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Longitudinal trends in postpartum mental health, cognition and steroid hormones

Chandler R. Marrs
University of Nevada, Las Vegas

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LONGITUDINAL TRENDS IN POSTPARTUM MENTAL HEALTH, COGNITION AND STEROID HORMONES

by

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2006

A dissertation submitted in partial fulfillment of the requirements for the

Doctor of Philosophy Degree in Psychology
Department of Psychology
College of Liberal Arts

Graduate College
University of Nevada, Las Vegas
May 2007
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Longitudinal Trends in Postpartum Mental Health, Cognition and Steroid Hormones

is approved in partial fulfillment of the requirements for the degree of

Doctor of Philosophy in Psychology

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ABSTRACT

Longitudinal Trends in Postpartum Mental Health, Cognition and Steroid Hormones

by

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The temporal association between psychiatric and cognitive disturbances during pregnancy and postpartum is clear in the literature. However, associations between these disturbances and puerperal hormones are equivocal. The present study followed nine primigravid women from late pregnancy through one year postpartum to investigate trends in psychiatric and cognitive disturbances relative to postpartum hormone changes. Participants completed a battery of neuropsychological instruments at 37 weeks of pregnancy, at 10 days and four-, eight- and twelve-months postpartum and provided salivary specimen from which dehydroepiandrosterone sulfate (DHEAS), testosterone, estradiol and estriol concentrations were quantified. Results showed psychiatric disturbances and cognitive decrements in late pregnancy that often worsened following parturition. Psychiatric symptoms generally resolved by four months postpartum and were associated predominantly with elevated DHEAS.
Cognitive performance improved across the year but spatial and verbal working memory remained impaired. Cognitive performance was not associated with hormone changes and inconsistently associated with mood symptoms.
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CHAPTER 1

INTRODUCTION

The two years surrounding pregnancy and childbirth are particularly difficult for many women with the risk of serious mental illness reportedly being 20 times higher than at any other period in a woman’s life (Panay, Sands & Studd, 1998). Despite the clear temporal relationship between childbearing and the onset of mental illness, researchers have yet to identify a causal relationship between them. Although most agree that the hormonal and metabolic adaptations required to sustain a pregnancy are profound and often confer significant risk to maternal physical health, there is no consensus that puerperal hormone changes mediate, or in any way elicit, disruptions in maternal mental health. Consequently, the prevailing hypothesis suggests that puerperal mental illness, commonly referred to and investigated as postpartum depression, is not the result of endocrine pathophysiology, but rather, a maladaptive psychosocial response to normal changes in reproductive hormones (Bloch et al., 2000).

This hypothesis, while understandable in light of the inconclusive endocrine research, contradicts epidemiological data that supports a clear temporal relationship between childbirth and psychiatric disturbances (Munk-Olsen, Laursen, Pederson, Mors & Mortensen, 2006). It also disregards a basic tenet of maternal endocrinology, namely, that the changes in puerperal hormone concentrations are vast and systemic.
and, thus, not limited to the traditionally investigated reproductive hormones of progesterone, estradiol and estriol.

An abundance of epidemiological research shows that the immediate postpartum period is marked by considerable mood lability that is experienced by approximately 80% of women (Dalton & Holton, 2001; Miller, 1999; O'Hara, Schlecte, Lewis & Wright, 1986; Spinelli, 1998). Approximately 15% of women suffer an episode of clinical depression following parturition (Cooper, Larouche, Drista & Bender, 2000; Dalton & Holton, 2001; Miller, 1999; Spinelli, 1998; O'Hara & Swain, 1996). Clinically significant anxiety is estimated to be present in 9-50% of women following parturition (Austin, 2004; Eberhard-Gran, Tambs, Opjordmoen, Skrondal & Eskild, 2003; Gard, Handley, Parsons & Waldron, 1986; Heron, O'Connor, Evans, Golding & Glover, 2004; Ross, Sellers, Evans & Romach, 2002). Upwards of 30% of women with obsessive compulsive disorder recognize the onset of their disorder as having coincided with pregnancy (Neziroglu, Anemone & Yariyura-Tobias, 1992; Abramowitz, Schwartz, Moore & Luenzman, 2003). Moreover, the postpartum period confers an increased risk for psychosis with 1-2 per 1000 pregnancies resulting in psychiatric hospitalization (Brockington & Meakin 1994, Klompenhouwer & van Hulst, 1991; Kumar, Marks, Platz, Yoshida, 1995 Vedibech & Gouliacv, 1995; Wisner, Peindl & Hanusa, 1993). With postpartum psychosis suicidality increases some 70-fold (Sharma, 2003).

Given the temporal association between childbirth and significant psychiatric disturbances, it seems likely that endocrine factors are responsible. However, according to the published research they are not, with most research showing only
tenuous connections between changes in the traditional reproductive hormones and depressed mood, (Harris et al., 1994; Kuevi et al., 1983; Meakin et al., 1995; Nappi, et al., 2001; Nott et al., 1976; O’Hara, et al., 1996; Paoletti, et al., 2006). Very few researchers have investigated other hormones potentially altered by pregnancy and the spectrum of psychiatric symptoms that might emerge concurrently (Buckwalter et al., 1999; Marrs 2006). Perhaps because of the paucity of conclusive research, puerperal psychiatric disturbances are not considered by the Diagnostic and Statistic Manual Version IV (DSM-IV) (American Psychiatric Association, 1994) to be related to an organic or general medical condition, but instead, are considered as time course specifiers attributable to any mood disorder that develops within 30 days following parturition (APA, 1994).

In the popular and, indeed, in the scientific press, the DSM-IV designation has been translated into a rubric of three disorders around which the vast majority of research is modeled. The mildest form of mood disturbance, called the “baby blues,” is marked by mild anhedonia and mood lability and is the most commonly investigated phenomena within this spectrum (Dalton & Holton, 2001; Miller, 1999; Spinelli, 1998). A more serious disorder called postpartum depression (PPD) typically, although not formally designated as such, refers to major depressive disorder (Andrews-Fike, 1999; Astuler, Hendrick & Cohen, 2000; Dean & Kendell, 1981; Gard, et al. 1986; Miller, 1999; O’Hara & Swain, 1996). This is followed by the most severe and arguably rarest form of puerperal mental illness, postpartum psychosis (Brockington, 2004; Brockington & Meakin 1994; Dean & Kendell; Klompenhouwer & van Hulst, 1991).
None of these “disorders” carry with them clearly identified or even agreed upon diagnostic criteria (Kumar, 2001; Kumar, et al., 1995; McGorry & Connell, 1990), nor do they address the probability of co-morbidity or the possibility of endocrine mediators. Rather, both the baby blues and postpartum depression are characterized according to varying levels of anhedonic depression, often measured by the popular 10-item Edinburgh Postnatal Depression Scale (EPDS) (Cox, Holden & Sagovsky, 1987; Dennis, 2004; Gueyney, Fermanian, Guelfi & Kumar, 2000) and other depression scales. Postpartum psychosis, on the other hand, has been variously linked to either bipolar I or an ambiguously defined affective psychosis (Brockington & Meakin 1994; Cooper, Campbell, Day & Kennerly, 1988; Dean & Kendell, 1981; Dean, Williams & Brockington, 1989).

Disagreement regarding the onset and course of these disorders is apparent in the research literature with psychiatric disturbances considered postpartum when they develop anytime within the first postpartum year (Andrews-Fike, 1999; Gavin, et al., 2005; Mowery & Lennon, 2001; Pfuhlmann et al., 1998; Sing & Kauer, 1999; Wisner, Peindl & Hanusa, 1993; Wisner, Peindl & Hanusa, 1995) even though data exists showing that from 50-70 % of all cases of puerperal mental illness develop within days of parturition (Klopemhouwer & van Hulst, 1991; Kumar, Marks, Platz & Yoshida, 1995; Munk-Olsen, Laursen, Pederson, Mors & Mortensen 2006; Stowe, Hostetter & Newport, 2005).

With the disparities in the definition and onset of puerperal mental illness and the limited range of psychiatric symptoms and reproductive hormones typically investigated, it is clear why endocrine antecedents have not been associated
conclusively with puerperal psychiatric disturbances. Since the medical literature is replete with evidence that endocrine disturbances elicit a myriad of psychiatric symptoms (for a review see Brambilla 1992; Hochberg, Pacak & Chourous, 2003), there is no reason to suspect that the vast hormone changes associated with pregnancy, parturition an even breastfeeding cessation and menstrual cycle resumption, would not do the same. It is also reasonable to presume that the sheer magnitude of hormone changes associated with childbearing, albeit considered "normal," might elicit abnormal reactions in other endocrine parameters and that psychiatric disturbances might be the markers of these changes.

During pregnancy, hormone production is up-regulated significantly and systematically to support the growing fetus. Steroidogenesis formally under maternal control becomes a dynamic multi-compartment endeavor with contributions from fetal, placental and maternal endocrine glands (Carr, 2001; Goland, Conwell, Warren & Wardlow, 1992; Mastorakos & Illias, 2003; O'Leary, Boyne, Flett, Beilby, James, 1991; Weiss, 2000). Once tightly controlled feedback loops are up-regulated and even overridden as steroid synthesis increases exponentially to support the pregnancy (Carr, 2001; Challis & Lye, 1998). Synthesis of hormone binding proteins and enzymatic metabolism are up-regulated in an attempt to compensate for the increased steroids, but even so, maternal concentrations of these hormones increase drastically throughout gestation (Carr, 2001; Challis & Lye, 1998; Harris, Lovett, Roberts, Read, Riad-Fahmy, 1993; Mastorokas & Illias, 2003)

Upon delivery, the fetal and placental components of this system are removed, precipitating an abrupt reduction in previously supra-physiological concentrations of
maternal steroids. Hormone values fall to below pre-pregnancy levels within three to four days and are thought to remain low until breastfeeding ceases and menstruation begins (Carr, 2001; Illingworth & McNeilly, 1998). Even under normal circumstances, such an abrupt change in internal chemistry would be expected to elicit both physiological and psychological reactions. As such, the widely experienced baby blues may represent a "normal" and expected response to these changes.

