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RESEARCH ARTICLE

Investigation of hormone levels in postpartum psychosis

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ABSTRACT

Objective: The etiology of postpartum psychosis (PP) remains unclear. In this study, we examined thyroid-stimulating hormone, free T4, free T3, cortisol, prolactin, follicle-stimulating hormone, luteinizing hormone (LH), and dehydroepiandrosterone sulfate (DHEAS) levels in PP.

Method: The study included 23 patients who were hospitalized with the diagnosis of PP within the first 4 weeks after delivery and 30 age-matched healthy controls. Organic etiological factors were excluded. Blood samples were obtained from all participants at the same time of the day. In PP patients, blood samples were obtained within the first 24 h after hospitalization.

Results: Mean ages of PP and control groups were 26.2±5.5 and 27.6±5.1 years, respectively. The frequency of vaginal delivery was significantly higher in the PP compared with the control group (p=0.011). The fT3 levels were significantly lower in the PP compared with the control group, while the fT3 levels were within normal physiological limits (p=0.034) and no significant differences were found with regard to other hormones. To examine the effect of breastfeeding on the results, the control group was further divided into two subgroups: breastfeeding (BFC) and non-breastfeeding (NBFC). The fT4 levels (within normal physiological limits) and prolactin levels were significantly higher in the PP compared with NBFC (p=0.013 vs p=0.007). LH levels were 3.11±3.47 mIU/mL in the PP group, 1.48±2.45 mIU/mL in BFC and 4.56±3.69 mIU/mL in NBFC, but for the LH levels, the only significant difference was between the control groups (p=0.027).

Conclusion: The results of thyroid function tests in our study suggest a condition that develops impaired thyroid functions secondary to acute psychotic episode rather than an underlying thyroid disease. Comprehensive prospective studies, including follow-up data, may better explain the relationships between thyroid function and PP. In our study, there was no evidence for the possible role of DHEAS, prolactin, and LH hormones. However, changes in the hormone profile according to breastfeeding status suggest that the effects of breastfeeding on hormones may also be important.

Keywords: Etiology, hormone, postpartum psychosis

INTRODUCTION

Postpartum psychosis (PP) is a serious mental illness with a combination of symptoms from different groups. Hallmark symptoms include mood fluctuations (depression and mania), disorganized behaviors, cognitive disorganization, hallucinations and delusions, sleep disturbance, and confusion (1). Due to the risk of suicide and infanticide, it should be treated urgently in terms of both maternal and infant health (2).

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The diagnosis of PP can be complex since PP is not a separate disorder in psychiatric classifications. Instead, in the brief criteria for psychotic disorders, it is recommended to include "postpartum onset" as a descriptor if the onset is during pregnancy or within 4 weeks of birth (3). PP is diagnosed as part of major depressive or bipolar disorders, with the specifiers being "peripartum onset" and "psychotic features." In most cases, the onset is within the first 4 weeks postpartum. However, there is inconsistency in the field of what constitutes the postpartum timeframe. Some clinicians note that episodes may occur beyond 4 weeks, so they believe that the time frame of the postpartum specifier should be extended to 6 months after delivery (4). The postpartum period varied across studies from a 2–32-day range (5) to up to a year (6). One study investigating the incidence of PP divided the postpartum period into two categories: within 90 days postpartum and after 90 days postpartum (7). Due to these differences in the definition of the postpartum period and the fact that it is not included as a separate disease in the diagnostic classifications, there may be difficulties in PP research (etiology, prevalence, etc.). In a recent systematic review of epidemiological data, the incidence of PP was reported as 0.89–2.6 per 1000 women and a prevalence of 5 per 1000 women (8). This study included all articles referring to the "postpartum" period.

A prior diagnosis of bipolar disorder and primiparity is a strong risk factor for PP; therefore, PP is considered an expression of bipolar disorder (1). Nevertheless, it should also be noted that a significant portion of the patients does not have a previous psychiatric history (9) and that approximately 30% of patients experience isolated PP episodes (10,11).

