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Impact of Altered Hormonal and Neurochemical Levels on Depression Symptoms in Women During Pregnancy and Postpartum Period

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Abstract

Introduction: Among the most prevalent psychiatric turmoils and the problems in human life, exhibit depression. Women are suffering from depression overmuch predominately than men and frequently cluster in the childbearing years. For women with pre-existing psychiatric ailments, Gestation and postnatal periods are large hazard times comparatively. This work designed to explore potential relation between depression and the fluctuation in the level of hormones and neurotransmitters. Methods: In the current work, ninety-five women aged 18-40 years consented to participate. They were allocated into three groups, which were as follow: Healthy non pregnant females (1st, control group), pregnant women during the third trimester (36-39 weeks) of gestation (2nd group) women in the early (1-2 days) postpartum period (3rd, group). Using a self-report questionnaire, we surveyed all eligible women at the Maternity and Children's Hospital in Azizia in Jeddah City. Depressive symptoms were accomplished by the help of Edinburgh Postnatal Depression Scale, Arabic version during the same period. After an overnight fast, blood samples were withdrawn for inspect of hormones (estrogen, progesterone and prolactin), neurotransmitters (Dopamine, Serotonin and Norepinephrine). Results: Pregnancy and postpartum groups exhibited significant increment in estrogen, progesterone, prolactin and norepinephrine levels accompanied by significant decline in dopamine and serotonin versus control group. Conclusion: It is clear that depression in late pregnancy and postpartum associates with some psychosocial, socioeconomic, neurotransmitters and hormonal variables.

Keywords: Depression, Pregnant Women, Postpartum Period, Hormonal Variables, Neurotransmitters.

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Introduction

Depression is the most widespread psychical health status in the public population (Sinyor et al., 2016). People in almost all countries and cultures and of all genders, ages and experiences are affected by this common disorder named depression, where it affects 350 million people all over the world (Pereira et al., 2010; WHO, 2012). Depression impedes extraordinarily an individual's vocational power (Stewart et al., 2003) and life quality (Mayor 2015).

Lack of delight in nearly every activity, lack of solicitude, iniquity feelings or weak self-worth feeling, insomnia, considerable changes in weight whether earn or loss, feelings of tiredness and confusion in concentricity are considered some of the depression guises (Lu et al., 2014). Furthermore, in its most hard shape can lead to ideation in suicide (Large 2016).

Women are twice more probable to evolve depression than men. At least for every five women, one will suffer from one depressive event in her life, which deem as greatest risk during the reproductive period. Throughout a woman's life changes occur in hormones level which may be contribute to increased chance of depression especially during puberty, pregnancy, and menopause, as well as after giving birth or experiencing a miscarriage where the hormonal changes are more pronounced (Kessler 2003).

In comparison to other periods in women's lives, pregnancy is considered a motive for depression (Pereira et al., 2010) and the postpartum period allows an increased risk of depression (Vesga-Lopez et al., 2008). Thus, one of the most predominant psychiatric turmoils during pregnancy is depression (Pereira et al., 2010). Probably, its baleful impacts lead to serious consequences for maternal and fetal health (Giardinelli et al., 2012).

From psychiatric and endocrine viewpoints, pregnancy may also have seen as an interval of sex hormone overbid but is more intricate than the else venereal phases. In pregnancy period, addition to estrogen and progesterone increments, elevations in

testosterone, cortisol and corticotrophin releasing hormone are noted and the response of immune may alter (Skalkidou et al., 2012). The postpartum period and perimenopause periods of hormonal deficiency, are characterized by grant a high jeopardy for depression in women (Soares 2014). However, the postpartum is exceedingly intricate, distinguished by shortage sex hormones, as well as hypothalamus–pituitary–adrenal (HPA) axis hormones (Skalkidou et al., 2012).

Andersson et al., (2006) stated that for women who previously have suffered psychiatric ailments, particularly for depression bouts in women, Gestation and postnatal periods are large hazard times, comparatively. Through pregnancy, depression is called antepartum (APD) or prenatal depression while after pregnancy, depression is called postpartum depression (PPD) (Paulson 2010).