However, inter-individual variability in hormone metabolism is tremendous. The abrupt withdrawal of puerperal hormones and consequent shift back to maternal control of steroidogenesis might elicit in some women aberrant compensatory reactions in steroid metabolism, which in turn might initiate psychiatric disturbances. Alternatively, puerperal hormone changes could un-mask previously unidentified impairments in maternal steroidogenesis. Since years of research have not identified any anomalies in the reproductive hormones related to psychiatric disturbances, it is likely that "non-reproductive" hormones are culpable. Indeed, new evidence suggests that this may be the case.

Unlike most investigations of puerperal mental health that examine relationships between the baby blues or postpartum depression and traditional reproductive hormones, Marrs (2006) examined a broader range of psychiatric symptoms using the Symptom Checklist-90-R (SCL-90-R) and administered a complete battery of neurocognitive instruments to a cohort of healthy, primigravid women. The SCL-90-R measures nine clusters of psychiatric symptoms including, anxiety, hostility, phobia, paranoia, psychoticism, somatization, obsessive compulsive behavior, interpersonal sensitivity and depression as well as a composite score that
estimates the severity of overall psychiatric distress. The psychiatric symptoms and
cognitive variables were compared to salivary concentrations of progesterone,
dehydroepiandrosterone sulfate (DHEAS), testosterone, estrone, estradiol and estriol
measured concurrently both in late pregnancy (n=32) and in the immediate
postpartum (n=28). With these considerations, Marrs (2006) demonstrated that
puerperal psychiatric disturbances were significantly and uniquely associated with
puerperal hormone changes. Specifically, diminished late pregnancy testosterone and
elevated pre- and postpartal DHEAS concentrations were correlated with the
spectrum of psychiatric symptoms measured by the SCL-90-R. Moreover, these
disturbances developed early, sometimes during pregnancy, were not limited to
depressive symptoms and were significantly more severe and more common than had
previously been reported. Fully 50 % of the women tested by Marrs exhibited
clinically relevant postpartal elevations in four or more symptom clusters including
elevations in psychoticism. SCL-90-R T-scores greater than 60 were considered
elevated.

In addition to identifying correlations between hormones and psychiatric
symptoms, the Marrs study uncovered atypical patterns in adrenal androgen
concentrations, namely elevated DHEAS concurrent with relatively low testosterone.
Serum DHEAS values, which have been investigated in relation to the onset of labor,
are reported to increase in the first two trimesters, remain stable in the third and return
to non-pregnant values following parturition (Milewich et al., 1978; Soldin et al.,
2005; Tagawa et al., 2004). In the Marrs study, salivary DHEAS concentrations were
high in late pregnancy and increased by an average of 34 % following parturition,
with those participants exhibiting the largest increases in DHEAS also suffering the most severe psychiatric disturbances. Moreover, four participants exceeded and others approached the clinical cutoff range that typically merits further testing for adrenal pathology.

Elevated DHEAS concentrations typically lead to elevated testosterone concentrations. Testosterone is presumed to increase significantly during pregnancy but fall to pre-pregnancy concentrations following parturition (Bammann, Coulam & Jiang, 1980). This appeared not to be the case in the Marrs study. Both pregnancy and postpartum testosterone concentrations were very low when compared to healthy non-pregnant women and were found to increase rather than decrease in five women following parturition, although as a group testosterone concentrations fell by 49%.

In addition, low late pregnancy testosterone concentrations were associated with a myriad of psychiatric symptoms during pregnancy but more importantly heralded the onset and exacerbation of postpartal psychiatric disturbances. Thus, lower late pregnancy testosterone combined with higher pre- and postpartum DHEAS concentrations not only represented an atypical pattern in hormone metabolism but also were linked with significant psychopathology.

The Marrs study also investigated cognitive performance and its relationship to hormone concentrations and psychiatric symptoms. The data revealed moderate cognitive impairment both pre- and post delivery across multiple cognitive domains including verbal and spatial memory, attention and cognitive processing speed. Impairment was most pronounced in verbal and spatial memory. When compared to age and IQ-adjusted normative standards, participants exhibited single digit to only
50th percentile rankings, with most verbal recall scores remaining below the 20th percentile for pregnancy and postpartum. These findings were consistent with results reported by Buckwalter and colleagues (1999) who reported equally low verbal memory scores at 36 weeks of pregnancy and one month postpartum. Although individual hormones were significantly associated with specific cognitive variables, in both the Buckwalter et al. (1999) and Marrs (2006) there were no consistent patterns across variables in these relationships. However, elevated hormone concentrations were significantly related to poorer cognitive performance in general on multiple cognitive tests (Marrs 2006).

Marrs (2006) provides perhaps the first evidence supporting a relationship between hormones and psychiatric symptoms. More importantly however, this study provided preliminary evidence for the development of an endocrine pathophysiology either related to, or un-masked by, puerperal hormone changes. In order to examine this possibility further, the current longitudinal research was undertaken. Building upon the Marrs (2006) study and continuing with women from that cohort, this research examined the relative changes in puerperal hormones, psychiatric symptoms and cognitive performance occurring from late pregnancy through the first postpartum year.

It was hypothesized that if the puerperal psychiatric symptoms were truly affiliated with endogenous endocrine factors, then the degree to which these hormone factors changed over the postpartum period would correspond to symptom severity. It was further hypothesized that elevated DHEAS would contribute significantly to the severity of psychiatric symptoms, particularly those associated with anxiety type
disorders, and to the equilibrium of other hormones along the androgen pathway. Specifically, it was proposed that if DHEAS concentrations remained elevated and above clinical reference ranges, psychiatric symptoms would continue and other hormone values would be altered. Finally, it was expected that cognitive deficits observed during pregnancy and postpartum would improve over the course of the postpartum year.
CHAPTER 2

LITERATURE REVIEW

Puerperal psychiatric disturbances develop in a significant number of women, sometimes with tragic consequences, yet their existence as distinct psychiatric entities remains under debate. Disparate definitions and diagnostic criteria plague much of the research with etiological investigations limited to a narrowly agreed upon set of anhedonic symptoms within a broadly defined time of onset. The possibility and, indeed, the probability that the postpartum period confers at least an equal risk for a wide range of psychiatric disorders is summarily disregarded with the vast preponderance of research focused on the baby blues and postpartum depression. Nonetheless, there is accumulating evidence suggesting that perinatal psychiatric disorders are unique phenomena whose symptoms: 1) may be more clearly delineated along a continuum of symptoms and severity rather than by categorical distinction, and 2) are temporally, if not causatively, related to the puerperium and the endocrine changes associated therein. Admittedly, the research is limited and consensus has been elusive making a thorough review of the literature necessary. The purpose of the first part of this literature review is: 1) to discern what is known about psychiatric co-morbidity during pregnancy and postpartum; 2) to delineate the onset and course of said disorders; and 3) to review potential hormonal factors associated therewith.
Marrs (2006) identified an array of neurocognitive decrements temporally associated with pregnancy and postpartum. As had been the case with other investigations, cognitive performance did not appear causally related to any one hormone or specific cluster of psychiatric symptoms. Rather cognitive impairment was associated with elevated hormones in general and only inconsistently associated with psychiatric symptoms. Given the degree of cognitive impairment observed by Marrs, particularly in verbal and spatial memory and the temporal association among the variables it is difficult to discount a relationship entirely. Thus, second section of this literature review will address both the short- and long-term cognitive sequelae associated with pregnancy and parturition and where applicable, with other clinical endocrine disorders.

Marrs (2006) also identified relationships amongst the adrenal androgens DHEAS and testosterone and a myriad of puerperal psychiatric symptoms. Inasmuch as this pattern of adrenal hormones has not been associated with known endocrine disorders and adrenal hormones in general have not been considered to be major determinants of pregnancy related psychiatric disruptions, a thorough review of the literature pertaining to these hormones is presented. The purpose of the final section of this literature review is: 1) to discuss the biological and pharmacological actions of these hormones; 2) to provide evidence of endocrine involvement in mental illness and the mental health issues associated with clinical endocrine disorders; 3) to discuss the potential physiological mechanism by which high DHEAS and low testosterone might develop.
Puerperal Mental Illness

Definition and Diagnosis

Heretofore puerperal mental illness has almost exclusively been regarded as either "baby blues," postpartum depression (PPD) and/or, in rare cases, postpartum psychosis. Baby blues, defined loosely as excessive crying and mood lability, is said to occur in up to 80% of all women in the days following parturition (Miller, 1999; Spinelli, 1998). Postpartum depression, considered a more severe form of baby blues, occurs in approximately 10-15% of all women (Miller, 1999; Spinelli, 1998). Postpartum psychosis on the other hand, occurs in 1-2/1000 births (Brockington, 2004; Jones et al. 2001; Kumar, 2001; Miller, 1999; Spinelli, 1998; Wisner, Peindl & Hanusa, 1993). Although baby blues are considered a normal consequence of childbirth, there is no consensus amongst researchers, clinicians or women's groups regarding the definition, diagnosis, course or treatment of either postpartum depression or postpartum psychosis. Accordingly, the postpartum period has only recently been recognized as a time course specifier applied to mood disorders by the Diagnostic and Statistical Manual IV (DSM-IV) and the International Classification of Diseases version 10 (ICD-10) of the World Health Organization when the illness arises within 30 or 45 days following childbirth, respectively (Kumar, 2001).

Consistent with the prevailing theoretical assumption, that childbirth confers no special vulnerability or etiological connection to mental illness, previous versions of both diagnostic manuals allowed for no designation of puerperal onset of mental illness. In fact, clinicians using the ICD-8 were instructed not to classify psychiatric disturbances associated with childbirth unless no other classification was deemed
appropriate. It is reported that most psychiatrists ignored those instructions (Kumar, 2001). In response, all mention of puerperal psychosis was deleted from the ICD-9, only to be reinstated in the ICD-10 in a fashion similar to the ICD-8.

