0	0-1		
Yes	13	6.0	3-16			5.0	1-9			5.0	1-6			0.0	0		

*P Value <0.05; IQR= Inter Quartile Range. Significant association was found between suicidality and F2and F3 subscale. Depression scores showed an association with F1, F2 & F3 subscales. Presence of infant serious illness was associated with F3 subscale of PBQ.
Defined as illness requiring admission and or specialist care

Figure a Scatter plot of scores on EPDS and PBQ scale
Figure b Loess line fitting showing the relationship between EPDS and PBQ scores

X axis - EPDS Scores
Y axis - PBQ Scores

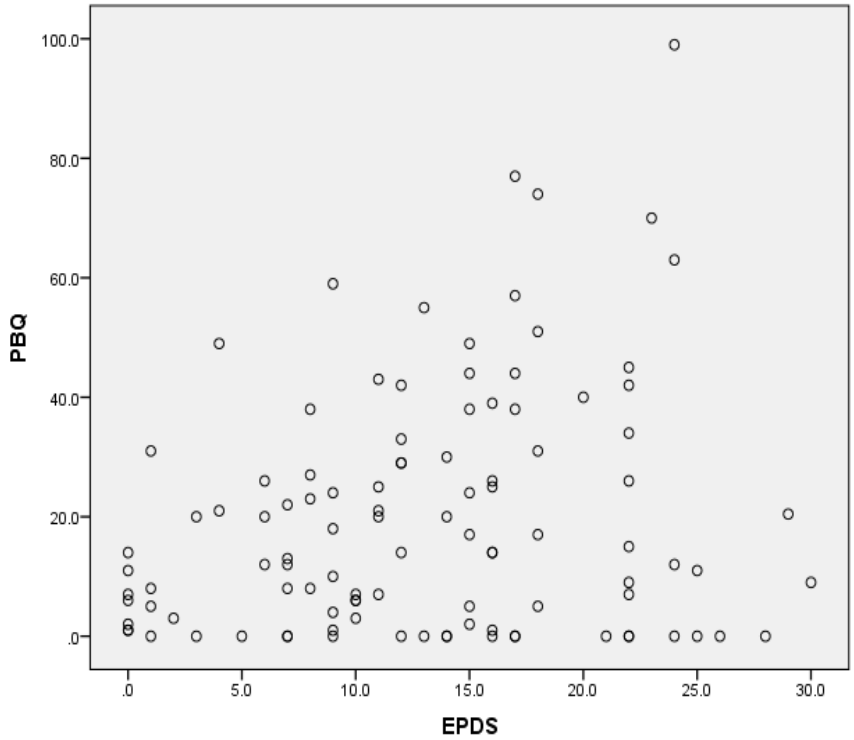

Figure a

X axis - EPDS Scores
Y axis - PBQ Scores

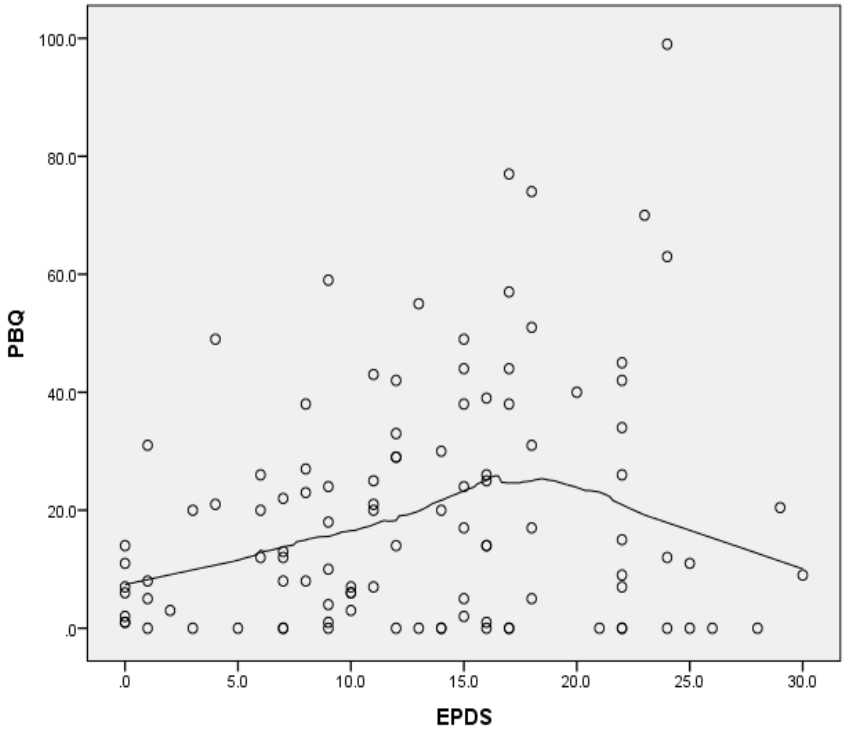

Figure b

Figure a1 Scatter plot of scores on BPRS and PBQ scale
Figure b1 Loess line fitting showing the relationship between BPRS and PBQ score

