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**CLINICAL STUDIES**

# Elevated serum copper levels in women with a history of post-partum depression

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## Abstract

Previous observations suggested that there may be an association between elevated serum copper (Cu) levels and post-partum depression (PPD). In this study, we examined Zn and Cu levels in women with completed pregnancies who had a history of PPD and compared them to women who did not have depression, and to women who reported having been depressed, but without a history of PPD. Cu levels were significantly higher in women having a history of PPD compared both to non-depressed women and to depressed women without a history of PPD. The mean serum Cu level of 78 women with a history of PPD was 131±39 μg/dL compared with 111±25 μg/dL in 148 women without such a history, and 106±20 μg/dL in non-depressed controls ($p$<0.001). Zn levels did not differ across the three groups. Cu/Zn ratios were significantly higher in the PPD-history-positive group, due to the significant differences in Cu levels. Cu and Zn levels were not significantly different in depressed and non-depressed men, nor between non-depressed women and non-depressed men. Depressed women had higher Cu, but not Zn, levels compared with men. The nature of the association between elevated Cu values and PPD is, as yet, unknown; however Cu has roles in a variety of physiological systems that may be implicated in the development of PPD.

**Keywords:** Copper; Depression; Post-partum depression; Zinc

## Article Outline

# Introduction

Over the past 15 years, the staff of the Pfeiffer Treatment Center (PTC) in Illinois, a diagnostic and treatment center for patients with predominantly mental and behavioral dysfunctions, has anecdotally observed that there appeared to be an association between elevated serum Cu levels and a history of post-partum depression (PPD).

The available literature that might support such an association is small and fragmentary. Copper (Cu) is an essential trace mineral that is involved in a large number of bodily metabolic processes, including co-factor status in enzymatic activities related to brain neurotransmitter function [1], [2], [3], [4] and [5]. Based on these considerations, studies have been reported on the relationship of Cu levels to mental depression [6] and [7].

Studies have also suggested that Cu may play an important role in the successful conclusion of pregnancy. During pregnancy, Cu levels gradually rise from a pre-pregnancy level of about 120 μg/dL, in association with increased levels of circulatory estrogens and progesterone. In four separate studies, mean Cu levels at the end of the third trimester were reported in the range of 170–220 μg/dL [8], [9], [10] and [11]. Recently, Alebic-Juretic and Frkovic [12] reported that serum Cu levels in pathological pregnancies diagnosed during the first trimester were lower relative to those of normal pregnancies. They also noted a non-statistically significant increase in serum Cu levels in pathological pregnancies identified in the third trimester. However, no specific data on post-partum complications and Cu levels were reported.

In order to examine in detail the staff's anecdotal observation of high Cu being associated with PPD, we reviewed all patient records over the past 15 years to statistically examine this purported association. In addition, since zinc (Zn) levels have been shown in most studies to demonstrate a reciprocal relationship to Cu levels, we also studied the association of serum Zn levels and Cu/Zn concentration ratios to a history of PPD.

PPD is a condition occurring in the post-natal period characterized by depressed mood, lack of energy, disruptions of sleep and appetite, loss of interest in previously enjoyable activities, and, in severe cases, suicidal and homicidal ideation and behavior. Most women experience at least some mild depressive symptoms in the immediate post-partum period, and 10–20% will experience a full-blown major depressive episode [13]. Between 5% and 14% of patients with PPD will experience suicidal ideation [14]. At the clinical observation level, there are no significant differences between depression occurring in the post-partum period and that occurring at other times. However, the occurrence of PPD in the relatively discrete time period following delivery has suggested that physiological factors related to pregnancy and its aftermath may be critical. As yet, however, no consistent correlations between gonadal hormone levels and depression have emerged [14].

Two important recent findings, however, suggest that women who develop PPD may possess physiological risk factors for developing this disorder. Women with a history of PPD showed a differential sensitivity to gonadal hormone manipulation compared with women who did

not have PPD [15]. The authors suggested that the findings may be related to a physiological trait that predisposed them to developing the disorder. Additional evidence for an inherited trait comes from family studies showing a clustering of cases of PPD in certain families [16].