Amongst the research community, the debate is no less controversial and contentious. The existence of puerperally induced mental illness was deemed impossible almost by caveat, based upon the findings of a few researchers. Specifically, Stecker and Edbaugh (1926) argued that “Old names die hard... all others who have studied this problem are unanimous in the belief that there is no psychosis which may be diagnosed as puerperal” (Kumar, 2001). This was followed by Founder et al. (1957) who stated unequivocally that “since these patients whose mental illness was apparently precipitated by childbirth did not differ substantially from control groups as regards diagnosis, previous mental illness or prognosis, the conclusion seems justified that postpartum illness is not a psychiatric entity.”

Fast forward almost fifty years and the debate has yet to be settled. As recently as 2004, a prominent researcher declared that postpartum psychiatric disorders were not discrete entities and any notion that this was the case “was disproved long-ago” (Brockington, 2004). Indeed, if it were not for some highly publicized tragedies presumably involving postpartum psychosis, it is not likely that research about this phenomenon would be moving forward at all. What research there is in this area has focused primarily upon baby blues and PPD. Moreover, perhaps because postpartum mental illness is not considered a true clinical entity, this research has involved an exceedingly narrow range of symptoms that occurs within a very broadly and inconsistently defined period of time.
Both popular and scientific research argue that PPD includes symptoms such as weeping, irritability, guilt, mood lability, low sex drive, forgetfulness, fatigue and anxiety (Dalton, 2001; Miller, 1999; Spinelli, 1998). The instrument of choice for detection of PPD has been the Edinburgh Postnatal Depression Scale (EPDS) developed by Cox, Holden and Sagovsky, (1987). The EPDS is a 10-item self-report measure that focuses on symptoms associated with anhedonic dysphoria. Each item in the EPDS is scored on a scale of 0-3 with three being the most severe. The EPDS has been well validated with over 20 studies published to date and is said to reliably identify baby blues and postpartum depression in 82% of the cases (Dennis, 2004) leaving 18% of the women undiagnosed. But what is postpartum depression? Judging from the accumulated literature it is a form of major or minor depression whose onset somehow coincides with childbirth. Coinciding with childbirth is variously defined as occurring during pregnancy (Spinelli, 1998; Johanson et al., 2000) or within 30 days following parturition (DSM-IV); is sometimes classified as the re-emergence of a previous depression during pregnancy or postpartum (Wisner et al., 1993); and/or depression occurring sometime within the first year postpartum (Andrews-Fike, 1999; Gavin et al., 2005). With such a narrowly defined disorder (depression as measured by the EPDS) and a vaguely defined onset and course, inconsistencies in research findings are not unexpected.

Similarly, postpartum psychosis is variously defined as affective psychosis, non-affective psychosis or mania (Brockington, 1990; Brockington & Meakin, 1993; Brockington, 2004; Sing & Kaur, 1999; Stewart. Klompenhouwer, Kendell & Hulst, 1991; Wisner et al., 1993; Wisner et al., 1995). Unlike PPD, the onset of postpartum
psychosis is accepted as rapid with research indicating that approximately 50-70% of all cases occur within the first two weeks following childbirth (Brockington, 1990; Brockington & Meakin, 1993; Brockington, 2004; Klompenhauer & Van Hulst 1991; Sing & Kaur, 1999; Stewart et al., 1991; Wisner et al., 1993; Wisner et al., 1995).

However, even given consensus on the time of onset, extant research on postpartum psychosis is still problematic. For example, many studies are retrospective, based upon either hospital or physician referral records, and are confounded by the presence of participants with previous histories of serious mental illness. This necessarily limits the possibility of discerning a relationship between childbirth and the precipitation of mental illness. At best, the research can only conclude that the stress of childbirth, like any other stressor, confers a risk of onset in women so disposed or a risk of relapse for women with histories of serious mental illness.

There is a small but emerging literature recognizing the need for more precise definitions of the psychiatric disturbances associated with childbearing. Such research suggests that psychiatric illnesses related to childbearing are: 1) distinct clinical entities; 2) are potentially hormonally mediated, although the research has yet to definitely bear this out; and 3) follow a continuum of severity and symptomatology from endpoints of baby blues to psychosis with varying degrees of depression, anxiety and obsessive compulsive behavior in between (Austin, 2004; Cooper & Murray, 1995; Halbreich, 2005; Pfuhlmann, Stober, Fransek & Beckman, 1998).

Data from Marrs (2006) support these generalizations. Results from this study indicated that psychiatric morbidity covered the spectrum of clinical disorders and began appearing in late pregnancy. Using the Symptom SCL-90-R to assess
psychiatric symptoms, Marrs found that fully half of the women tested had elevated postpartum SCL-90-R T-scores (>60) in four or more symptom clusters. The most severe participants showed significant psychiatric distress across all nine psychiatric symptom clusters measured. For some of these women SCL-90-R symptom T-scores were two and three standard deviations above the normative means. The Marrs research demonstrated that the current investigative focus on baby blues and PPD may underestimate the prevalence and depth of psychological suffering in otherwise healthy women.

Prevalence

A vast body of literature suggests that PPD occurs in 10-15% of all pregnancies (Bloch, Rotenberg, Koren & Klein, 2005; Gavin et al., 2005). A frequently cited meta-analysis by O’Hara and Swain (1996) found the prevalence of PPD to be 13%. Onset of PPD has been variously defined as occurring within the first month postpartum (DSM-IV), within three months (Wisner et al., 2004), within six months (Boyce et al., 2000; Ross et al., 2003) or one year following parturition (Gavin et al., 2005). A report by Stowe, Hostetter and Newport (2005) found that 66% PPD cases developed within three weeks of parturition and argues that a re-appraisal of onset criteria in many research paradigms is needed. The incidence of postpartum psychosis is estimated at 1-2 per 1000 births (Brockington, 1990; Brockington & Meakin, 1993; Brockington, 2004; Klompenhauer et al. 1991; Jones et al., 2001; Klompenhouwer & Van Hulst 1991; Sing and Kaur, 1999; Stewart, et al. 1991; Wisner, et al. 1993; Wisner et al. 1995) and is generally accepted as rapid with many cases reported in the days following parturition and up to 70% of all cases
developing within the first two weeks postpartum (Brockington & Meakin, 1993; Klompehouwer & Van Hulst, 1991; Kumar, Marks, Platz, Yoshida, 1995). Both postpartum depression and postpartum psychosis are generally accepted as clinical disorders and researched as such, but are not technically clinical entities. Rather postpartum is a time course specifier that can be applied to the “current or most recent major depressive, manic, or mixed episode in major depressive disorder, bipolar 1 disorder or bipolar 2 disorder; or to brief psychotic disorder” (p. 387, DSM-IV) that occurs within 30 days of parturition. This specifier is not applied to anxiety disorders or other psychotic disorders such as schizophrenia. This is likely due to the rapidity with which disorders of postpartum manifest and the consequent failure to meet the DSM-IV duration of illness criteria for the anxiety and schizophrenic disorders.

Both popular and scientific research suggest that PPD includes symptoms such as weeping, irritability, guilt, mood lability, low sex drive, forgetfulness, fatigue and anxiety (Dalton, 2001; Miller, 1991, Spinelli, 1998). The diagnostic instrument of choice has been the EPDS, which measures symptoms of anhedonic depression, with three questions regarding anxiety. The Hamilton Depression Rating Scale or the Beck Depression Inventory are sometimes used concurrently (for a review see Gavin et al. 2005). Most recently, researchers interested in assessing co-morbid anxiety have begun supplementing EPDS assessments with separate anxiety scales. However, the many researchers still rely on post hoc analysis of the three anxiety questions contained in the EPDS. The range of total scores on the EPDS that are considered symptomatic has varied from as low as 10 to as high as 16 (Heron et al., 2004; Gavin et al., 2005; Johanson et al., 2000; Nappi et al., 2001; Ross et al., 2003).
As would be expected, given the limited scope of the EPDS scale, the discrepancies in scoring and arguments over time of onset, previous attempts to reliably predict postpartum depression during pregnancy have faltered. Over 70 psychosocial risk factors for PPD have been identified and tested, including but not limited to, a history of depression or mental illness, socioeconomic factors and difficult or abusive family relations (Halbreich, 2005). However, none of these risk factors has been shown to reliably predict the onset of PPD (Bernaazzani, Saucier, David & Borgeat, 1996; Bloch et al. 2005; Costa, LaRouche, Drista & Brender, 2000; Halbeich, 2005; Honey, Bennett & Morgan, 2003).

The lack of methodological consistency amongst researchers has led some to revisit both the definition and measurement of PPD. Accordingly, there is accumulating evidence that suggests that a broader definition of the disorder and a more limited window of onset are warranted (Austin, 2004; Halbreich, 2005; Pfuhlman, et al. 1998; Reicher-Rossier & Fallahpour, 2003; Stowe, Hostetter & Newport, 2005). The case for expanding the definition of potential postpartum disorders is not difficult, particularly when one considers the prevalence and distribution of disorders in any given population and the high rates of co-morbidity within individual diagnoses (Rush et al., 2005). Indeed, one might expect a similar distribution and pattern of co-morbidity in pregnant women.

In recent years a number of studies have emerged indicating that puerperal psychiatric co-morbidity exists more often than not. Both epidemiological and empirical research, particularly with anxiety and obsessive compulsive disorders (OCD), show that the rate of co-morbid anxiety disorders with both syndromal and
sub-syndromal major depression is consistently elevated in both community and hospital populations of perinatal women (Austin, 2004; Altsuler, Hendrick & Cohen 2000; Brandes, Soares & Cohen, 2004; Britton, 2005; Kumar et al., 2004; Reicher-Rossler & Fallahpour, 2003; Ross et al., 2005). Moreover, some studies indicate that anxiety based disorders show greater perinatal incidence than do depressive disorders (Ross et al., 2005), but the evidence here is limited.