X axis - BPRS Scores
Y axis - PBQ Scores

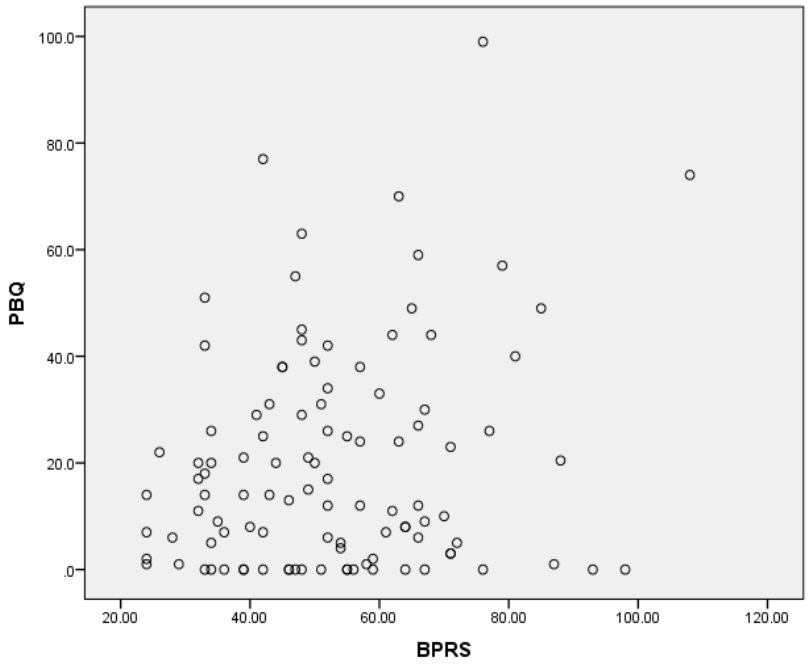

Figure a1

X axis - BPRS Scores
Y Axis - PBQ Scores

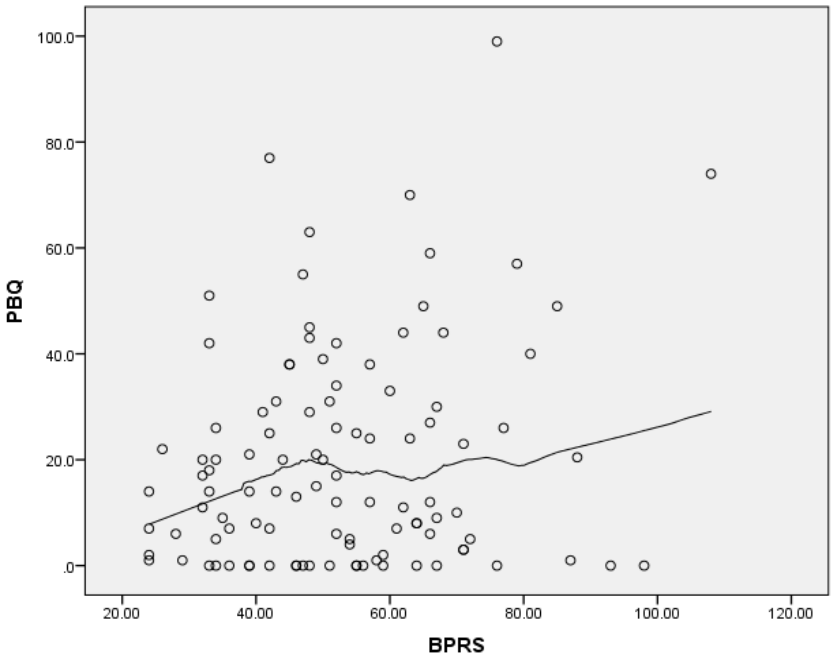

Figure b1

ANALYSIS OF THE SNPs IN THE STUDY

An example for of Hardy-Weinberg calculation

Cases Group *HMCN1* polymorphism rs2891230	Genotype	Expected	Observed
	AA	19.72	20
	AG	51.57	51
	GG	33.72	34
	A allele frequency = 0.43		G allele frequency = 0.57
	Calculated $X^2 = 0.01$ X^2 (calculated) < X^2 (table) [$X2$=3.841, df=1, p=0.05]		

There was no statistically significant difference between observed and expected genotype frequencies among cases for *HMCN1* polymorphism under Hardy-Weinberg. Rejection of null hypothesis fails. Cases were in Hardy-Weinberg equilibrium for *HMCN1* polymorphism. Similar calculations were done for other polymorphisms in the study for both cases and controls. All polymorphisms in the study were found to be in Hardy-Weinberg equilibrium.

Comparison of cases (onset within 6 months) and controls for differences in gene polymorphisms

Table Comparison of Genotype and Allele Frequencies of *ESR1* Polymorphism rs9340799 (XbaI)

	Genotype Frequency				Allele Frequency	
	Group	A/A	A/G	G/G	A-Allele	G-Allele
ESR1 rs9340799 (XbaI)	Cases (N= 105)	41 (39.0 %)	51 (48.6%)	13 (12.4%)	133 (63.33%)	77 (36.66%)
	Controls (N= 101)	40 (39.6%)	44 (43.6%)	17 (16.8%)	124 (61.39%)	78 (38.61%)
				Chi-square =0.98; P = 0.61, df=2	Chi-square =0.16; P = 0.68 df=1	

The groups did not show any significant difference in genotype frequency and allele frequency of *ESR1* polymorphism rs9340799 (XbaI)

Table Comparison of Genotype and Allele Frequencies of *ESR1* Polymorphism rs2234693 (PvuII)

	Genotype Frequency				Allele Frequency	
	Group	C/C	C/T	T/T	C-Allele	T-Allele
ESR1 rs2234693 (PvuII)	Cases (N= 105)	18 (17.1 %)	49 (46.7%)	38 (36.2%)	85 (40.47%)	125 (59.52%)
	Controls (N= 101)	14 (13.9%)	53 (52.5%)	34 (33.7%)	81 (40.1%)	121 (59.9%)
				Chi-square =0.802; P = 0.67, df= 2	Chi-square =0.006; P = 0.94, df=1	

The groups did not show any significant difference in genotype frequency and allele frequency of *ESR1* polymorphism rs2234693 (PvuII)