Depression might be consequence to multifactorial. A collection of unrests in neurotransmitter, bad organization of hormones and genetic or psychosocial factors is probably contributing in the occurrence of a depressive episode and this assumption is generally accepted for the time being (Naninck et al., 2011).

The hormones responsible for reproduction or physiological variations which probably trigger psychiatric symptoms in women who have affected by the alteration in hormones no doubt they are in a partnership, as noticed promptly following delivery (Spinelli 2005). Accordingly, diverse depressive disorders are likely bind with imbalance in hormones as confirmed in a lot of studies (Bloch et al., 2011).

In the 3rd trimester of pregnancy, estradiol and progesterone were elevated up until 50 and 10 times the greatest menstrual cycle levels, respectively. In postpartum period, by the third day estradiol backs to early follicular stage levels as well, plasma progesterone levels are usually normalizing by 3rd to 7th day. When mothers do not breastfeed, an altitude in progesterone levels occurs and usually resuming the ovulation amidst 1.5 to 3 months within postnatal duration. Analogous to the visible ordinary vacillations in hormones of ovary through gestation and the postnatal, neuroactive steroids (NASs) were rising through gestation then significantly reducing during the postpartum period (Gilbert Evans et al., 2005) The observed unrest in centric serotonin (5-hydroxytryptamine; 5-HT) efficiency is a main cause as reported by several clinical or preclinical studies, whilst variety of monoaminergic neurotransmitters such as norepinephrine or dopamine were included too (Nestler et al., 2006).

Many researches have attempted to bind antepartum or postpartum depression with a bad organization of women hormones level and/or NASs (Murphy et al., 2001; Nappi et al., 2001). Nowadays, it is completely recognized that several steroidal hormones (e.g., estrogen, progesterone, testosterone, and dehydroepiandrosterone (DHEA) are active neurologically. Actually, the brain includes a lot of receptors for estrogen, progesterone and DHEA. Several functions in the brain involving regulation of mood are affected by these hormones. There is a positive engagement between estrogen and serotonin levels. Estrogen shortage is accompanied by dropping in serotonin levels, which participating in the negative mood and personality shifts associated with depression (Kikuchi et al., 2010).

After taking all the above mentioned reasons in the consideration, this study is an attempt to scout about possible association between the alteration in the level of hormones and neurotransmitters and depressive symptoms during the third trimesters and the early postpartum to compare and discuss the findings with non-pregnant women.

Subjects and Methods

Study layout

Study location and date

The fundamental target of this study was to distinguish biochemical variables correlated with prenatal and postpartum depression amongst females at the Maternity and Children's Hospital in Azizia in Jeddah City from March 2015 until August 2015. The study and its consent procedures were done via Research Committee of the king Abdulaziz University, the Institutional Research Review Board (IRB) of health ministry and finally military hospital.

Subjects: In a prospective cohort study, collaboration of ninety-five women from variety of nationalities with an age range of 18-40 years was done. Initially, any woman with a chronic medical ailment (hypertension, Diabetes, renal, cardiac and sickle cell disease) was precluded. Thereafter, Women were separated into three groups. The 1st group comprised 25 apparently healthy non pregnant women, which were selected to participate as a normal group for comparison (control) with age group and sex matching of the other groups. The 2nd group involved 35 expectant ladies, which were chosen at last three months of their gestation. The 3rd group included 35 women who had their babies delivered at the Maternity and Children's Hospital in Azizia in Jeddah City, in 1–2 days postpartum.

Methods

1. **Socio-demographic variables** of pregnant mothers and postpartum blues, which encompass age, ethnicity, marital status, educational status, if the pregnancy was planned or not, family support system, family history of postpartum depression and current medications/supplements, etc.
2. For measurement of antepartum (ADS) and postpartum depressive symptoms (PDS), the Edinburg Postnatal Scale (EPDS) – the Arabic language version – was utilized. The EPDS (Cox *et al*., 1987) comprises a personal- report questionnaire of ten- items, each question must read carefully. Subsequently, the persons have to select among 4 statements/responses, which best depicts

their feelings throughout the past week. On a severity scale of 4 points each item is scored (0-3). The severity scale may achieve an overall score up to 30 and greater scores pointing to larger symptom severity.