Postpartum Anxiety

Although there is a vast body of literature on postpartum depression and baby blues, 760 articles from 1995-2002 (Brockington, 2004), there are relatively few on peripartal anxiety. Much of this research is based upon the co-occurrence of anxiety in women already diagnosed with depression and often assessed by post-hoc factor analysis of the few anxiety dimensions endorsed in the depression scale of choice. Nonetheless, the research that does exist argues very strongly for a significant relationship between the puerperium and the onset of anxiety disorders with or without major depression.

Ross et al., (2002), assessed depression and anxiety using the EPDS and Brief Symptoms Inventory (BSI) in a community sample of 150 obstetric women, found clinically significant anxiety present in 50% of clinically depressed women across all test times (prenatal, 6 and 16 weeks postpartum). Moreover the three EPDS anxiety questions (3, 4, and 5) accounted for approximately 40% of the total EPDS score. The authors also noted significantly higher sub-clinical obsessive compulsive behaviors in pregnant women versus non-pregnant controls and versus postpartum.
A large Norwegian study (n=2730) evaluated the relative distribution and prevalence of anxiety and depression in postpartum (n=416) and non-postpartum (n=1,794) women. Using the Hopkins Symptom Checklist-25 (SCL-25), a self-report tool that evaluates depressive and anxious symptoms, researchers found that anxiety was equally likely in each group of women but that the risk for depression was higher in the postpartum group (Eberhar-Gran et al., 2003). Of interest, researchers found that crying easily and often did not confer a risk for other depressive symptoms. Researchers speculated that crying, a symptom often attributed to depressive symptomatology, particularly in PPD when assessed using the EPDS, should not be considered an indicator of depression (Eberhar-Gran et al., 2003). These results appear to contradict the findings of Ross et al. (2003) but Eberhar-Gran and colleagues utilized different instruments and did not disclose test times relative to gestation or parturition.

Using the State-Trait Anxiety Inventory, Britton (2005) found moderate anxiety in 24% of 422 new mothers, 1% of whom experienced severe anxiety. The study was conducted prior to the patients’ release from a US maternity hospital, sometimes within hours of delivery. The mean length of hospital postnatal stay was listed at 49.9 +/- 1 hour but the mean delivery to test time was not given. Britton found that elevated anxiety was associated with lower maternal age, education and income. As might be expected, first time mothers experienced greater anxiety than multiparous women. Interestingly, mothers of male infants experienced more anxiety than mothers of female infants and previous psychiatric diagnosis had no bearing on anxiety levels except in women with pre-existing depression.
Using a community based sample of 68 postpartum women, Wenzel, Haugen, Jackson and Robinson (2003) found the prevalence of generalized anxiety disorder (GAD) to be higher than major depression (4.4% versus 2.9%) at eight weeks postpartum. Moreover, 27% of the participants endorsed sub-syndromal levels of anxiety compared to 8.8% who endorsed mild non-clinical depression. In a similar study by the same authors, the prevalence of GAD was found to be higher in postpartum women than in a representative sample of other women (Wenzel et al., 2005). Interestingly, in a previous study by Wenzel and colleagues (2001), it was noted that the most common complaint of postpartum anxiety was autonomic hyperactivity. This is similar to non-puerperal patients, except that postpartum women did not associate those symptoms with fear of death.

Postpartum Obsessive-Compulsive Disorder

Over the last 15 years multiple retrospective studies have delineated the prevalence of obsessive compulsive disorder (OCD) onset during pregnancy and childbirth (for a review see Abramowitz et al., 2003). OCD is an anxiety disorder marked by recurrent distressing thoughts, ideas, or doubts (obsessions) combined with urges to neutralize those thoughts via compulsive rituals (compulsions). In non-postpartum OCD, the content of the obsessions varies across patients but typically revolves around concerns of accidentally causing harm to oneself or others (Abramowitz, et al. 2003; Brandes, Soares & Cohen, 2004). The primary characteristic of perinatal OCD is uncontrollable and often violently aggressive intrusive thoughts and images about harming one’s child (Wisner et al., 1999). Thoughts of harming one’s child are a common but relatively under-recognized
component of postpartum psychological distress. In the only study of its kind, Jennings, Ross, Popper and Elmore, (1999) measured the prevalence of intrusive thoughts in recently delivered women and found that upwards of 41% of all depressed mothers experienced intrusive thoughts while only 7% of non-depressed mothers reported intrusive thoughts. Likewise Wisner et al. (1999) and Wenzel, Gorman and Stuart (2001) found thoughts of harming one’s infant and fears of imminent danger to be the most common obsessional content in postpartum women. This suggests that intrusive thoughts may be in part engendered by the postpartum period.

In a comprehensive review of peripartal OCD symptomatology, Abramowitz et al. (2003) speculated that pregnancy and postpartum confer a unique vulnerability to the onset of OCD for some women. This is supported by numerous epidemiological studies indicating that the women’s age of onset of OCD is bimodally distributed and temporally related to childbirth. Several studies show that the number of new cases of OCD increases in females who have had children between the ages of 22-24 and 29-32 versus those who have not. Estimates of peripartal onset are approximately 39% (Neziroglu et al., 1992). Conversely, for women who have never had children age of onset is typically much earlier and between the ages of 13-16 years (Neziroglu et al., 1992). Although these data are impressive, the studies listed are based upon retrospective self-report. Very few studies have actually prospectively measured perinatal OCD.

Postpartum Psychosis and Bipolar Disorder

The nosological status of postpartum psychosis has vacillated widely over the last 60 years. Prior to the emergence of formal classification systems and since

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antiquity, psychotic episodes temporally associated with parturition were recognized as discrete nosological entities (Kumar, 2001). With the advent of modern operational criteria the existence of this disorder has been called into question, presenting obvious difficulties for clinicians and researchers alike. This is particularly so because most research in this area has been retrospective, relying solely on the diagnostic information ascribed in medical records.

Nevertheless, buried deep within this research, there are data suggesting that postpartum psychosis is a distinct nosological entity. What comes to mind here are the atypical symptom presentation and the research showing that 10-14% of cases of puerperal psychosis occur in women with no previous or familial psychiatric histories and no subsequent non-puerperal episodes (McGorry & Connolly 1990). For these women, puerperal psychosis seems to be a discrete entity. Unfortunately, new onset puerperal psychosis has not been investigated thoroughly.

When reading the case literature and research on postpartum psychosis one is left with a nagging sense of discordance between the disorder that supposedly does not exist and subsequent diagnostic criteria assigned thereto. Indeed, many professionals in the field argue postpartum psychosis is easily and blindly identified by its atypical presentation (Brockington, 2004; Hays & Douglas, 1984). That notwithstanding, the symptoms of postpartum psychosis are marked by several factors that differentiate it from its non-puerperal counterparts.

First, postpartum psychosis is marked by rapid onset of symptoms following parturition (Klompenhouwer, 1991). The rapidity of onset makes classification difficult, especially in the early stages of the syndrome when its duration has not yet
met specified temporal criteria required for making particular diagnoses. Some speculate that there is a prodromal period beginning in late pregnancy but this supposition has not been established empirically (Dalton, 1994; Miller, 1999). Moreover, the putative prodrome appears to include restlessness, insomnia and mood lability, symptoms with striking similarity to the normal physiological changes associated with late pregnancy and postpartum (Hays & Douglas, 1984). Frank symptoms are reported to begin within two weeks of parturition with some investigators reporting onset within days of delivery (Kumar et al., 1995).

Unfortunately, researchers have variously identified postpartum psychosis as beginning up through the first three months (Mowery & Lennon, 2001; Wisner, Peindl & Hanusa, 1993; Wisner, Peindl & Hanusa, 1995), the first six months (Pfuhlmann et al., 1998; Sing & Kauer, 1999), and even a year postpartum making arguments either for or against a separate disorder considerably weaker. If postpartum disorders are truly nosologically distinct from other psychopathologies, then their onset should be temporally related to the puerperium and should occur only during subsequent pregnancies or hormonally similar events.

Symptoms of postpartum psychosis include confusion, perplexity, irrational ideation and disorientation, instability or rapidly changing sensorium and psychotic hallucinations, extreme mood lability, restlessness, and insomnia (Brockington & Meakin, 1994; Hays & Douglas, 1984; Klomenphauer, McCory & Connell 1990; 1991; Miller, 1999). The severe confusion and disorientation and rapidity of onset are what have led many to argue for a separate disorder (Hays & Douglas, 1984; Videbech & Goulicav, 1995), while the apparent cycling of moods and restlessness
(and perhaps the lack of other suitable diagnostic criteria) have lead many researchers to associate postpartum psychosis with bipolar 1 disorder. This even though there does not appear to be the concomitant grandiosity or focused attention typically associated with the bipolar disorders and the postpartum mood cycling looks to be extremely rapid, consistent with extreme mood lability rather than the temporal cyclicity evident in the bipolar disorders.

*Bipolar Disorder and Affective Psychosis*

A contingent of investigators and clinicians hold that postpartum psychosis is a functional psychosis that can be sufficiently categorized under the diagnosis of unipolar affective psychosis (major depressive disorder with psychotic features) or bipolar disorder, presumably a bipolar 1, mixed episode. However, neither exact classifications are given in the literature nor is justification for inclusion in or exclusion from a particular diagnostic category elucidated.

The most consistent argument for the classification of postpartum psychosis under the rubric of bipolar disorders comes from epidemiological studies that suggest women with histories of bipolar disorder have a 1 in 5 chance of having a psychotic episode postpartum compared to the 1 in 500 chance of women without such histories (Stewart et al., 1991). In addition, approximately 39%, but upwards of 60%, of women have their first manic episode after childbirth (Mowery & Lennon, 2001) with a family history of bipolar disorder increasing that risk substantially.