Table Comparison of Genotype and Allele Frequencies of *HMCN1* Polymorphism rs2891230

HMCN1 rs2891230	Genotype Frequency			Allele Frequency	
	Group	A/A	A/G	G/G	A-Allele	G-Allele
	Cases (N= 105)	20 (19.0 %)	51 (48.6%)	34 (32.4%)	91 (43.33%)	119 (56.66%)
	Controls (N= 101)	28 (27.7%)	40 (39.6%)	33 (32.7%)	96 (47.52%)	106 (52.48%)
			Chi-square =2.60; P = 0.27; df =2		Chi-square =0.73; P = 0.39; df =1	

The groups did not show any significant difference in genotype frequency and allele frequency of *HMCN1* polymorphism rs2891230

Table Comparison of Genotype and Allele Frequencies of *METTL13* Polymorphism rs2232825

METTL13 rs2232825	Genotype Frequency			Allele Frequency	
	Group	C/C	C/T	T/T	C-Allele	T-Allele
	Cases (N= 105)	86 (81.9%)	17 (16.2%)	02 (1.90 %)	189 (90.0%)	21 (10.0 %)
	Controls (N= 101)	93 (92.1%)	07 (06.9%)	01 (1 %)	193 (95.5 %)	09 (04.6 %)
			Chi-square = 4.69 P=0.09; df = 2		Chi-square = 4.68 P=0.03*, df = 1	

A significant difference was noted for comparison of allele frequencies between the groups for *METTL13* polymorphism. However, comparison for genotype frequencies between the groups did not show any significant difference.

Table Association of Clinical Severity as Measured by BPRS and EPDS Scores with T Allele of *METTL13* Polymorphism rs2232825 (Dominant Model) among Cases.

Variable	Genotype CC N=86	Genotype CT/TT N=19	t	p
Mean BPRS scores (sd)	53.00 (16.9)	51.2 (18.9)	0.41	0.68
Mean EPDS scores (sd)	12.64 (7.2)	14.3 (8.7)	-.87	0.38

The dominant model of genotype groups of *METTL13* polymorphism rs2232825 did not show any significant difference in terms of clinical severity.

Table Comparison of Genotype and Allele Frequencies of *5-HTTLPR* Polymorphism

5HTTLPR (5-HT transporter length polymorphic region)	Genotype Frequency			Allele Frequency	
	Group	L/L	L/S	S/S	L-Allele	S-Allele
	Cases (N= 105)	24 (22.9%)	46 (43.8%)	35 (33.3%)	94 (44.7%)	116 (55.2%)
	Controls (N= 101)	18 (17.8%)	54 (53.5%)	29 (28.7%)	90 (44.5%)	112 (55.4%)

	Chi-square = 1.98; P = 0.37, df= 2	Chi-square = 0.002 P = 0.96 df= 1

The groups did not show any significant difference in genotype frequency and allele frequency of *5-HTTLPR* polymorphism

Table Comparison of Genotype and Allele Frequencies of *OXTR* Polymorphism rs53576

	Genotype Frequency				Allele Frequency	
OXTR rs53576	Group	A/A	A/G	G/G	A-Allele	G-Allele
	Cases (N= 105)	32 (30.5%)	38 (36.2%)	35 (33.3 %)	102 (48.6%)	108 (51.4 %)
	Controls (N= 101)	24 (23.8%)	54 (53.5%)	23 (22.8%)	102 (50.4%)	100 (49.5 %)
	Chi-square = 6.33 P = 0.04* df=2				Chi-square = 0.08 P = 0.77 df=1	

A significant difference was noted for comparison of genotype frequencies between the groups. However, comparison for allele frequencies between the groups did not show any significant difference.

Table Association of Clinical Severity as Measured by BPRS and EPDS Scores with G Allele of *OXTR* Polymorphism rs53576 (Dominant Model) among Cases.

Table: Association of Clinical Severity with *OXTR* - Dominant Model N=105				
Variable	Genotype AA n=32	Genotype AG/GG n=73	t	p
Mean BPRS Scores (s.d)	58.0 (21.6)	50.3 (14.4)	2.1	0.03*
Mean EPDS Scores (s.d)	12.6 (7.0)	13.0 (7.7)	-.22	0.82

Genotype AA group had significantly higher mean BPRS scores as compared to AG/GG genotypes of *OXTR* polymorphism.

Comparison of cases with an onset within 6 weeks of delivery and controls for differences in gene polymorphisms

Table Comparison of genotype and allele frequencies of *ESR1* polymorphism rs9340799 (XbaI) among cases (onset ≤ 6 weeks of childbirth) and controls.

	Genotype Frequency				Allele Frequency	
ESR1 rs9340799 (XbaI)	Group	A/A	A/G	G/G	A-Allele	G-Allele
	Cases (N=65)	28 (43.1 %)	30 (46.2 %)	07 (10.8 %)	86 (66.1 %)	44 (33.8 %)
	Controls (N= 101)	40 (39.6 %)	44 (43.6 %)	17 (16.8 %)	124 (61.3 %)	78 (38.6 %)
	Chi-square =1.18; P = 0.55, df=2				Chi-square =0.77; P = 0.37 df=1	

The groups did not show any significant difference in genotype frequency and allele frequency of *ESR1* polymorphism rs9340799 (XbaI)

Table Comparison of genotype and allele frequencies of *ESR1* polymorphism rs 2234693 (PvuII) among cases (onset ≤ 6 weeks of childbirth) and controls.