3. Radio Immunoassay (RIA) kit was utilized to determined estrogen, progesterone and prolactin. Likewise, dopamine, serotonin and norepinephrine were assessed by ELISA kit.

Statistical analysis

By utilizing Statistical Package of Social Science SPSS (version 22), with a significance threshold of $p \leq 0.05$, statistical analyses were done. Analysis of variance (ANOVA) was applied to appreciate variations among pregnant, postpartum and control groups to examine the linkage between parameters and symptoms of depression Spearmen's correlations were computed.

Results

In this study, all of participated 95 women were recruited from the hospital and completed the questionnaires applied in this study. Division of the females into three groups was carried out. Table (1) illustrate the data of the three participant groups. The number of individuals and the percentage of each group compared to the total percentage of participants were 35 (36.8%), 35 (36.8%) and 25 (26.3%) for pregnant, postpartum and normal control group, respectively. Participants were 18-40 years old, married or divorced, had low to median education levels and were employed or not. Diverse categories of females as housewives, employed outside the home and students in university or in secondary education were participated in this study. Some individuals of each category (different percentages) were among the three participated groups: pregnant, postpartum and normal control group as exhibited in table (1).

The distribution of marital status of pregnant and postpartum women was not predictors whose significance in the view of statistical analysis; however, the distribution of employment status of pregnant and postpartum women was significantly different. The majority of participants were planning and attempting to get their pregnancy, (54.3 %) for pregnant and (65.7%) for postpartum group. It is noted that the majority of participants were Saudi (73.9%) and 22.4% of different nationalities. The data illustrated that the participants having family depression history were 4%, 14.3%, 11.4% for the normal control, pregnant and postpartum groups, respectively; furthermore, it was showed that their depression and anxiety were 12%, 45.7%, 37.1%, respectively (Table 1).

Table 1- Demographic and psychosocial characteristics of the 95 study participants

	Control N (%)	**Pregnant N (%)**	**Postpartum N (%)**
Number of participants	25(26.3)	35(36.8)	35(36.8)
Age (years)			
(18-30)	12(48)	22(62.9)	22(62.9)
(31-40)	13(52)	13(37.1)	(37.1)
Educative level			
Nun study	1(4)	4(11.4)	1(2.9)
Primary school	4(16)	4(11.4)	8(22.8)
Secondary school	1(4)	5(14.3)	5(14.3)
Elementary school	5(20)	15(42.9)	8(22.8)
College degree	14(56)	7(20)	13(37.2)
Employment status			
Employed	21(84)	4(11.4)	8(22.8)
Unemployed	0	30(85.7)	25(71.4)
Student	4(16)	1(2.9)	2(5.7)
Marital status			
Single	8(32)		
Married	15(60)	34(97.2)	34(97.2)
Separated	1(4)	1(2.8)	1(2.8)
Widow	1(4)		
Nationality			
Saudi	17(68)	31(88.6)	25(71.4)
Non-Saudi	8(32)	4(11.4)	10(28.6)
Depression and anxiety			
Yes	3(12)	16(45.7)	13(37.1)
No	22(88)	19(54.3)	22(62.9)
History of depression in the family			
Yes	1(4)	5(14.3)	4(11.4)
No	24(96)	30(85.7)	31(88.6)
Pregnancy			
Wanted		19(54.3)	23(65.7)
Unwanted and unplanned		16(45.7)	12(34.3)
Income			
Low		28(80)	18(51.4)
High		7(20)	17(48.6)

The serum levels of estradiol, progesterone; prolactin, serotonin, dopamine and norepinephrine in control, pregnant (at the end of the 3rd trimester) and postnatal groups are displayed in the Table (2). In the normal subjects, serum estradiol values ranged from 54.08 - 255.41 pg/ml with the mean value of 97.61pg/ml, which were highly significant between all groups (p= 0.000). Additionally, serum estradiol values of third trimester pregnant subjects were significantly high relative to normal controls (p = 0.000).

In normal, pregnant and postpartum groups, the mean value of serum progesterone was 0.66 ng/ ml, 60.21 ng/ ml and 20.27 ng/ ml, respectively, as demonstrated in Table (2). There was highly significant increment (p= 0.000) in progesterone and prolactin values of pregnancy and postpartum groups in comparison with normal controls.