Most of this research has been done retrospectively on data collected from medical records in Scandinavian and Norwegian countries (Dean, Williams & Brockington, 1989; Klompenhouwer, 1991; Kumar et al., 1995; Mower & Lennon,
As discussed earlier, the ICD has not continuously provided for the designation for either a discrete postpartum entity or even a postpartum specifier (Kumar, 2001) so researchers must compare delivery records with psychiatric admissions within a given period of time and cull together diagnostic and historical information based upon those records (Dean, Williams & Brockington, 1989; Klompenhouwer, 1991; Kumar et al., 1995; Mower & Lennon, 2001; Singh & Kauer, 1999; Wisner, Peindl & Hanusa, 1993; Wisner Peindl & Hanusa, 1995). Because the prevalence of this disorder is small, psychiatric admissions within six months and even 12 months of delivery are commonly included within the research criteria (Dean, Williams & Brockington, 1989; Klompenhouwer, 1991; Kumar et al., 1995; Mower and Lennon, 2001; Singh & Kauer, 1999; Wisner, Peindl & Hanusa, 1993; Wisner Peindl & Hanusa, 1995). This methodological decision, while understandable in light of the limited prevalence rate, necessarily compromises arguments either for or against discrete nosological status. It is very difficult to make an argument that postpartum psychosis is distinct from other psychoses when the criteria for inclusion into a particular study or diagnostic group is so broad and allows women with potentially non-childbirth related psychoses into the mix. Moreover, women with previous histories of psychiatric disorder, either puerperal or non-puerperal, are routinely included in analyses (Brockington & Meakin, 1994; Brockington, Oates & Rose, 1990; Dean, Williams & Brockington, 1989; Sing & Kauer, 1999; Wisner, Peindl & Hanusa, 1995). This is true of the few prospective projects as well (McGorry & Connell, 1990). Again, without clear distinction between those with
previous histories of serious psychiatric disorders and those without such histories, it is difficult to distinguish this syndrome from its non-puerperal counterparts.

In addition to methodological problems in the research, there are logical errors in the conclusions reached. Namely, the increased incidence in onset and recurrence of bipolar disorder, particularly in women with familial or personal histories of the disorder, does not demonstrate a nosological linkage between the two disorders. Rather, it indicates that pregnancy is a significant stressor that brings with it a risk of relapse or onset in women so disposed.

The research on prognosis or risk of relapse following a puerperal psychotic episode, though no more consistent than the aforementioned research, provides some evidence for separate disorders. It must be noted, however, that many of the studies cited in the following section do not always distinguish between new onset or recurrence, neither do they clearly elucidate symptom criteria. Thus, the numbers presented below are merely estimates culled together from the various projects for the purpose of discussion herein.

In women with histories of non-puerperal psychiatric affective psychosis there is an increased risk of both puerperal and non-puerperal psychotic episodes and functional prognosis is poor. The risks are consistent with those in the general population except in the immediate puerperium where the risk of major psychiatric illness increases several fold (McGorry & Connell, 1990). In women with family histories (first degree relatives) of psychiatric disorder and a puerperal psychotic episode there is an increased risk of future non-puerperal and puerperal episode.
Prognosis is mixed. Moreover, there is a ten-fold increase in puerperal psychosis for first degree relatives (McGorry & Connell, 1990).

In women who have had puerperal psychotic episodes with no personal or familial history of psychiatric disorder, the risk of non-puerperal episodes is increased, compared to women without puerperal psychosis, but the risk appears to decrease over time (Hays & Douglas, 1984; Ramsey, 1994). However, the risk of subsequent puerperal psychotic episodes has variously been found equal to or greater than women without such histories with estimates of 20-60% recurrence of postpuerperal episode (Brockington & Roper, 1987; Davidson & Robertson, 1989; Videbech & Gouliacv, 1995). Prognosis and post-episode functional ability in these women is good, if there are no non-puerperal breaks, with estimates of upwards 96% achieving full functioning compared to 47% of women with personal or family histories (Dean, Williams & Brockington, 1989). The risk for subsequent puerperal episodes is high with more than one third of women across studies having subsequent episodes following parturition (McGorry & Connell, 1990).

Lacking from the above data are clear diagnostic criteria, delineation between first onset versus previous history, and between subsequent puerperal versus non-puerperal recurrences. What should be investigated is whether or not there are women, for whom the puerperium only, confers a risk of psychosis.

_Epidemiology and Psychiatric Admissions in Postpartum_

Epidemiological studies on postpartum mental illness are focused largely on postpartum depression and postpartum psychosis. There are very few studies that address other psychological disturbances. Of those studies, most fit into one of two
categories, the prevalence of presenting disorder in inpatient populations relative to childbirth or the prevalence in outpatient referrals relative to childbirth. Very few data exist regarding prospective prevalence of disorder in community samples.

Wisner and colleagues (1993) reviewed medical records for a large cohort (n=1172) of women with both inpatient and outpatient psychiatric referrals relative to childbearing status. The data were divided into two groups, childbirth related onset of illness (CBROI) (n=168) and non-childbirth related onset of illness (NCBROI) (n=1004). Pre-index episodes of psychiatric disorders were not identified. Investigators found several significant demographic differences between the two groups. The CBROI group was an average of five years younger and had fewer children than the NCBROI group. The onset of illness in the CBROI group was earlier, particularly for affective and non-affective psychosis, but nonetheless similar to the NCBROI group with similar rates of prevalence in both groups for affective, anxiety and psychotic disorders.

The women in the CBROI group were, however, more frequently diagnosed with an adjustment disorder than the NCBROI group. The prevalence of adjustment disorder in the CBROI group may represent a catch-all diagnosis insofar as these women may not have met criteria for other disorders and might simply have been diagnosed with the adjustment disorder for lack of a more appropriate category. Wisner et al. (1993) also reported that of women who have ever had a child, the prevalence of psychological disorders was somewhat higher than expected at 14%. Based upon these findings the authors argued that postpartum women are as likely as nulligravid women to experience a range of psychiatric difficulties, not simply
depression, and may be at a higher risk for these disturbances following parturition, particularly in the case of younger primigravid women.

In a study looking at both onset and co-morbidity, Kumar, Marks, Platz and Yoshida (1995) found 56 out of 100 consecutive admissions to a mother-baby psychiatric ward occurred within two weeks of delivery with a diagnosis of affective psychosis. Twenty-four were diagnosed with non-psychotic disorders and 20 with pre-existing schizophrenia. Of the 56 women diagnosed with affective psychosis, 26 were experiencing an acute, first onset of mental illness. As was observed by other investigators, a consistent theme across disorders was the presence of intrusive thoughts or delusions about harming their infants.

In one of the very few prospective studies on perinatal mental illness, Wenzel et al. (2001) reported prevalence rates for anxiety disorders in a community sample of 788 postpartum women. Approximately 11% of study participants reported having had at least one panic attack in the previous 30 days. Eight and 9% reported having obsessions and compulsions, respectively. Co-morbid depression and panic disorder was reported in 1% of the population while co-morbid depression and OCD was present in 2.4% of the participants. No data were listed regarding the prevalence of depression alone. However, dysphoria was reported in all but 200 of the participants. The definition of dysphoria was not elucidated.

*Time Course of Perinatal Psychiatric Disorders*

Over the last 20 years numerous studies have addressed the prevalence and time course of perinatal depression (for a review see Gavin et al., 2005). The consensus appears to be that antenatal depression is highly associated with postnatal
depression and that symptoms from pre-existing conditions remain stable longitudinally (Beeghly et al., 2002; Gavin et al., 2005). What has not been addressed is whether there is stability in symptoms for new onset antenatal or postnatal depression cases. However, there are some indications that the time course is quicker and the prognosis is better for new onset puerperal psychosis versus non-puerperal psychosis or mania. Moreover, the incidence of a non-puerperally based relapse is significantly less following puerperal psychosis than it is following non-puerperal psychosis (Williams & Brockington, 1989).

For other psychiatric disorders, such as panic disorder and OCD, there are a few reports suggesting that symptoms follow a similar pattern as has been found in perinatal depression, although there has been speculation that pregnancy provides a protective effect. That is, pregnancy hormones (presumably, progesterone because of its anxiolytic capacity, although not ever tested) are believed to prevent the onset or recurrence of anxiety. Cohen et al. (1996) investigated this hypothesis in a small sample (n=10) of pregnant women with a pre-existing diagnosis of panic disorder and found that pregnancy was not protective. Symptoms remained stable in each of the trimesters for seven of the ten women tested. The group was followed through the first three months postpartum. At the postpartum evaluation, 9 of 10 women met diagnostic criteria for panic disorder and 7 of 10 had to increase medication over previous levels.

Consistent with his previous work Cohen and associates (2005) found that the state of pregnancy did not protect women with long standing histories of depression from relapse. In this study, 201 women (mean age 34.1 years) with lifetime histories
of major depression ranging from five years to over 20 years were tracked through pregnancy. Criteria for entry into the study included: that these women had a history of major depression; were less than 16 weeks pregnant; were euthymic from the last menstrual period through the proceeding three months; and were currently receiving, or had within the last 12 months received antidepressant medication.

Approximately 92% of the participants entered the study while taking a variety of serotonin reuptake inhibitors. The remaining participants were on tricyclics or a combination of medications. During the course of the study 43 women were able to decrease or discontinue medication without relapse. Seventy-two women prevented relapse by maintaining or increasing current dosages. Eighty-six women relapsed during the course of the study, of those 56 had either decreased or discontinued medication. The remaining 30 women either maintained or increased their medication dosages and still relapsed. These data suggest that in women with lifetime histories of major depression, pregnancy does not confer protection against an episode of major depression.

The authors argue that in light of the risk of relapse, antidepressant medication should be maintained throughout the pregnancy. There were, however, several limitations to this study. First, although standardized diagnostic and measurement instruments were used for assessment, namely the Structured Clinical Interview (I/P) (SCID-I/P) and the Hamilton Depression Rating Scale for Depression (HAM-D), there were no data given on baseline scores compared to relapse, severity of relapse, time from discontinuation to relapse, time to re-medication, pattern of discontinuation (abrupt or tapered). Nor was information given regarding which medications
generated higher rates of relapse or whether or not chronicity and/or severity of disorder predicted relapse.