ESR1 rs2234693 (PvuII)	Genotype Frequency				Allele Frequency	
	Group	C/C	C/T	T/T	C-Allele	T-Allele
	Cases (N=65)	09 (13.8 %)	32 (49.2 %)	24 (36.9 %)	50 (38.4 %)	80 (61.5 %)
	Controls (N= 101)	14 (13.9 %)	53 (52.5 %)	34 (33.7 %)	81 (40.1 %)	121 (59.9 %)
				Chi-square = 0.20; P= 0.9, df= 2	Chi-square = 0.08; P = 0.76, df=1	

The groups did not show any significant difference in genotype frequency and allele frequency of *ESR1* polymorphism rs2234693 (PvuII)

Table Comparison of genotype and allele frequencies of *HMCN1* polymorphism rs2891230 among cases (onset ≤ 6 weeks of childbirth) and controls.

HMCN1 rs2891230	Genotype Frequency				Allele Frequency	
	Group	A/A	A/G	G/G	A-Allele	G-Allele
	Cases (N=65)	14 (21.5 %)	30 (46.2 %)	21 (32.3 %)	58 (44.6 %)	72 (55.3 %)
	Controls (N= 101)	28 (27.7 %)	40 (39.6 %)	33 (32.7 %)	96 (47.5 %)	106 (52.4 %)
				Chi-square =1.00; P = 0.60, df =2	Chi-square =0.26; P = 0.60, df =1	

The groups did not show any significant difference in genotype frequency and allele frequency of *HMCN1* polymorphism rs2891230

Table Comparison of genotype and allele frequencies of *METTL13* polymorphism rs2232825among cases (onset ≤ 6 weeks of childbirth) and controls.

METTL13 rs2232825	Genotype Frequency				Allele Frequency	
	Group	C/C	C/T	T/T	C-Allele	T-Allele
	Cases (N=65)	51 (78.5%)	12 (18.5%)	2 (3.1 %)	114 (87.7%)	16 (12.3%)
	Controls (N= 101)	93 (92.1%)	07 (06.9%)	01 (1 %)	193 (95.5 %)	09 (4.5 %)
				Chi-square = 6.3; P=0.04*, df = 2	Chi-square = 7.00 P=0.008* df = 1	

A significant difference was noted for comparison of both genotype frequencies and allele frequencies between the groups for *METTL13* polymorphism. The percentage of T-allele was more among cases.

Table Association of clinical severity as measured by BPRS and EPDS scores with T allele of *METTL13* polymorphism rs2232825 (Dominant Model) among cases.

Variable	Genotype CC N=51	Genotype CT/TT N=14	t	p
Mean BPRS scores (sd)	52.5 (17.3)	52.2 (19.6)	0.06	0.94
Mean EPDS scores (sd)	12.15 (6.8)	13.3 (9.1)	-.53	0.59

The dominant model of genotype groups of *METTL13* polymorphism rs2232825 did not show any significant difference in terms of clinical severity.

Table Comparison of genotype and allele frequencies of SERT polymorphism among cases (onset ≤ 6 weeks of childbirth) and controls.

	Genotype Frequency				Allele Frequency	
5-HTTLPR (5-HT transporter length polymorphic region)	Group	L/L	L/S	S/S	L-Allele	S-Allele
	Cases (N=65)	14 (21.5%)	30 (46.2%)	21 (32.3%)	58 (44.6 %)	72 (55.3 %)
	Controls (N= 101)	18 (17.8%)	54 (53.5%)	29 (28.7%)	90 (44.6 %)	112 (55. %)
				Chi-square=0.87; P = 0.64, df= 2	Chi-square=0 P= 1, df= 1	

The groups did not show any significant difference in genotype frequency and allele frequency of *5-HTTLPR* polymorphism.

Table Comparison of genotype and allele frequencies of *OXTR* polymorphism rs53576 among cases (onset ≤ 6 weeks of childbirth) and controls.

	Genotype Frequency				Allele Frequency	
OXTR rs53576	Group	A/A	A/G	G/G	A-Allele	G-Allele
	Cases (N=65)	22 (33.8 %)	24 (36.9 %)	19 (29.2 %)	68 (52.3 %)	62 (47.6 %)
	Controls (N= 101)	24 (23.8 %)	54 (53.5 %)	23 (22.8 %)	102 (50.4 %)	100 (49.5 %)
				Chi-square = 4.4; P = 0.11, df=2	Chi-square = 0.10; P = 0.7, df=1	

The groups did not show any significant difference in genotype frequency and allele frequency of *OXTR* polymorphism.

Association of gene polymorphisms with presence of family history and/ or past history of psychiatric illness among cases as compared to controls

Table Association of genotype and allele frequencies of *ESR1* polymorphism rs 9340799 (XbaI) with presence of family history (F/h) and/or past history (p/h) of psychiatric illness (psy.ill.) among cases as compared to controls

	Group	Genotype Frequency			Allele Frequency	
ESR1 rs 9340799 (XbaI)		A/A	A/G	G/G	A-Allele	G-Allele
	F/h &/ or p/h of psy.ill.among cases (N=53)	19 (35.8%)	26 (49.1 %)	08 (15.1 %)	64 (60.3 %)	33 (39.6 %)
	Controls (N= 101)	40 (39.6%)	44 (43.6 %)	17 (16.8 %)	124 (61.3 %)	78 (38.6 %)
		Chi-square =0.42; P=0.80, df=2			Chi-square =0.59; P = 0.44 df=1	

The groups did not show any significant difference in genotype frequency and allele frequency of *ESR1* polymorphism rs9340799 (XbaI).

Table Association of genotype and allele Frequencies of *ESR1* polymorphism rs2234693 (PvuII) with presence of family history (F/h) and/or past history (p/h) of psychiatric illness (psy.ill.) among cases as compared to controls.