The serum serotonin value of normal subjects ranged from 50.0-209.0 ug/dl with mean value of 107.92 ug/dl. Statistical analysis using ANOVA test showed that the serotonin values were highly significant between all groups (p= 0.000). Dopamine mean values were 57. 56 pg/ml, 26.89 pg/ml and 21.11 pg/ml in the normal, pregnant and postpartum groups, respectively. Serum serotonin and dopamine values in the third trimester pregnant and postpartum subjects were decreased significantly with respect to the normal controls (p= 0.000) (Table 2).

As we see in table (2), the serum norepinephrine values exhibited highly significant difference between all groups (p= 0.000). The statistical assessment revealed highly significant increase in

norepinephrine of trimester pregnant subjects (p = 0.000), whereas only significant increase was observed in postpartum subjects related to the normal controls (p= 0.046).

The outcomes of table (3) elucidates that there was a significant positive correlation among estradiol and progesterone, prolactin, cortisol, copper and norepinephrine levels amongst all groups (normal, healthy women, third trimester pregnancy and 2 days postpartum), while estradiol was significantly negatively correlated with dopamine, Mg, zinc, folate and B_{12} and D vitamin levels.

Moreover, the prolactin level showed up significant positive correlation with estradiol, progesterone, cortisol, copper and norepinephrine. In contrast, prolactin and progesterone levels were significantly negatively correlated with Ft_3, serotonin, dopamine, Mg, zinc, vitamin B_{12}, folate and vitamin D levels.
Amidst all groups, serotonin revealed a significant positive correlation with Ft_3, Ft_4, dopamine, Mg, folate and vitamin B_{12} levels. Conversely, it was significantly negatively correlated with progesterone, prolactin, TSH and norepinephrine levels.

Significant negative correlations between dopamine and estradiol, progesterone, prolactin, cortisol, copper and norepinephrine levels were seen, but it was significantly positively correlated with Ft3, Ft4, serotonin, zinc, folate and vitamin B_{12} levels. On the contrary, Significant positive correlations among norepinephrine and estradiol, progesterone, prolactin, cortisol and copper levels were observed, but it was strongly negatively correlated with serotonin, dopamine, Mg, zinc, folate and B_{12} and D vitamin levels (Table 3).

Table 2- Serum concentrations of hormones (estradiol, progesterone, prolactin) and neurotransmitter (serotonin, dopamine, norepinephrine) in healthy control women (N=25), pregnant (N=35) and postpartum women (N= 35) groups.

Variable	Group	Mean	Std. Deviation	P-value	Sig.
Estradiol (pg/ml)	Control	97.61	47.26	0.000	H. Sig
	Pregnant	2921.04	473.03		
	Postpartum	133.67	116.92		
	Total	1151.11	1390.50		
Progesterone (Ng/ml)	Control	0.66	0.66	0.000	H. Sig
	Pregnant	60.21	4.66		
	Postpartum	20.27	15.72		
	Total	29.82	26.49		
Prolactin (ul/Uml)	Control	232.08	140.69	0.000	H. Sig
	Pregnant	3599.22	923.95		
	Postpartum	3408.77	1042.00		
	Total	2642.97	1676.67		
Serotonin (ug/dL)	Control	107.92	48.92	0.000	H. Sig
	Pregnant	65.31	44.88		
	Postpartum	64.31	36.72		
	Total	76.16	46.81		
Dopamine (pg/mL)	Control	57.56	16.07	0.000	H. Sig
	Pregnant	26.89	6.48		
	Postpartum	21.11	8.69		
	Total	32.83	18.31		
Norepinephrine (pg/mL)	Control	342.05	139.07	0.000	H. Sig
	Pregnant	505.48	136.37		
	Postpartum	411.81	120.77		
	Total	427.96	145.73		

The ANOVA test was used to test the differences in means between three groups; namely the Pregnant, Postpartum and the control.
HS: Highly significant (p-value < 0.01)

Table 3- Spearman Correlation coefficients of all parameters studies in normal healthy women, pregnant and postpartum (all groups)