# Methods

We studied the Cu and Zn levels measured in the blood of men and women. Study subjects were patients at the PTC, Warrenville, Illinois, a clinic specializing in the evaluation and treatment of patients with various mental and behavioral disorders. The study was approved by the PTC Human Studies Committee. Charts were selected from a database of 14,000 patients seen in the clinic between 1990 and 2002. From this database, the charts of all women (574) and men (328) between 30 and 60 years of age were examined. This age group was selected to better match the age of the non-depressed control group, and since relatively few potential subjects fell outside these age parameters. The following study groups were established: non-depressed controls, depressed subjects, and, within the group of depressed subjects, groups with and without a history of PPD. Non-depressed and depressed men were also studied for comparison. Depressed study subjects had been diagnosed and treated for depression by primary care physicians or psychiatrists prior to their evaluation at PTC. Cases of PPD met the DSM-IV post-partum specifier (occurring within 4 weeks of delivery) based on the patients' histories. Cases of bipolar disorder or cases with other psychiatric comorbid conditions were not included in the data analysis. Data on all medications taken by the subjects were obtained from the charts both to examine responses to various treatments and to explore the relationship between medication treatment and Cu and zinc levels. Charts also were reviewed for clinical factors such as co-morbid medical conditions, types of treatment, duration of illness, age at onset, and clinical history of depression, including the presence or absence of PPD, information that is routinely obtained for all patients with at least one completed live birth. Age- and sex-matched control groups of 28 women and 26 men were comprised of individuals participating in a "wellness" program at the clinic who had no significant history of medical or psychiatric problems, but had been seen in the clinic for advice on maintaining good health and preventing illness.

Samples for Cu and Zn levels were routinely collected in trace-metal-free, acid-etched tubes to avoid contamination from other sources of Cu and zinc. Samples were separated within 45 min of collection, and then transferred to plastic tubes for transport to the laboratory. All samples were analyzed uniformly with atomic absorption spectroscopy using inductively coupled plasma-mass spectrometry (Laboratory Corporation of America, Elmhurst, IL). Laboratory values for serum Cu and Zn were obtained at the first visit to the clinic.

Data extracted from the records were analyzed using the statistical software package, SPSS (SPSS Inc., Chicago, IL). Group means are reported as the mean±the standard deviation of the mean. Group comparisons were made using two-tailed independent-sample *t*-tests. For all statistical studies, a *p*-value of less than 0.05 was considered statistically significant (Table 1).

Table 1.

Copper and zinc parameters in males and females

| | N | Cu | *p* | Zn | *p* |
|---|---|---|---|---|---|
| All women | 513 | 116±3 | 0<0.01 | 73±14 | NS |
| Not depressed | 28 | 106±20 | NS | 77±12 | NS |
| Depressed | 485 | 116±31 | <0.01 | 73±15 | NS |
| All men | 354 | 92±17 | NS | 79±14 | NS |
| Not depressed | 26 | 98±12 | NS | 78±15 | NS |
| Depressed | 328 | 91±17 | NS | 78±14 | NS |

Units for Cu and Zn are µg/dL. Mean±standard deviation. Two-tailed *t*-test.

NS non-significant at the $p>0.05$ level.
[a] Compared with all men.
[b] Compared with non-depressed women.

# Results

Women with a history of PPD exhibited elevated serum Cu levels (131 µg/dL) compared to levels for non-depressed controls (106±20 µg/dL, $p<0.001$) or to depressed women without a history of PPD (111±25 µg/dL; $p<0.001$). In addition, PPD-positive women had elevated Cu/Zn ratios (Cu/Zn=1.96) compared with PPD-negative women (Cu/Zn=1.63; $p<0.001$). There was no significant difference with respect to Zn levels between the PPD-positive and PPD-negative groups (75±16 vs. 74±14 µg/dL). See Table 2.

Table 2.

Copper and zinc parameters in women in relation to history of PPD

| Group | N | Cu | *p* | Zn | *p* |
|---|---|---|---|---|---|
| Non-depressed controls | 28 | 106±20 | | 77±12 | |
| Depressed, no PPD | 148 | 111±25 | | 75±16 | |
| Depressed, with PPD | 78 | 131±39 | <0.001[a] | 74±17 | NS |

Units are µg/dL.

NS non-significant at the $p>0.05$ level.
[a] Comparing subjects with and without a history of PPD and subjects with PPD to non-depressed controls.

The observed elevations in serum Cu could not be explained by physiological changes related to pregnancy, because of the similarity in Cu and Zn levels between the 128 depressed women who had experienced at least one pregnancy and the 221 women who had not: (Zn, 73±13 µg/dL without children, versus 75±17 µg/dL with children; Cu,

117±28 μg/dL, without children; 118±32 μg/dL with children). All of these comparisons were statistically non-significant.

Age was not a significant source of variability in the data. A Pearson product moment correlation coefficient for the relationship between age and serum Cu was 0.045 ($p$=0.391.) Nor was there a significant difference in age across the three study groups: Mean age of controls was 45.7±7.0; for non-PPD depressed subjects, 43.0 ± 7.4; and for PPD subjects, 41.0±6.8.