	Group	Genotype Frequency			Allele Frequency	
ESR1 rs2234693 (PvuII)		C/C	C/T	T/T	C-Allele	T-Allele
	F/h &/ or p/h of psy.ill. among cases (N=53)	10 (18.9 %)	24 (45.3 %)	19 (35.8 %)	44 (41.5 %)	62 (58.4 %)
	Controls (N= 101)	14 (13.9 %)	53 (52.5 %)	34 (33.7 %)	81 (40.1 %)	121 (59.9 %)
		Chi-square =0.96; P = 0.61, df= 2			Chi-square =0.05; P = 0.81, df=1	

The groups did not show any significant difference in genotype frequency and allele frequency of *ESR1* polymorphism rs2234693 (PvuII).

Table Association of genotype and allele frequencies of *HMCN1* polymorphism rs2891230 with presence of family history (F/h) and/or past history (p/h) of psychiatric illness (psy.ill.) among cases as compared to controls.

		Genotype Frequency			Allele Frequency	
HMCN1 rs2891230	Group	A/A	A/G	G/G	A-Allele	G-Allele
	FH &/ or PH Psy.Ill.among cases (N=53)	08 (15.1%)	26 (49.1%)	19 (35.8%)	42 (39.6 %)	64 (60.3 %)
	Controls (N= 101)	28 (27.7 %)	40 (39.6 %)	33 (32.7 %)	96 (47.5 %)	106 (52.4 %)
	Chi-square =3.2; P = 0.20, df =2				Chi-square=1.7; P = 0.18, df=1	

The groups did not show any significant difference in genotype frequency and allele frequency of *HMCN1* polymorphism rs2891230.

Table Association of genotype and allele Frequencies of *METTL13* polymorphism rs2232825 with presence of family history (F/h) and/ or past history (p/h) of psychiatric illness (psy.ill.) among cases as compared to controls

	Groups	Genotype Frequency			Allele Frequency	
METTL13 rs2232825		C/C	C/T	T/T	C-Allele	T-Allele
	F/h &/ or p/h of psy.ill among cases(N=53)	44 (83.0%)	07 (13.2%)	2 (3.8%)	95 (89.6 %)	11 (10.4 %)
	Controls (N= 101)	93 (92.1%)	07 (06.9%)	01 (1 %)	193 (95.5 %)	09 (4.5 %)
	Chi-square = 3.21; P=0.20, df = 2				Chi-square = 4.01 p=0.04*, df = 1	

A significant difference was noted for comparison of allele frequencies between the groups for *METTL13* polymorphism. However, comparison for genotype frequencies between the groups did not show any significant difference.

Table Association of genotype and allele Frequencies of SERT polymorphism with presence of family history (F/h) and/ or past history (p/h) of psychiatric illness (psy.ill.) among cases.

	Groups	Genotype Frequency			Allele Frequency	
5-HTTLPR (5-HT transporter length polymorphic region)		L/L	L/S	S/S	L-Allele	S-Allele
	F/h &/ or p/h of psy.ill among cases (N=53)	11 (20.8%)	23 (43.4%)	19 (35.8%)	45 (42.5 %)	44 (57.5 %)
	Controls (N= 101)	18 (17.8%)	54 (53.5%)	29 (28.7%)	90 (44.6 %)	112 (55. %)
	Chi-square = 1.43; P = 0.48, df= 2				Chi-square = 0.89; P = 0.34, df= 1	

The groups did not show any significant difference in genotype frequency and allele frequency of SERT polymorphism.

Table Association of Genotype and Allele Frequencies of *OXTR* Polymorphism rs53576 with Presence of Family History (F/H) and/ or Past History (P/H) of Psychiatric Illness (Psy.Ill.) among Cases.

	Groups	Genotype Frequency			Allele Frequency	
		A/A	A/G	G/G	A-Allele	G-Allele
OXTR rs53576	F/h &/ or p/h of psy.ill among cases (N=53)	16 (30.2%)	21 (39.6%)	16 (30.2%)	53 (50 %)	53 (50 %)
	Controls (N= 101)	24 (23.8%)	54 (53.5%)	23 (22.8%)	102 (50.4%)	100 (49.5 %)
		Chi-square = 2.67; P = 0.26, df=2			Chi-square = 0.00; P = 0.93, df=1	

The groups did not show any significant difference in genotype frequency and allele frequency of *OXTR* polymorphism.

Multifactor Dimensionality Reduction [MDR] Analysis of SNPs

Summary of MDR analysis for the SNPs *5-HTTLPR*, *ESR1*- Xba1, *ESR1*-PvuII and *HMCN1*

Order	Best Model SNPs	Cross Validation Training Balanced Accuracy	Cross Validation Testing Balanced Accuracy	Cross Validation Consistency
1	*5-HTTLPR*	0.55	0.46	5/10
2	METTL-13 *5-HTTLPR*	0.59	0.43	4/10
3	*5-HTTLPR* *ESR1*-Xba1 *ESR1*-PvuII	0.64	0.51	9/10
4	*5-HTTLPR* *ESR1*-Xba1 *ESR1*-PvuII *HMCN1*	0.69	0.48	9/10

The testing accuracy of 0.51 was highest for the 3-locus model of *5-HTTLPR*, *ESR1*-Xba1 and *ESR1*-PvuII as compared to the other models. However, it was below the desired level of at least 0.55 for a model to be considered as relevant.