Parameters	Estradiol	Progesterone	Prolactin	Serotonin	Dopamine	Norepinephrine
Estradiol (pg/ml)	1	+0.894**	+0.456**	-0.159	-0.257*	+0.407**
Progesterone (ng/ml)	+0.894**	1	+0.586**	-0.279**	-0.428**	+0.412**
Prolacin (ul/Uml)	+0.456**	+0.586**	1	-0.340**	-0.690	+0.324**
Serotonin (ug/dl)	-0.159	-0.279**	-0.340**	1	+0.451**	-0.235*
Dopamine (pg/ml)	-0.257*	-0.428**	-0.690**	-0.336**	1	-0.246*
Norepinephrine (pg/ml)	+0.407*	+0.412**	+0.324**	-0.235*	-0.246*	1

* P-value < 0.05, ** p-value < 0.01 (+ means Positive relationship, - means negative relationship).

Discussion

The strongest predictor of postpartum depression is depression during pregnancy, experience of strenuous life juveniles during pregnancy, reduced social backing and preceding history of depression (Robertson et al., 2004).

The spectacular physiological juveniles occurring after birth caused investigators to guess that postpartum mood turmoils produce as consequence of a biochemical or hormonal etiology. On the other hand, studies concerning assured hormones like estradiol and ACTH, which worth more reconnoitering, have been supine or conflicting relative to most biological changeable believed to be etiologic (Hendrick et al., 1998).

In high-income countries, a methodical review of propagation and incidence of prenatal depression had shown an ascendant tendency in depression incidence during the initial 3 months of postnatal (Gavin et al., 2005). Contrary to this finding, Fisher et al., (2011) declared that problems related psychical health in perinatal were not observed in traditional cultures, including low-income settings, because women were given structured postpartum care, which included a status of honor, relief from normal household tasks, and a 40-day of mandated rest, which are protective. The outcome to some extent asserts this. During this period, woman and the baby ordinarily are not neglected alone; they are usually in care of her mother, mother of her husband or other family women. Additionally, the household onus is achieved by relatives help. Nevertheless, the highest existence of depression is remarkable after 2-3 months postpartum. Fatigue connected with childcare, maladies and anxiety concerning social and economical positions

and blemishes linked with gender may be reasons affect the postpartum period depression (Nasreen 2011).

Shortly before parturition estrogen levels boost to above 1000× their naturalistic levels, thereafter retract considerably after delivery with placenta ejection (Pawluski et al., 2009). This abrupt descent in estradiol and progesterone is assumed to lead to a paramount action in the postpartum blues, a juvenile perceives in majority of females instantly following childbirth and may switch into PPD (Douma et al., 2005). These outcomes propose that low or unexpected drooping in these hormones may predispose susceptible females to depression.

Estrogen and progesterone are consequently typical nominees for a function in etiology of perinatal cerebral turmoil (Kammerer et al., 2006) by influencing performing brain sections. These hormones work on monoamine affluent areas such locus coereleus and raphe, which participate in cog of mood (Ostlund et al., 2003). In women with or without postnatal depression, the studies concerning checking up estrogen and progesterone peripheral levels have generally evidenced negative (Bloch et al., 2003). Postnatal depression associates with other venereal endocrine concerning mood turmoils, chiefly premenstrual syndrome, which denotes to its relation with a sex hormonal component (Sugawara et al., 1997).

The present data showed that the levels of serum estradiol and progesterone were increased significantly (p =.000) at the end of the third trimester of pregnancy group as compared with non-pregnant control group (Table 3) then dropped after 2 days in postpartum group. These outcomes are in unison with Cohen et al., (2006) who pretend that estrogen and progesterone grades were regular increased during gestation unto quite before birth. While, in the postpartum period squeaky reductions in circulating progesterone and estrogen levels were noticed.

Current study exhibited highly significant promotes in the level of prolactin in late pregnancy and postpartum women versus the normal control group (Table 2). Matching with these outcomes, Leake et al., (1983) decided that levels of prolactin were high in both gestation and immediately after birth periods. Prolactin fundamental levels collapse with lengthy breast feeding, in spite of carry on lactation to produce peak grades that are twice as altitude as foundation line levels. Additionally, prolactin increments induced by pregnancy seem necessary for neurogenesis. Increment was found in maternal disquiet and impairment in maternal attitude next parturition due to shortages or siege of prolactin within gestation (Larsen and Grattan, 2010).