Conducting large-sample systematic studies on the etiology of PP is highly difficult due to its low incidence. As a result, the etiology of PP remains unclear. Nevertheless, sleep disturbances, autoimmune factors, neuroendocrine changes, and genetic factors have shown to contribute to PP etiology. Moreover, studies have also focused on neuroendocrine changes due to rapid hormonal changes occurring after birth. This hypothesis is plausible given the postpartum hormonal changes that coincide with the onset of PP (12). The placenta plays an important role in the secretion of steroid hormones. The estrogen, progesterone, and prolactin levels increase significantly in late pregnancy compared with the prepregnancy period. Cortisol hormone is also synthesized from the placenta. The prolactin level remains high throughout breastfeeding, whereas other hormones decrease dramatically after delivery. In contrast, the endogenous steroid hormones, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS), remain relatively constant throughout the peripartum period (13). Postpartum serum concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are low in the first weeks. The hormones continue to be investigated in the etiology of postpartum mood and psychotic episodes.

Studies on estrogen and progesterone levels, which have effects on the monoaminergic system, and receptor sensitivity have shown inconsistent results (4,14,15). Evidence on the role of prolactin, FSH, and LH hormones stems from studies on PP and mood disorders (16). However, to our knowledge, these hormones have not been studied in PP. In addition to some evidence on thyroid hormone dysfunction and the relationship between cortisol and PP, some recent studies have highlighted the importance of DHEAS biosynthesis (17,18).

In light of these data, the aim of this study was to examine the levels of thyroid hormone, cortisol, prolactin, FSH, LH, and DHEAS in PP.

METHOD

The study was approved by the local ethics committee (B.30.2.YYU.0.01.00.00/69). This study was performed in line with the principles of the Declaration of Helsinki. Due to the rarity of PP, data for the study were collected over 2 years. Similar to the study by Bergink et al. (19), we included patients with the following diagnoses along with the specifier "onset postpartum" and the condition that the onset of symptoms must occur within the first 4 weeks postpartum: mania with psychotic features, mixed episode with psychotic features, or brief psychotic disorder. All patients were evaluated according to the clinical version of the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV). A control group was formed from age-matched healthy women who were in the first 4 weeks postpartum and had no psychiatric disorders through the Department of Obstetrics and Gynecology. The control group was also evaluated using SCID-CV.

To rule out the effect of antipsychotics on hormones, patients using antipsychotics were excluded from the study (n=2). Complete blood count, extensive biochemistry, routine electroencephalogram, and cranial magnetic resonance imaging were performed for each patient,

and organic etiological factors were excluded. As a result, 23 consecutive patients hospitalized with the diagnosis of PP and 30 healthy controls were included in the study. All patients continued to breastfeed before hospitalization. To control the effect of breastfeeding, half of the control group was selected from those who were not breastfeeding.

In both groups, blood samples were obtained from the antecubital vein at 08:00 AM. In PP patients, blood samples were obtained within the first 24 h after hospitalization. Samples were centrifuged and serums were separated. Thyroid-stimulating hormone (TSH), fT4, fT3, cortisol, prolactin, FSH, LH, and DHEAS levels were analyzed in the biochemistry laboratory.

Sociodemographic Data Form: The form contained questions regarding age, educational status, residential area, mode and number of deliveries, gender of the infant, and family history of mental disorders.

SCID-CV: SCID-CV is a semistructured interview used for establishing the major DSM-IV Axis I diagnoses (20). The scale was adapted to Turkish by Ozkurkcugil et al. (21) and the validity and reliability of the scale were confirmed in the same study.

Statistical Analysis

Data analysis was performed using SPSS for Windows version 13.0 (SPSS, Inc. Co., Chicago, IL, USA). Descriptive statistics were expressed as mean, standard deviation (SD), minimum, and maximum values for continuous variables and were expressed as frequencies (n) and percentages (%) for categorical variables. Continuous variables were compared using the Kruskal–Wallis test and categorical variables were compared using the Chi-squared test. A p-value of <0.05 was considered significant.

RESULTS

Sociodemographic characteristics: Mean ages of the PP and control groups were 26.2±5.5 and 27.6±5.1 years, respectively. The frequencies of vaginal delivery and family history of psychiatric treatment were significantly higher in the PP compared with the control group (p=0.011 vs p=0.003) (Table 1). Ten (43.5%) of the patients had a previous diagnosis of psychiatric disorders. The frequency of isolated PP was 26% (Table 2).

Hormone results: Although the fT3 levels were within normal physiological limits, they were significantly lower in the patient group compared with the control group (p<0.05). No significant difference was found with regard to other hormones (Table 3).