Association of *OXTR* polymorphism with Postpartum Bonding Questionnaire (PBQ) Factors among Cases

Table Association of Genotype and Allele Frequencies of *OXTR* polymorphism rs53576 with *F1 Impaired bonding* among cases

OXTR rs53576	Genotype Frequency				Allele Frequency	
	F1 Score	A/A	A/G	G/G	A-Allele	G-Allele
	Normal (n= 66)	18 (27.3%)	28 (42.4%)	20 (30.3%)	64 (48.5%)	68 (51.5%)
	High (n= 39)	14 (35.9%)	10 (25.6%)	15 (38.5%)	38 (48.71%)	40 (51.28%)
			Chi-square = 2.99; P = 0.22, df=2		Chi-square = 0.00; P = 0.97, df=1	

The groups did not show any significant difference in genotype frequency and allele frequency of *OXTR* polymorphism.

Table Association of Genotype and Allele Frequencies of *OXTR* polymorphism with *F2 Rejection and pathological anger* among cases

OXTR rs53576	Genotype Frequency				Allele Frequency	
	F2 Score	A/A	A/G	G/G	A-Allele	G-Allele
	Normal (N= 93)	28 (30.1%)	34 (36.6%)	31 (33.3 %)	90 (48.38%)	108 (51.61%)
	High (N= 12)	4 (33.3%)	4 (33.3%)	4 (33.3%)	12 (50.0%)	12 (50.0 %)
			Chi-square = 0.06 ; P = 0.96, df=2		Chi-square = 0.17; P = 0.67 df=1	

The groups did not show any significant difference in genotype frequency and allele frequency of *OXTR* polymorphism.

Table Association of Genotype and Allele Frequencies of *OXTR* polymorphism with *F3 Infant focused anxiety* among cases

OXTR rs53576	Genotype Frequency				Allele Frequency	
	F3 Score	A/A	A/G	G/G	A-Allele	G-Allele
	Normal (N= 96)	27 (28.1%)	38 (39.6%)	31 (32.3 %)	92 (47.9%)	108 (52.1 %)
	High (N= 9)	05 (55.6%)	0	4 (44.4%)	10 (55.6%)	08 (44.4 %)
			Chi-square = 5.95; p = 0.05, df=2		Chi-square = 0.60; P = 0.43 df=1	

The groups showed a borderline level difference in genotype frequency but not with allele frequency of *OXTR* polymorphism

Table Association of Genotype and Allele Frequencies of *OXTR* polymorphism with *F4 Incipient infant abuse* among cases

	Genotype Frequency				Allele Frequency	
	F4 Score	A/A	A/G	G/G	A-Allele	G-Allele
OXTR rs53576	Normal (n= 93)	27 (29.0%)	34 (36.6%)	32 (34.4 %)	88 (47.31%)	98 (52.68%)
	High (n= 12)	05 (41.7%)	04 (33.3%)	03 (25.0%)	14 (58.33%)	10 (41.66 %)
				Chi-square = 0.87; P = 0.64; df=2	Chi-square = 1.03; P = 0.30; df=1	

The groups did not show any significant difference in genotype frequency and allele frequency of *OXTR* polymorphism

DISCUSSION

Socio-demographic factors

The cases and controls were comparable in terms of age. The significant differences found in the study for geographical background, education level, religious background, family type, income , age at marriage, duration of marriage in months, are likely to be the result of sampling method. The differences in family type and consanguinity rates among the groups can also be accounted by the sampling difference. We observed high rates of consanguinity among controls as compared to cases. Studies have reported consanguinity rates up to 30.2% in Karnataka (Bittles, 2002). The consanguinity rates are likely to be lower among the cases because of the stigma associated with mental illness resulting in isolation and social exclusion (Byrne, 2000). Higher rates of discord were reported by subjects in cases group as compared to controls. Marital disharmony rate of 23.9% has been reported in earlier literature in women with postpartum psychiatric disorders (Fatoye and Fasubaa, 2002)*Clinical Presentation*

In the present study, acute polymorphic psychosis presentation was the most common type of clinical presentation and this finding was in line with the earlier literature (Sit et al., 2006). Bipolar illness was the most common diagnosis among those who had a past history of psychiatric illness in the present study. Postpartum period acting as a trigger for puerperal episodes in women with bipolar illness has been documented in the earlier literature (Jones and Craddock, 2001). Acute and transient psychotic disorder was the second most common diagnosis in the past history category. Recurrences of acute & transient psychotic disorders are known and childbirth is likely to act as a triggering factor. Nearly 62% of subjects in the present study had an episode by 6 weeks of delivery though the onset criterion in the present study was up to 6 months following delivery. The risk is reported to be high during the first 90 days after childbirth and the risk of psychiatric admissions continue up to 2 years after the childbirth (Kendell et al., 1987).

The overall EPDS scores were above the cut-off levels among cases and more than 50 % of cases scored above the cut-off levels indicating that depressive symptoms are common during an episode of postpartum psychosis. Depressive symptoms in first onset postpartum psychosis are reported to be associated with a later onset and longer duration of illness episode (Bergink et al., 2011). Our findings regarding thyroid

dysfunction are in agreement with the earlier literature reporting of thyroid dysfunction in women with postpartum psychosis. Women with postpartum psychosis are at risk for autoimmune thyroiditis and clinical thyroid failure (Bergink et al., 2011). Additionally, we also found higher rates for other general medical problems such as diabetes and hypertension during pregnancy among subjects with postpartum psychosis Non-psychiatric puerperal medical complications have been reported to occur more commonly in those with a history of prior hospitalization for a psychiatric illness (Hellerstedt et al., 2013).