The research concerning pathophysiology of depression has centralized on the dopamine, norepinephrine, and serotonin (Dunlop and Nemeroff, 2007). Low or variable grades and efficiency of the 3 monoamine neurotransmitter systems were documented in minds of depressed persons (Nemeroff, 2008). Serotonin was considered as the major neurotransmitter accountable for depression.

Consistent with these data, Netter (2006) sustained that depression scores in non-pregnant adults were more pronounced in persons who have reduced dopamine levels. In the gravid females, the jointly elevation in dopamine and serotonin levels was compatible through gestation as well, it was harmonic with the reacting phenomena such proved previously (Nutt, 2006). The dopamine, norepinephrine and serotonin systems interact among them, propose that each system affects and overlaps with the effects of the other systems (Trivedi, 2006).

Martinowich and Lu (2008) stated that serotonergic dysfunction represents the main function in case of depression pathogenesis. The precursor of serotonin tryptophan is low in patients with depression (Dhaenen, 2001). It has been known that tryptophan drop causes setback in patients who have depression history (Neumeister et al., 2004). Deficiency of monoamines such as serotonin might be the reason of major depression (Gardner and Boles, 2011). Depletion of tryptophan availability owing to increased catabolism in the placenta during pregnancy causes limitation in synthesis of peripheral and encephalic 5-hydroxytryptamine in the peripartum (Munn et al.,1998).

Moreover, after delivery, the brain tryptophan availability index decreases by 15% (Bailara et al., 2006). In the early postpartum period, this lower index is partly correlated with free amino acids that contend with tryptophan not with the tryptophan values in plasma. Increment in circulating these amino acids produced a considerably weakened tryptophan transfer through hurdle of blood (Maes et al., 2001).

As summarized in table (2), existence of considerable drop in serotonin level in prenatal and postnatal periods versus the healthy control women. Our findings were in agreement with abundant research that have utilized marginal measures of serotonergic efficacy. These studies concluded that females who suffer from PPD have decrease attainable tryptophan grades (Maes*et et al.,* 1992*),* reduction in levels of platelet serotonin (Maurer-Spurej *et al.,* 2007) and changed linking of transporter locations of platelet serotonin (Newport *et al.,* 2004).

The data recorded here revealed lower dopamine value in prenatal period. Additionally, postnatal biochemical measures stated that the mothers with depressive symptoms had lower dopamine level (Table 2). In harmony with these results, Dailly et al., (2004) suggested that depression associates with dopamine transmission. Decreased value of dopamine were noticed in pregnancy which accompanied by depression (Field *et al.,* 2004). Furthermore, norepinephrine and cortisol levels were increased, while dopamine values were depleted through the last three months of pregnancy in depressed pregnant women (Hendrick 2008). A practically considerable and gradual lack of dopamine (DA) efficacy with progress of age was found, generally consequence to a miss out, therefore researches which compare measures of DA in depressed group with control group need accurate conformity for age (Volkow *et al.,* 2000).

Diversified sources of proof uphold a function for minimized dopaminergic neurotransmission during intense depression. Physiographic variations and subsequent lowered DA signaling might due to each of minified DA liberate from presynaptic neurons and weakened allusion transfer, which produce from variations in receptor number or function and/or changed allusion transformation inner the cells (Boadie *et al.*, 2007).

Converging lines of evidence propose that norepinephrine (NE) is of main importance in the pathophysiology and processing of depressive disturbances (Stahl, 2008). Here, the findings showed a highly significant change in NE level between all groups. Amongst pregnant and postpartum groups which were recorded to have depression, there was an increase in NE levels pointing to that depression may produce physiologic stress. Similar to these results, Weber et al., (2007) decided that NE level increases with specific sorts of psychological provocation. Besides, an elevation in the catecholamine grades is in proportionate with an inclusive stress response (De Diego et al., 2008).

Conclusion

The present study revealed that there was an association between some neurotransmitters, hormonal variables and depression in late pregnancy and postpartum.

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