Table 1: Demographic and clinical characteristics of the groups

	PP (n=23)		Control (n=30)		p
	n	%	n	%	
Age	26.2±5.5		27.6±5.1		0.353
Educational status					0.467
Primary school	3	13	7	23.3	
Middle school	4	17.4	2	6.7	
High school	1	4.3	2	6.7	
University	1	4.3	4	13.3	
Uneducated	14	60.9	15	50	
Residence					0.450
Urban	13	56.5	20	66.7	
Rural	10	43.5	10	33.3	
Delivery					**0.011***
Vaginal	15	65.2	9	30	
Cesarean	8	34.8	21	70	
Infant sex					0.431
Male	14	60.9	15	50	
Female	9	39.1	15	50	
Number of deliveries					0.561
Primiparous	6	26.1	12	40	
Second	8	34.8	9	30	
≥Third	9	39.1	9	30	
Family history of PP					**0.003***
Absent	17	73.9	30	100	
Present	6	26.1	0	0	

PP: Postpartum psychosis; *: P<0.05.

Table 2: Previously diagnosed psychiatric disorders in the PP group

Bipolar disorder	n=1/23 (4.3%)
Postpartum psychosis	n=6/23 (26%)
Major depression	n=1/23 (4.3%)
Psychotic disorders	n=1/23 (4.3%)
Obsessive–compulsive disorder	n=1/23 (4.3%)

PP: Postpartum psychosis. Ten out of 23 PP patients had a history of psychiatric disorders.

To examine the effect of breastfeeding on the results, the control group was further divided into two subgroups: breastfeeding (BFC) and non-breastfeeding (NBFC) (Table 4). Compared with NBFC, fT4 and prolactin levels were significantly higher in the PP group. LH levels in the PP group (3.11±3.47 mIU/mL) were higher than the BFC group (1.48±2.45 mIU/mL) and lower than the NBFC group (4.56±3.69 mIU/mL);

Table 3: Comparison of hormone levels between the patient and control groups

	Patient (n=23) Mean±SD	Control (n=30) Mean±SD	p
TSH (mIU/mL)	1.47±0.63	1.88±1.07	0.106
fT4 (ng/dL)	1.02±0.16	0.95±0.12	0.064
fT3 (pg/mL)	2.52±0.28	2.68±0.26	**0.034***
Cortisol (µg/dL)	11.92±5.77	10.26±4.28	0.235
Prolactin (ng/mL)	113.76±71.54	83.79±67.46	0.125
FSH (mIU/mL)	3.58±1.89	3.99±3.09	0.578
LH (mIU/mL)	3.11±3.47	3.02±3.46	0.924
DHEAS (µg/dL)	177.97±70.91	152.28±84.82	0.250

SD: Standard deviation; TSH: Thyroid-stimulating hormone; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; DHEAS: Dehydroepiandrosterone sulfate; *: P<0.05.

however, the only significant difference was between the control groups (p=0.027). (The post hoc comparison results are as follows: PP vs. BFC, p=0.099; PP vs. NBFC, p=0.236; BFC vs. NBFC, p=0.013).

DISCUSSION

In this study, we aimed to examine the levels of some hormones which may play a role in the etiology of PP. To our knowledge, DHEAS, FSH, LH, and prolactin levels have not been investigated, and the effect of breastfeeding has not been evaluated in PP patients.

In our patient group, the mean age was 26.2±5.5 years, 26.1% (n=6) of the patients were primiparous, and most of the patients (65.2%) had a vaginal delivery. In other studies, similar mean ages have been reported for PP (22,23). Primiparity has often been reported as a risk factor in the literature (24–27). On the contrary, the primiparity rate in our study was 26.1%, which could be associated with the cultural characteristics of the individuals in our region as well as the high rates of early marriage and birth and the small sample size of our study. In some studies, cesarean delivery has been associated with PP (28,29) while some other studies have reported no such relationship (7,23). In our hospital, the rate of vaginal delivery is 64.3%, and the cesarean section rate is 35.7%. In our study, although the vaginal delivery rate in the PP group (65.2%) was higher than the control group (30%), it was similar to the vaginal delivery rate in our hospital. Small sample size, age-matched, and inclusion of the first consecutive matched person in the control group may have affected the outcome regarding the cesarean section rate in the control group.