The significant difference observed regarding planned pregnancy is probably due to concerns associated with conception in women with mental illness. It is possible that in view of regular contact with hospital services there is likely to be an increased awareness about the need for planned pregnancy among cases. We found that as compared to controls, the primiparae constituted the majority (51.4%) among the cases. Amongst all the obstetric factors, primiparity has been consistently shown as a risk factor for postpartum psychosis. The relationship between primiparity and postpartum psychosis may be due to the reasons that women with postpartum psychosis are less likely to conceive again, becoming a mother for the first time is a highly stressful period and due to role of immunological factors in pathogenesis of postpartum psychosis (Blackmore et al., 2006). Our finding of high rates of abortion among women with postpartum psychosis is in line with the earlier literature (Kendell et al., 1987). It is also reported that women with serious mental illnesses have higher rates of abortion along with other reproductive health problems (Ozcan et al., 2014). This highlights the need for awareness about the abortion risk and possible preventive measures during the time of pre-pregnancy counselling along with suitable preventive measures. Earlier studies have reported of factors such as having a female baby, complications during pregnancy and delivery, and instrumental deliveries to be associated with postpartum psychosis (Kendell et al., 1981, 1987). Our study findings are similar and provide further evidence for the association of these factors with postpartum psychosis. Though the exact mechanisms are not clear it may be possibly due to elevated cortisol for prolonged periods as a response to stress arising from the above mentioned complications. Immune factors may also play a role in pathogenesis of the adverse outcomes.

Regarding the family loading of psychiatric illness, it was found in our study that nearly one third had a positive history in the family and 7.6% of subjects had a history of mental illness in the first degree relative. We also found higher rates of postpartum courses of psychiatric illness in the family and in first degree relatives. Family history of psychiatric illness and postpartum psychiatric illness are reported to be significant risk factors for postpartum psychosis in women with bipolar illness (Jones and Craddock, 2001). Hence, these factors have to be discussed during the pre-pregnancy counselling for women with pre-existing psychiatric illness. On anthropometric measures though a significant difference was found for BMI differences, the BMI was within normal limits for both cases and controls. The cases had greater mean weight as compared to controls. This could be probably due to sampling differences, intake of psychotropics among cases and also because of disorders such as thyroid dysfunction.

Regarding the infant health, history of neonatal intensive care and serious physical illnesses in infant were higher among cases as compared to controls. Our findings are in contrast with the study that did not report any such association (Bergink et al.,

2011). It is important to note that in the study done by Bergink V et al 2011 only the first onset postpartum psychosis formed the subjects.
Clinically, our study findings emphasize the need for hospital delivery with adequate resuscitation and neonatal care facilities for women with pre-existing illnesses such as bipolar illness.

Characteristics of Mother-Infant Bonding Problems in Postpartum Psychosis and Associated Factors

In our study the percentage of mothers scoring high on PBQ factors was significantly high among cases as compared to normal healthy controls. Our study found a correlation between severity of psychopathology and PBQ factors. We found a weak but positive correlation between BPRS and risk of abuse. This finding is in agreement with earlier observation of severely symptomatic mothers being abusive towards infant (Chandra et al., 2002). Hence, such mothers need careful clinical observation and interventions for early resolution of symptoms. We found that more than one-third of the mothers showed a general impairment in bonding. High scores on *Rejection and anger* factor were present in 11.4% and a similar percentage of subjects scored high on *Risk of abuse*. High scores on *Infant focused anxiety* factor were present in 8.6% of subjects. Higher education was associated with *Infant focused anxiety* factor. Self-reported suicidality was associated with *Infant focused anxiety* factor, depressive symptoms with *Impaired bonding* and *Rejection and anger* factors. Serious physical illness in infant was associated with *Infant focussed anxiety* factor. Borderline level associations were found for education levels with *Rejection and anger* factor; self-reported suicidality with *Rejection and anger* and also for depressive symptoms with *Infant focussed anxiety*. These relationships need further examination in future studies. The findings of our study highlight the presence and nature of impaired mother-infant bonding in mothers with postpartum psychosis. Paucity of literature in this area limits a direct comparison. Findings from the present study indicate the need to further understand the phenomena of 'infant abuse' in mothers with postpartum psychosis across different cultures.

SNPs association with Postpartum Psychosis and Bonding

Our results suggest that *METTL13* rs2232825 locus or a linked functional locus may modulate the vulnerability to postpartum psychosis. Additionally, *OXTR* rs 53576 is also likely to play a role in pathogenesis of postpartum psychosis.
A significant physiological change that occurs during the period after childbirth is the drastic fall in the estrogen levels (Meinhard et al., 2014). A genome-wide linkage analysis study first reported the role of *METTL13* gene in postpartum depressive symptoms (Mahon et al., 2009). In the present study we found a modest evidence for *METTL13* gene polymorphism (rs2232825; minor allele T) for being associated with postpartum psychosis. A similar association was found in those who were at higher risk of developing due to a past history of psychiatric illness and/or family history of psychiatric illness as compared to healthy controls. The *METTL13* gene includes methyltransferase activity and DNA methyltransferases have been reported to be involved in estrogen receptor-induced gene transcription (Green and Galea, 2008; Mahon et al., 2009). Methylation and estrogen hormone levels are reported to be among the factors that regulate the ER-alpha expression (Pinzone et al., 2004). *METTL13* has also been reported to be involved in oncogenic pathways and is reported to affect metabolic pathways and cell signalling (Takahashi et al., 2011; Zhang et al., 2016). There appears to be no previous report on the role of *METTL13*

gene polymorphism in postpartum psychosis though a possible role in bipolar disorder in women has been described (Mill et al., 2008). While our study did not find association of postpartum psychosis with *HMCN1* polymorphism, we found a higher percentage of heterozygotes among cases. This finding of higher percentage of heterozygotes is in line with a recent Brazilian study that addressed the role on *HMCN1* polymorphism in postpartum depression (Alvim-Soares et al., 2014). The authors suggested the phenomenon of molecular heterosis wherein the heterozygous state results in a greater or lesser expression of trait as compared to homozygous state to explain the association of heterozygous state with postpartum depression (Alvim-Soares et al., 2014).