The expected effect of oral contraceptive agents was noted in all women in the study, with an increase in serum Cu of 22% in the depressed patients and 25% in the PPD-depressed group. These findings are consistent with published data [17]. Eliminating oral contraceptive users from the data analysis had no effect on the statistical outcome.

Since all women subjects – both with and without a history of PPD – had reported symptoms of depression at the time of their initial evaluation, we also studied Cu and Zn levels in a comparison group of non-depressed women and in depressed and non-depressed men (Table 1). Women reporting depressive symptoms had higher Cu levels than the non-depressed control women (depressed: 116±31; non-depressed: 106±20 μg/dL; $p$<0.01). Zn levels did not differ significantly between these two populations. In addition, Cu levels for the entire group of women were significantly higher than those in men (All women: 116±30; All men: 92±17 μg/dL; $p$<0.01).

# Discussion

The most striking finding of this study was the elevated serum Cu levels in subjects with a history of PPD. Since elevations of serum Cu can be associated with elevated ovarian hormone levels, we examined the possible relationship between age and Cu levels in this cohort of 30–60 year-old women, and found there was no significant correlation between age and Cu parameters. It is therefore unlikely that ovarian hormone levels explain the findings of this study, since both pre- and post-menopausal women were included in this analysis.

The psychiatric diagnoses of the subjects in this study were based on the patient history, including their report of having taken anti-depressant medications and having seen a psychiatrist or psychologist for their depression. Since "depression" is a descriptor for a range of severities of illness, further studies might well address groups of formally diagnosed subjects to examine the relationship of Cu and Zn metabolism in other discrete forms of depression.

We also considered the possibility that another medical condition associated with elevated Cu might have been over-represented in our sample of 78 PPD females, but identified only one such subject, a woman with ulcerative colitis, a condition associated with elevated Cu levels [18], had an elevated Cu level of 234 μg/dL. Removing this subject from the data analysis had no effect on the level of significance found in the $t$-test analyses of group mean differences.

The elevated serum Cu elevations observed in our subjects with PPD raises the possibility of a causal link between high serum Cu and PPD. The conversion of dopamine (DA) to norepinephrine (NE) in the brain is a Cu-dependent step, with approximately eight Cu atoms loosely bound to each molecule of the enzyme DA $\beta$-hydroxylase [19]. Mouse studies indicated a 24% increase in brain DA and a 91% decrease in NE following a Cu-deficient diet [20]. Two rat studies reported decreases in NE levels of 35% and 32%, respectively,

following Cu deprivation [3] and [5]. Studies of the impact of increased Cu levels on DA and NE in brain have never been reported, but it is possible that elevated serum Cu may result in altered levels of brain DA and NE in PPD women.

Other possible causal links between elevated Cu and PPD include its role in many cellular processes of potential relevance to the expression and clinical course of depression, including acting as cofactors in enzymatic pathways, such as cell energy production via cytochrome c oxidase, [21] signal transduction, [1] and intracellular calcium mobilization [2].

It is also possible that elevated serum Cu is a non-causal phenomenon that is associated with PPD. For example, Maes et al. [6] and [7] have suggested that depression involves an inflammatory or auto-immune dysregulation. Either of these conditions would tend to elevate Cu and deplete Zn levels. This suggests the possibility that an inflammatory or autoimmune mechanism is involved in the development of PPD, and that Cu is a marker for PPD. Studies of other markers of inflammation or auto-immunity in women with a history of PPD are needed to explore this relationship.

A limitation of this study is the absence of current, formal diagnostic evaluations of the test subjects. While all the patients presented with a diagnosis of depression from referring physicians and psychiatrists, future studies should involve standardized evaluative techniques for severity and sub-types of depression to enable an improved characterization of the test subjects. The chart review nature of this study precluded obtaining consistent, reliable information on such factors as the age of onset of illness and its duration. Future studies would benefit from a more systematic, prospective, collection of this type of data. Another limitation is the possibility that the test subjects do not represent the full spectrum of PPD patients by virtue of seeking services at the same clinic, or because many of them had a history of unsuccessful medication or counseling treatments. In addition, future studies should examine the relationship of psychiatric drug treatment and the observed findings.

The diagnosis, etiology and treatment of PPD are issues of considerable current discussion [22] and [23]. Patients in this study had experienced their episodes of PPD months to years prior to their evaluation at the clinic, suggesting that serum Cu levels remain elevated long after the episode of PPD or, alternatively, are elevated in this population even before their episode of PPD. These possibilities suggest that elevated serum Cu may be a useful marker to identify women with a predisposition to PPD, and also a “trait” marker which may assist in diagnosis of women experiencing depression during the post-partum period. It remains for future research to determine whether therapeutic interventions designed to normalize serum Cu levels can have a beneficial effect on PPD patients – either in treating their depression or in blocking the development of their depression.

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