Using a prospective/retrospective mixed design, Wisner and colleagues (1996) evaluated the relationship between panic attacks and childbearing using psychiatric records of 22 women over the course of five years and 45 combined pregnancies. In each of these cases, the onset of panic disorder predated the pregnancy. As was the case in Cohen et al. (1996), neither panic intensity nor frequency changed during pregnancy for the majority of women (69%). But contrary to Cohen’s findings, if there was a change, symptoms typically improved during pregnancy (27%). For most patients (69%), assessed at unspecified times postpartum, there was no change in symptom intensity or frequency. However, approximately 31% experienced an increase in panic attacks postpartum. But again, at what point participants were assessed was not disclosed, nor was the absolute difference in intensity, frequency or quality of the panic during the puerperium.

In perhaps the largest study to date, Heron et al. (2004) prospectively tracked the prevalence and course of anxiety and depression from pregnancy to eight months postpartum in 8323 English women. The study, part of the Avon Longitudinal Study of Parents and Children (ALSPAC), was conducted via self-report questionnaire. Eighty-five percent of eligible women completed the survey at all test times. Depression was estimated based upon a score of >10 on the EPDS while anxiety was measured by the Crown-Crisp Experiential Index (CCEI) and indicated by a score of 9 out of 16 points. Over the course of the study, antenatal and postnatal depression scores were moderately correlated at each test time. At 8 weeks postpartum only
8.9% of the women exhibited depression and a third of those women were new cases. Additionally, 11% of the participants experienced depression only during pregnancy.

The prevalence of anxiety followed a pattern similar to that of depression, with correlations between antenatal and postnatal test times. Seventy-three percent of the total population reported no elevation in anxiety at any test time. However, at eight weeks postpartum, 8.1% reported elevated anxiety, of which approximately one fourth of the cases were new. In each instance antenatal psychological distress predicted postnatal distress.

**Cognitive Sequelae of Pregnancy and Childbirth**

Similar to the research on puerperal mood changes, the research on puerperal cognitive changes is plagued by methodological inconsistencies. With few exceptions, research in this area focuses upon subjective perceptions of memory impairment, usually during pregnancy and the immediate postpartum. Of the few studies utilizing objective measures, most have not measured concurrent hormone values and none have been able to substantiate what is commonly referred to as the "pregnancy brain drain" (Brett & Baxendale, 2001) or "maternal amnesia" (Brett & Baxendale, 2001) or the more technical term "benign encephalopathy of pregnancy" (Poser, Kassierer & Peyser, 1986).

Jarrahi-Zadeh et al. (1969) measured both subjective and objective cognitive and affective modalities in 86 women at various times during their last trimester and on the 3rd day postpartum. These data were compared to data obtained from a group of 21 controls. The cognitive measures included Trails B and the Porteus Maze test. Both are tests of executive function and processing speed. Investigators found a
significant difference between pregnant and non-pregnant controls and between postpartum and non-pregnant controls in Porteus Maze completion times and concluded that pregnant and postpartum women showed difficulties in concentration and planning compared to non-pregnant controls. The authors also noted a high prevalence of memory complaints amongst pregnant and postpartum women.

Brindle et al. (1991) found that pregnant women showed significant deficits in implicit but not explicit memory at 36 weeks compared to controls and reported a significantly higher subjective rating of impairment (59% vs. 11%). In 1993, Sharp and colleagues found similar results reporting that pregnant women were significantly impaired in incidental learning tasks, in word list recall, and word-stem completion when compared to controls. Sharp et al., (1993) Jarrehi-Zaddeh et al. (1969) and Brindle et al., (1991) also collected subjective reports of memory which revealed that 81% of the pregnant women rated their memory as impaired compared to 16% of the control subjects.

Eidelmen, Hoffman and Kaitz (1993), using a between subjects design, looked at memory deficits in 100 postpartum (days 1-3) women using the Weschler Logical Memory Test and the Weschler Visual Reproduction Test. They found that though significant memory deficits on both scales appeared on day one they resolved by day three. Interestingly, they tested fathers and found that they too showed impaired performance on the logical memory test but not on the visual reproduction test on day one, perhaps indicating that stress, exhaustion and all of the other overwhelming emotions that occur immediately after delivery may influence memory function.
In a longitudinal case-control study assessing memory in 10 pregnant and 10 non-pregnant women, Keenen et al., (1998) found that pregnant women performed significantly worse during the third trimester as compared to controls in the paragraph recall task. The investigators noted no other differences in performance at either the first or second trimester or postpartum test times. Moreover, although the control group demonstrated significant practice effects across time, the performance of the pregnant women declined from the first until the third trimester, but improved somewhat during the second trimester. Recall scores improved between the third trimester and postpartum, returning to first trimester scores. The authors failed to note when postpartum testing occurred.

Deficits in selective attention were noted by de Groot, Adam and Hornstra (2003) at 36 weeks pregnancy but had resolved by 32 weeks postpartum. The data demonstrated that pregnant women performed significantly worse than did controls and showed little to no priming effect. Crawley, Dennison and Carter (2003) found no differences between pregnant and non-pregnant controls in three cognitive modalities tested during the second and third trimesters as well as at six weeks and one year postpartum.

The measures used by these investigators included the Stroop test, Trails A and a self-designed text memory task. In addition to these objective measures, Crawley et al. (2003) assessed subject perception of memory impairment and found that a significant portion of the women tested reported a higher incidence of perceived memory deficit during the third trimester than compared to other trimesters, non-pregnant controls and postpartum. A second study by the same authors and
published within this manuscript confirmed the subjective assessment results. The authors concluded that perceptions of cognitive impairment are likely subtle and may be associated with either depressed mood or the expectation of cognitive decline.

In perhaps the largest and most comprehensive work to date, Vanston (2005) measured cognitive performance and salivary hormones in 45 pregnant and 45 non-pregnant age- and education-matched controls five times, three during pregnancy (12 weeks, 24 weeks and 37 weeks) and on two occasions postpartum (six weeks and at the resumption of menstruation). The cognitive tests included the WAIS III Symbol Search (perceptual speed and accuracy) and Digit Symbol Coding (visual motor coordination), Purdue Pegboard (motor processing speed), California Verbal Learning Test (CVLT) (verbal memory), Silverman Eals Object Location Memory Task (object location memory), Listening Span (verbal working memory), Computation Span (arithmetic working memory) and the Shepard-Metzler Mental Rotation Test (MRT) (spatial working memory). The results indicated no significant differences between the pregnant and non-pregnant group on any of the tests for cognitive performance and no significant correlations between any of the hormones measured (progesterone, DHEAS, testosterone estrone, estriol and estradiol) and any of the cognitive tests. In fact the mean scores for the pregnant participants were higher, though not significantly, than the non-pregnant controls during pregnancy and at both postpartum test times.

Determining whether the lack of difference between groups in cognitive performance demonstrated that both groups were equally proficient or equally impaired is difficult inasmuch as only partial sections of various cognitive tests were
administered. However, comparison of the mean score for the first three CVLT trials administered in this study, show that both groups scored above the normative mean with an average of 12 of 16 words retained per list. Likewise performance on the WAIS III symbol search and symbol coding suggested slightly above average performance with percentile ranking in 58-60th percentile.

These performance levels are consistent with the 14 years of education averaged by both groups and seem to challenge the anecdotally accepted perception of pregnancy-related cognitive deficits. However, methodological issues may have limited the interpretive validity of these findings. The inclusion of multiparous women in both the experimental and control groups was particularly troubling. If some aspect of pregnancy were to have deleterious effects on cognitive ability, it would be expected during the initial pregnancy when the mother has yet to adapt to either her new physiological status or to the psychosocial stressors associated with motherhood that await her.

The researcher did find that when the gender of the child was assessed in relation to performance, women who had been pregnant with males performed better on tasks of working memory (the listening and computation span tasks and the MRT), than did women who had been pregnant with females. Interestingly, the researcher was unable to identify significant differences in the androgenic hormone concentrations between the groups and the improved performance for the mothers of male children persisted through the postpartum test sessions, long after the effects of puerperal hormone changes would have dissipated.
The discrepancy between the perceived deficits and what is empirically measurable has led some researchers to speculate that either mood disruptions commonly associated with pregnancy and postpartum underlie the perceived memory deficits (Crawley, Dennison & Carter, 2003) or that the perinatal memory deficits are just not salient (Crawley, 2002). Crawley (2002) found that only 2% of a sample of 198 pregnant women spontaneously reported memory deficits. Based upon this finding, the author argued that perinatal memory deficits must not be that important. This is contrary to accounts by professional women who report impaired job performance during the latter stages of pregnancy and early postpartum and suggest that “the maternal amnesia syndrome is a reality that most mothers are too frightened to admit…and yet will talk of with obvious relief when they realize it is common, normal and temporary” (Baildam, 1991). It is also contrary to findings of Buckwalter et al. (1999) and Marrs (2006), where significant decrements in cognitive ability were identified across multiple domains and perceptions of cognitive ability tended to overestimate performance postpartum (Marrs, 2006).

Buckwalter and associates (1999) measured cognitive performance, mood and serum cortisol, progesterone DHEA, testosterone and estradiol concentrations using a standard battery of neuropsychological instruments in 19 women at 36 weeks of pregnancy and at one month postpartum. They found that pregnant women performed significantly worse on several aspects of the CVLT compared to normative data for women of similar age and education. They were particularly impaired on trials 1 and 5, scoring in only the 6th and 5th percentiles respectively and showed significantly lower learning slopes ranking only in the 32nd percentile. Accordingly, subjects
performed significantly worse in both the short and long free recall tasks (17th percentile for both) indicating potential problems in either retention and/or attention. They also performed more poorly on short and long cued recall tasks (21st and 16th percentiles, respectively) and had a higher than normal number of intrusions.

In addition to the deficits listed above, the pregnant women showed significant impairment on Trails A, 21st percentile, but not Trails B. They also performed more poorly on Trails B, the Stroop test, the Boston naming test and Digit Span Backward when pregnant (46th, 47th, 16th percentiles respectively), but the change in performance levels from pregnancy to postpartum failed to reach statistical significance.