Thyroid dysfunction in PP patients has been demonstrated in various studies, and autoimmune thyroid dysfunction has been suggested as a possible etiologic factor (17). Postpartum thyroiditis (PPT) is defined by autoimmune thyroid inflammation and elevated thyroid antibody titers, occurring within the first year after delivery. During pregnancy, immunity is suppressed; after pregnancy, there is transient virulent autoimmunity. In this respect, PPT appears to be a rebound phenomenon (30). Positive thyroid peroxidase antibodies during pregnancy have been associated with postpartum thyroid dysfunction (30). The rate of postpartum autoimmune thyroid diseases in the general population has been reported to be 5%–7%, while higher rates have been reported in PP (17). In the study by Stewart et al. (31), with 30 PP patients and 30 age-matched controls, no significant difference was found in terms of thyroid antibodies and functions. In a recent study that included patients with PP within 6 months of birth, higher isolated fT4 levels, greater total thyroid

Table 4: Comparison of hormone levels between the patient and breastfeeding and non-breastfeeding control groups

	PP (n=23)	Control (n=30)		p
		Breastfeeding (n=15) Mean±SD	Non-breastfeeding (n=15) Mean±SD	
TSH (mIU/mL)	1.47±0.63	1.70±0.84	2.05±1.27	0.416
fT4 (ng/dL)	1.02±0.16[a]	0.99±0.11[a]	0.90±0.11[b]	**0.013***
fT3 (pg/mL)	2.52±0.28	2.67±0.19	2.68±0.31	0.122
Cortisol (µg/dL)	11.92±5.77	9.88±4.87	9.99±3.95	0.647
Prolactin (ng/mL)	113.76±71.54[a]	118.11±65.8[a]	49.48±50.6[b]	**0.007***
FSH (mIU/mL)	3.58±1.89	2.83±2.32	5.14±3.39	0.105
LH (mIU/mL)	3.11±3.47[a,b]	1.48±2.45[b]	4.56±3.69[a]	**0.027***
DHEAS µg/dL	177.97±70.91	172.50±99.97	123.43±65.29	0.123

a, b: The difference between the groups that take different letters is significant; PP: Postpartum psychosis; TSH: Thyroid-stimulating hormone; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; DHEAS: Dehydroepiandrosterone sulfate; SD: Standard deviation; *: P<0.05.

volume, and right lobe volume were found, with no significant difference in TSH and fT3 levels (32). It has been suggested that this situation may be associated with an increase in body mass index during pregnancy and the right lobe being more vascular than the left, and the results were evaluated as euthyroid hyperthyroxinemia. Although fT3 levels were within normal physiological limits in our study, they were significantly lower in the PP group. When examined according to breastfeeding status, this difference disappeared, and fT4 levels were found to be significantly lower in the NBFC group this time. All thyroid function values were within normal physiological limits. These findings may indicate a secondary outcome to acute PP episode. Indeed, acute psychiatric presentations such as psychosis can themselves block the hypothalamic–pituitary–thyroid axis and lead to what is known as "non-thyroid disease" (32). Altered thyroid function may occur more as a response to the underlying acute psychopathological process rather than actual thyroid disease (33). Additionally, because our study does not include subsequent follow-up data, no interpretation can be made with our current data in terms of progression to the euthyroid sick syndrome. The fact that thyroid autoantibodies were not measured in our study can be considered a limitation. There is still a need for more comprehensive and prospective studies on this subject.

Hypothalamic–pituitary–adrenal (HPA) axis dysfunction, steroid-induced psychosis, and the findings of HPA axis hyperactivity in patients at risk of developing psychosis indicate the role of glucocorticoids in psychosis (34,35). However, the data on the relationship between PP and glucocorticoids are scarce. In two recent studies that evaluated patients with bipolar and schizoaffective disorder, high cortisol levels were associated with a postpartum psychotic episode (36,37). On the contrary, in our study, no significant difference was found between the PP and control groups with regard to cortisol levels. Due to the heterogeneity in the definition of PP, patients with different diagnoses can be considered as having PP. Accordingly, studies including more homogeneous and even isolated cases of PP may provide more substantial etiological findings.

It has been suggested that the sudden drop in hormones following childbirth may lead to dopaminergic hypersensitivity in some sensitive women (38). Elevated prolactin levels have been associated with psychotic symptom severity (39). High prolactin levels have been reported in patients with schizophrenia and first episode psychosis who did not use antipsychotic medication (40,41). In addition, dopamine receptor agonists used for hyperprolactinemia have been associated with the risk of manic/psychotic episodes (42–44). All these data are accepted as evidence for the role of prolactin. Taken together, these studies suggest that the changing prolactin levels may affect psychotic symptoms, and, given the fluctuations in prolactin levels in the peripartum period, prolactin may affect PP. However, to the best of our knowledge, prolactin levels have not been studied in PP patients until now. In our study, no findings were found to support these assumptions, and no significant differences were found in terms of prolactin levels. Considering the low sample size, further research is needed on this subject.