We did not find any association with *ESR1* polymorphisms which is in concurrence with the findings from an earlier study among individuals of European descent (Jones et al., 2000). Also, there was a lack of an association between *5-HTTLPR* polymorphism and postpartum psychosis in our study which is similar to the findings from an earlier study that failed detect significant difference in genotypic and allelic frequencies of 5-HTTLPR between postpartum psychosis and controls (Kumar et al., 2007). The lack of association as found in our study is similar to an earlier study involving subjects with puerperal psychosis (n=26) and bipolar illness (n females = 127) (Jones and Craddock, 2001).

We found a modest association for genotypic differences in *OXTR* polymorphism between cases and controls. Allelic differences did not show any significant difference. Individuals with AA genotype in our study had greater severity of symptoms in the form of higher BPRS scores as compared to those individuals with AG/GG genotypes. Oxytocin is primarily involved with prosocial behaviour but is also linked to aggression and envy. It is interesting to note that the same hormone is linked to contrasting social behaviours. Oxytocin hormone increase responses to social cues irrespective of they being positive or negative in nature and this observation is used to explain the role in contrasting behaviours. The individual responses to social cues tend to differ and genetic polymorphism may have an underlying role for the same. *OXTR* rs53576 d is reported to be associated with prosocial behaviours. The GG genotype individuals in general tend to express higher levels of empathy (Smith et al., 2014), trust behaviour (Krueger et al., 2012), self-esteem, and optimism (Saphire-Bernstein et al., 2011). However, the GG genotype individuals are also vulnerable for negative expressions especially in the presence of a history early childhood adverse circumstance (Bradley et al., 2011). It is interesting to note that AA individuals in our study were clinically more symptomatic as compared to AG/ GG individuals. This observation from our study suggests the possible role of *OXTR* polymorphism in symptom manifestation of postpartum psychosis.

We did not find any evidence for epistasis among the *HTTLPR*, *ESR1* and *HMCN1* polymorphisms as the highest testing accuracy was only 0.51 in the MDR analysis in an additive model.

Association of *OXTR* polymorphism with Mother-Infant Bonding

We found a borderline level association for genotypic frequencies of *OXTR* rs53576 polymorphism with *Infant focused anxiety parameter of PBQ.* The allelic difference did not show any association. *Impaired bonding, Rejection and pathological anger,* and *Incipient infant abuse* did not show any association with genotypic and allelic

frequencies of *OXTR* polymorphism. In view of a borderline level association (p=0.05) and also because of multiple testing, a caution is necessary in interpreting this observation.

Strengths of the study

The strengths of the study include structured clinical interview of age matched subjects, use of standard measures for assessment of depression, symptom severity and mother infant bonding in an ethnically similar population. The subject recruitment was done by a trained psychiatrist along with independent confirmation of diagnosis by another trained psychiatrist. Infants were staying with the mother through the period of illness.

Limitations of the study

Our study is limited by the sample size. A period of up to 6 months following the delivery of a baby was considered as *onset* of illness though an onset by first 4 to 6 weeks is considered for biological studies. However, it is important to note in the present study nearly 62% of study subjects had an onset by 6 weeks following the delivery. We did not exclude women with a past history of psychiatric illness. Limitations of the study also include reliance on self-reports of mothers about bonding and lack of objective observation of mother-infant interaction. The role of breastfeeding in mediating the mother-infant bonding in mothers with postpartum psychosis was not examined. Some of the statistically significant findings may be due to multiple testing.

Conclusions

Postpartum psychosis commonly manifests as acute polymorphic psychosis. Socio-demographic factors have an association with postpartum psychosis. Presence of past history of psychiatric illness, family history of psychiatric illness is common. Adverse obstetric outcomes, poor infant health, and medical problems are associated with postpartum psychosis. Mother-infant bonding parameters are impaired in nearly a third of subjects. *METTL13* rs2232825 locus or a linked functional locus may modulate the vulnerability to postpartum psychosis. *OXTR* rs53576 may have a role in symptom manifestation of postpartum psychosis

Clinical Implications of the study

Those subjects with a past history of psychiatric illness or family history of psychiatric illness need counselling at the time of planning for pregnancy. Women with bipolar illness in the reproductive age are particularly at risk for postpartum psychosis. A screening for depressive symptoms using EPDS may be necessary in patients presenting with postpartum psychosis. Emphasis needs to be placed on hospital delivery where resuscitation facilities are available. Infant born to high risk mothers would need an examination by a paediatrician. Women with postpartum psychosis who manifest with prominent depressive symptoms, self-reported suicidality and those who have an infant with serious physical illness show significant impairments in bonding. Focused intervention of mother-infant bonding would be necessary to foster bonding.

Future research

A focus on the first-onset postpartum psychosis illness may yield novel results. Future studies need to address the issues such as course of impaired mother-infant bonding as the psychosis resolves, corresponding changes in infant behaviour, and the role of infant temperament. The role of early childhood adverse life circumstance in mediating the manifestation of postpartum psychosis needs to be examined. The role of caregivers in mother-infant bonding needs to be addressed in future studies. The role of oxytocin hormone, *OXTR* polymorphisms, and *OXTR* gene methylation in relation to mother-infant bonding needs to be examined further.

Further, it would be interesting to study the epigenetic mechanisms underlying the manifestation of postpartum psychosis.

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