The Marrs (2006) study measured cognitive performance using a complete battery of neurocognitive instruments in a cohort of healthy primigravid women at 37 weeks of pregnancy and within 10 days postpartum and found cognitive deficits across multiple domains when compared to age, gender and IQ-matched normative data. In tests of verbal memory as measured by performance on the CVLT-II, participants scored below the 20th percentile on the immediate and long term recall tasks in late pregnancy and early postpartum. Spatial memory, as measured by the Rey Complex Figure Test (CFT), was similarly impaired for many of the participants with mean rankings for recall during pregnancy in the 29th percentile and in the 41st percentile postpartum.

To put these scores in perspective, the scores observed by Marrs (2006) and also by Buckwalter et al. (1999) were similar to or below scores that have been observed in patients with moderate closed head injuries (Bigler, Rosa, Schultz, Hall
& Harris, 1989), obsessive compulsive disorder (Roh et al., 2005), schizotypy (Gooding & Braun, 2004), and schizophrenia (Fenning, Mottes, Ricter-Levin, Treves & Levkovitz, 2002) and were marked by a consistent failure to organize information appropriately. Marrs also noted mild decrements in attention, cognitive and motor processing speed. Although psychiatric disturbances were present in over half of the participants in the Marrs study, they were not consistently related to poor cognitive performance. In fact depression levels were positively correlated to verbal memory. These findings were in stark contrast to the research by Crawley and associates (2002; 2003) who claimed that because women did not readily offer concerns regarding cognitive impairment that the impairment was not salient or some how associated with either mood changes or the expectation of cognitive impairment rather than impairment itself.

Summary

_Puerperal Mental Illness_

It is evident that much work is still needed. There is a relative paucity of data that addresses puerperal psychiatric co-morbidity and even fewer studies that have investigated the onset and longitudinal course of these symptoms. Of the reports that do exist, all suggest that co-morbidity is the rule rather than the exception, but when these symptoms emerge and how they progress is unknown.

While the onset of postpartum psychosis is generally accepted as being rapid and the prognosis is typically viewed as being good, the research is flawed relying heavily on retrospective data gleaned from hospital or psychiatric referral records. Women with previous psychiatric illnesses were included in the analyses and
diagnostic or inclusion criteria frequently varied from project to project making
delineation between the strictly pregnancy-related disorders from the re-emergence of
pre-existing disorders difficult at best. Finally, the research presented thus far does
not address the possibility that endocrine factors might contribute to or precipitate
these disorders.

**Puerperal Cognitive Changes**

Puerperal cognitive changes are anecdotally accepted but have thus far largely
eluded consistent empirical measurement. Some investigators have identified deficits
(Brindle et al. 1991; Buckwalter et al., 1999; de Groot, Adam & Hornstra, 2003;
Jarrahi-Zadeh et al., 1969; Marrs, 2006; Sharp, 1993) and others have not (Crawley,
Dennison & Carter, 2003; Vanston, 2005). The discrepant findings are likely related
to methodological differences between studies. Although puerperal cognitive deficits
are commonly attributed to either mood and/or hormone changes associated with
pregnancy and postpartum, only three studies to date have investigated the relatedness
of these three variables (Buckwalter et al., 1999; Marrs, 2006; Vanston, 2005) and
none was able to provide strong support either for or against those associations.
The Endocrinology of Pregnancy and Parturition

The temporal association between psychiatric disturbances, cognitive impairment and pregnancy and postpartum is clear and generally supported by the literature. What has not been addressed is how pregnancy might precipitate these changes. Some have argued that psychosocial factors adversely influence puerperal mental health (Andrews-Fike, 1999). Others have suggested that changes in the reproductive hormones such as progesterone and estradiol trigger pre-existing conditions (Bloch et al., 1999; 2000; 2005). While neither possibility can be disputed fully, the research has yet to account for the substantially increased risk for mental illness during the two years surrounding pregnancy and birth in otherwise healthy women or for the temporal proximity to the onset of these disorders with the vast changes in puerperal internal chemistry.

If the argument is to be made that puerperal endocrine changes somehow mediate puerperal psychiatric and even cognitive disturbances then the basic components of the endocrine and central nervous systems must be shown to interact with each other. Provided below is an overview of basic endocrinology relative to pregnancy and parturition. Emphasis is placed upon the hormones potentially associated with puerperal psychiatric and cognitive disturbances and their respective interactions with central nervous system activity.

Basic Endocrinology

The endocrine system utilizes hormones as chemical messengers for communication between cells to regulate metabolism, reproduction and growth. Together with the central nervous system, the endocrine system is responsible for
maintaining biological homeostasis. Hormones are synthesized in the endocrine glands and secreted into the circulatory system where they then may bind with receptors located exterior or interior to the cell from which they were released (autocrine regulation), with receptors on adjacent cells (paracrine regulation) or they may travel great distances to interact with other endocrine glands and target tissues (endocrine regulation). The synthesis of individual hormones is dependant upon enzyme availability and, thus, other peripheral tissues including adipose can synthesize great quantities of some hormones. Both the peripheral and central nervous systems also synthesize hormones and in some cases produce larger quantities than those found in circulation (Baulieu & Robel, 1990).

The hypothalamus integrates signals from both the external and internal environment to control the stimulation and inhibition of the trophic hormones released by the pituitary gland. Together the hypothalamus and pituitary and other adrenal glands form three endocrine circuits that regulate homeostasis, reproduction and growth: the hypothalamus-pituitary-adrenal (HPA) axis, the hypothalamus-pituitary-gonadal (HPG) and the hypothalamus-pituitary-thyroid (HPT) axis respectively. The HPG sometimes called the HPO (ovarian) when referring to female physiology regulates reproduction and will be the focus of this discussion.

Non-Conception Cycles

The HPO circuit regulates the female menstrual cycle and supports pregnancy through a series of positive and negative feedback loops. The hypothalamus stimulates the pituitary's release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) by releasing the gonadotropin-releasing hormone (GnRH). The
release of hypothalamic GnRH elicits the pituitary release of FSH and LH. As the follicle development proceeds, FSH and LH stimulate the release of estradiol which ultimately inhibits continued FSH secretion. Concurrently, the release of estradiol causes the increase of LH, which in turn causes the release of more estradiol. Estradiol concentrations are thought to peak immediately before ovulation. The peak in estradiol then signals the decline of GnRH and LH following ovulation on about day 15 of the cycle (Kaplan, Pesce & Kazmierczak, 2003).

After ovulation, during the luteal phase, estradiol concentrations wane prior to reaching a second and ultimately higher peak (Kaplan, Pesce & Kazmierczak, 2003; Schultheiss, Dargel & Rohde, 2003). During this time, progesterone concentrations increase until day 21-23 when the corpus luteum forms. If fertilization did not occur at ovulation, within a few days of luteal formation, luteolysis occurs, the endometrium sheds and menstruation begins.

*Hormone Changes from Conception and Pregnancy through Parturition*

After ovulation and fertilization, the 2-8 cell embryo travels through the fallopian tubes into the uterine cavity and within 3-6 days following conception, the blastocyst now floating within the uterine cavity, unattached to the endometrium, begins secreting chorionic gonadotropin hormone (β-hCG) to hasten endometrial maturation and strengthen its ultimate implantation. After implantation, the embryo continues to secret β-hCG to maintain the biosynthetic capacity of corpus luteum and endometrium. The corpus luteum produces progesterone, 17α-hydroxyprogesterone, (17α-OH progesterone) estradiol and androstenedione for the first 6-8 weeks of pregnancy. Between weeks six and eight, a period called the fetal-placental shift.
corpus luteum function declines and placental and eventually fetal steroidogenesis take over.

Pregnancy steroidogenesis is a multi-compartment process (Figure 1). Cholesterol in the form of low density lipoproteins (LDL) and very low density lipoproteins (VLDL) from maternal circulation binds with placental receptors that are up-regulated by estradiol and cross into the placenta (Carr 2001). The side chains of the cholesterol molecule are cleaved by the enzyme CYP11A1 and converted into pregnenelone. Progesterone is derived from pregnenelone as are maternal and placental androgens and estrogens, glucocorticoids and mineralcorticoids.

From conception until parturition maternal plasma progesterone concentrations, derived primarily from placental steroidogenesis (90%), increase from less than 1-2ng/mL at conception to 100-300 ng/mL at term (Braunstein, 2003; Carr, 2001). The role of progesterone during pregnancy is to suppress myometrial contractions (Challis & Lye, 1998) although researchers are finding that testosterone may also be involved in this process (Perusquia, Navarrete, Jasso-Kamel & Montano, 2005). Maternal ovaries are mostly quiescent from approximately eight weeks of pregnancy until menstruation begins following parturition but provide a major source of 17α-OH progesterone through-out the pregnancy, nevertheless. Concentrations of this hormone increase from approximately 1-2 ng/mL at conception to approximately 7 ng/mL at term (Mooney & Giudice, 2002).

The placenta is the major source of estradiol and estrone but because it lacks the CYP 17 enzymes 17α-OH and 17, 20 lyase, placental estrogens are derived from both maternal and fetal adrenal androgens rather than progesterone (Challis & Lye,
Research suggests that maternal DHEA and fetal DHEA contribute equally to the production of estradiol and estrone (Challis & Lye, 1998; Rainey, Rehman & Carr, 2004). Estradiol and estrone concentrations increase throughout gestation with values for both hormones ranging from 1.4 ng/mL at conception to 6-30 ng/mL at term (Mooney & Guidice, 2002).

Estriol, synthesized by hepatic and peripheral conversion of the adrenal androgens, typically circulates at very low concentrations during non-conception cycles (Carr, 2001). During pregnancy however, the fetal adrenals produce vast quantities of DHEA and DHEAS, from which 90% of estriol is derived (Challis & Lye, 1998; Rainey, Rehman & Carr, 2004). Since most of the estriol is released into circulation, maternal estriol concentrations increase from less than 0.1 ng/mL at conception to 10-30 ng/mL at term (Mooney & Giudice, 2002). Estriol, because of its fetal origins, is often used as a marker of fetal health and survival (Challis & Lye, 1998).