Although there is no study examining DHEAS levels in PP, recent theoretical and animal studies have focused on DHEAS levels and the steroid sulfatase (STS) axis (45,46). STS is most highly expressed in the placenta, and its primary role is to hydrolyze the compounds including DHEAS and 16a-OH-DHEAS that are secreted into the placenta by the fetus (47). As a result, DHEA is formed, which is an important precursor for estrogens and androgens (48). Studies suggest that the STS axis plays an important role in normal maternal behavior and postpartum mood disorders (18,49). In women with STS deficiency, low postpartum DHEA levels caused by impaired DHEAS desulfation may result in hyperactivation of the immune system (50). Previous studies have reported a positive association between serum DHEAS levels and psychoticism in healthy individuals and in women with postpartum psychiatric distress (51). In some other studies, decreased antipsychotic response explained by menopause was found to be associated with decreased concentrations of adrenal androgens (e.g., DHEA, DHEAS, and androstenedione) in women with psychotic disorders (52). The STS/DHEA(S) axis may increase predisposition to PP (18). To our knowledge, our study is the first to examine DHEAS levels in PP. In our study, DHEAS levels were higher in the PP group than in the control group, though no significant difference was established ($p>0.05$). More comprehensive clinical studies are needed on this issue.

Gonadotropin hormones affect human mental health and behaviors during periods such as premenstrual dysphoria, pregnancy, postpartum period, and menopause. Studies have reported an association between FSH and LH levels and mood disorders and postpartum depression (53–55). In one study, increased LH levels were detected in male

patients with a bipolar manic episode. In another study, baseline LH levels were higher and FSH levels were lower in female patients with bipolar disorder (56,57). Brain regions that play a role in the pathophysiology of psychotic disorders are relatively more affected by gonadal hormones (58). Meaningfully, these findings suggest that gonadal hormones may play a role in the etiology of PP. However, to the best of our knowledge, FSH and LH levels have not been examined in PP. In our study, no significant difference was found between the PP and control groups with regard to FSH and LH levels, while some differences were found between BFC and NBFC with regard to LH. Of note, the LH levels were higher in the PP group than in BFC, while no significant difference was established. This finding could be attributed to the small sample size of our study. Therefore, these findings should be replicated in future studies with larger samples. On the other hand, LH levels were found to be significantly higher in NBFC compared with the other two groups, which could be due to the negative feedback effect of prolactin on LH.

The exclusion of patients using antipsychotic medication is the strength of the study. However, our study had some limitations. First, as in many studies, our sample size was small due to the rare prevalence of PP. This may have affected our results. Second, although our thyroid function tests results were normal, thyroid autoantibodies were not evaluated. Third, due to the cross-sectional design of the study, long-term clinical features and hormonal changes were not investigated. Fourth, the use of DSM-IV-TR instead of the newer DSM-5 criteria can be considered a limitation of the study. Fifth, the unexpectedly high rate of cesarean section in the control group may indicate a limitation in the selection of the control group. In this respect, it may be more accurate to match the groups in terms of delivery method.

CONCLUSION

The results of thyroid function tests in our study suggest a condition that develops impaired thyroid functions secondary to acute psychotic episode rather than an underlying thyroid disease. Comprehensive prospective studies, including follow-up data, may better explain the relationships between thyroid function and PP. In our study, there was no evidence for the possible role of DHEAS, prolactin, and LH hormones. However, changes in the hormone profile according to breastfeeding status suggest that the effects of breastfeeding on hormones may also be important.

Contribution Categories		Author Initials
Category 1	Concept/Design	M.I., O.O.
	Data acquisition	M.I.
	Data analysis/Interpretation	M.I., O.O., R.U.
Category 2	Drafting manuscript	M.I., O.O.
	Critical revision of manuscript	M.I., O.O., R.U.
Category 3	Final approval and accountability	M.I., O.O., R.U.

Ethical Approval: This research was approved by the Ethics Committee of Yuzuncu Yil University Faculty of Medicine on March 25, 2014, with number B.30.2.YYU.0.01.00.00/69.

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