With fetal contributions to DHEA/DHEAS production, maternal circulating concentrations of those hormones are thought to increase in first two trimesters but plateau in the third (Milewich et al., 1978; Soldin et al., 2005; Tagawa et al., 2004). As a function of the increased DHEA, maternal testosterone concentrations are believed to increase throughout pregnancy (Bamman, Coulam & Jiang, 1980). It is postulated that as the pregnancy progresses more fetal DHEA is converted to testosterone and to the estrogens, to support the growing fetus and ultimately initiate parturition and thus lower circulating concentrations of DHEA are noted at term (Gant, Hutchinson, Siiteri & MacDonald, 1971). The control of human parturition is
complex process involving multiple hormones and systems and is beyond the scope of this discussion (for a review see Challis, Matthews, Gibb & Lye, 2000), however, there are data suggesting that the withdrawal of progesterone, together with a surge in estradiol, estriol and cortisol initiates uterine contractility in animal models (Olson, Mijovik & Sadowsky, 1995). In human parturition the data are inconclusive (Challis, Matthews, Gibb & Lye, 2000).

With the delivery of the fetus and placenta, maternal sources of steroid production are lost and circulating concentrations of most steroid hormones drop to pre-pregnancy values within 2-4 days of parturition (Illingworth & McNeilly, 1998). Resumption of menstruation and the cyclical production of progesterone and estradiol is reported to occur within two months in non-lactating women and can occur in some women while lactating, but typically does not resume until lactation ceases or is diminished significantly (Bolaji, Tallon, Meehan, O’Dwyer & Fottrell, 1992; Illingworth & McNeilly, 1998).

**Hormone Synthesis and Protein Binding**

All steroids are synthesized from cholesterol (Figure 2). Cholesterol can be synthesized from acetate in many tissues including the skin and the intestines but the main site of production is in the liver (Niewoehner, 1998). During pregnancy, neither the fetus nor the placenta contains sufficient enzyme activity to convert acetate to cholesterol and thus require maternal cholesterol for steroid synthesis (Challis & Lye, 1998). From cholesterol, the CYP 450 scc (side chain cleavage) also denoted as the CYP11A1, 20,22-desmolase and/or 20,22 lyase cleave either part or all the carbon side-chain converting the 27-carbon cholesterol skeleton into the 21-carbon
pregnenelone (C21 pregnane group, progestins and corticosteroids). Total removal of the side chain results in the androstane (androgens) group of hormones (C19).

Pregnenelone is the precursor hormone for the ovarian production of estrogens, the testicular production of androgens and the adrenal production of glucocorticoids, mineralcorticoids, androgens and estrogens. Ovarian and testicular production of steroids is subject to control by pituitary LH, whereas adrenal activity is modulated by pituitary adrenocorticiotropin hormone (ACTH) (Niewoehner, 1998). Conversion from pregnenelone to the respective pregnane and androstane hormones is dependant upon the presence or absence of four enzymes that are widely distributed throughout the periphery and within the central nervous system. These enzymes include desomalase (lyases) which catalyze cholesterol side chain cleavage; hydroxylase, which adds a hydroxyl group to the steroid; hydroxysteroid dehydrogenase which catalyze reversible oxidation/reduction reactions and aromatase, catalyzes a series of reactions that ultimately remove C19 methyl group necessary for the conversion of androgens to estrogens (Kaplan, Pesce & Kazmierczak, 2003).

Steroid hormones synthesized in the various endocrine glands and secreted into circulation are highly lipophilic and can be metabolized and eliminated easily in the liver. As such, steroids circulate tightly bound to carrier proteins such as sex hormone binding globulin (SHBG), corticosteroid binding globulin (CBG) and albumin or they travel as conjugated hormones (sulfates or glucuronide derivatives) (Faigle & Schenkel, 1998). Only a small percentage of steroid hormone circulates free and unbound to proteins. The fraction of circulating free hormone is estimated to
range from 1-8% of the total concentration of hormone (Faigle & Schenkel, 1998). It is argued that only free hormone or that which is not bound to protein, is capable of binding to the hormone receptor and initiating a cellular response and/or being metabolized into constituent compounds. Recent discovery of a transporter protein that facilitates the endocytosis of bound hormone through the cell membrane may challenge this notion in the future (Hammes et al., 2005).

Consideration of free/bound ratio is important nevertheless. Much of the research involving hormones is conducted using plasma/serum. Hormone concentrations from plasma/serum represent the total amount of hormone in circulation, including that which is protein bound (Vinning, McGinnley & Rice, 1983). Both procedural and mathematical manipulations have allowed investigators to estimate the ratio of free to bound hormone, but with inconsistent results (Vermeulen, Verdonck & Kaufman, 1999). Although the free versus bound ratio is tightly controlled, there are instances where the equilibrium is altered and/or difficult to assess such as in some disease states and potentially during pregnancy (Vermeulen, Verdonck & Kaufman, 1999).

Binding protein concentrations and functionality are suspected of changing significantly during pregnancy and presumably again following parturition (Vermeulen, Verdonck & Kaufman, 1999; Margarson & Soni, 1998). These changes, if empirically supported (there is a woeful paucity of research of these factors in pregnant/postpartum women), would affect the ratio of free to bound hormone and could alter the interpretative validity of hormone data depending upon the method of measurement.
To more accurately reflect the free fraction of steroid hormone and in fact to provide a less invasive means by which to measure steroid hormone values, assays were developed that quantify hormone concentration in saliva. Inasmuch as most steroids are small neutral molecules, they freely pass through the membranes of the salivary gland via passive diffusion and are not suspected of being affected by flow-rate. However, some reports indicate that progesterone values increase as a function of salivary flow-rate (Lequin, van den Boogaard, Vermeulen & Danhof, 1986). More polar molecules such as DHEAS move through the tight junctions of acinar cells into the oral cavity via ultrafiltration, a process that is flow-rate dependent (Vinning, McGinley & Rice, 1983). Salivary stimulation decreases DHEAS concentrations measured from saliva (Vinning, McGinley & Rice, 1983). Thus, care must be taken to minimize the potentially confounding variable of salivary stimulation when investigating this and other hormones, a factor minimally addressed in the literature.

Measurement of steroid hormones in saliva provides an accurate measure of the free fraction of the hormone, when proper controls are employed. Correlations between free and bound hormone are significant and range from .5- .9 depending upon methodology, the lab and the hormone being measured, but are not absolute (Hoffman, 2001). This may suggest that the equilibrium between free and bound hormone is more dynamic than currently accounted for and/or may reflect the lack of inter-laboratory procedural standardization.

**Neuroactive Steroids and Neurosteroids**

If an argument that peripheral changes in endocrine parameters due to pregnancy affect psychiatric well being is to be made, then peripherally synthesized
steroid hormones must have access to and bind with central nervous system (CNS) receptors and elicit some cellular response in regions not associated directly with reproduction. Indeed, the highly lipophilic steroid hormones cross the blood brain barrier (BBB) easily and freely where they bind to both membrane and nuclear receptors dispersed throughout the brain. It is well established that the brain is both a major target for and source of steroid hormones (for a review see Baulieu, 1998).

Researchers have thus far identified progesterone, androgen and estrogen receptors in the hippocampus, amygdala, cerebellum, basal forebrain, locus ceruleus, raphe nucleus, hypothalamus and pituitary in the both central gray and glial cells (Stomati, Genzzani, Petraglia & Genzzani, 1998). Steroid hormone receptors have also been located in and shown to exert significant trophic affects when bound to their cognate ligand in peripheral myelinated nerve tissue (Baulieu, 1999). Accordingly, pharmacological and genetic manipulation of circulating hormone concentrations and/or central hormone binding capacities demonstrates significant hormone/behavior effects, particularly in rodent social behavior and learning (Birzniece et al., 2006; Chestler & Juraska, 2000; Frye & Sturgis, 1998; Johansen, Birzniece, Lindblad, Olson & Backstrom, 2002) but also in human models (Hampson, 1990; Kampen & Sherwin, 1994; Maki, Zonderman & Resnick, 2001).

In addition to the neuroactive actions of peripherally synthesized steroids, many steroids are synthesized in the brain itself and act locally within the brain or efflux into circulation to modulate peripheral events (Asaba et al., 2000; Steckelbroeck et al., 2004). The concept of neurosteroids, postulated by Baulieu and colleagues in the early eighties, was developed in recognition of the fact that brain
concentrations of some steroids, such as DHEA would remain elevated weeks after peripheral sources were removed. Researchers have since identified most of the enzymes required for de novo steroidogenesis within the central nervous system suggesting that the brain is a major source of steroid production (Martini, Melcangi & Maggi, 1993; Steckelbroek et al., 2004).

**Neurosteroids, Neurotransmitters and Behavior**

The effects of steroid hormones are mediated through a variety of extracellular and intracellular mechanisms. Original theories of endocrine mediated behavior change stressed the long term changes in cellular function generated by transcription. The recognition of rapid and quickly dissipating cellular change led to the discovery of extra-cellular steroid receptors. Finally, recent investigations have identified “ligand-independent” steroid receptor and intra-cellular signaling pathway activation whereby environmental factors stimulate receptor mediated protein transcription, up-regulating receptor expression in the absence of the cognate ligand binding (Braustein, 2004).

Because of their lipid status, unbound hormones easily diffuse through the cell membrane where it binds to heat shock proteins (Hsp) and is shuttled to the cell nucleus. After dissociating from the Hsp, the hormone binds with a nuclear receptor. The hormone-receptor complex then enters the nucleus, binds to hormone response elements on the DNA, activates or suppresses transcription factors and triggers RNA dependent protein synthesis to regulate changes in cell structure and function. Transcriptional effects develop over an extended course and as a consequence, the
hormone/behaivior relationship was thought to involve only long term changes in cell activity (Birzniece, 2006).

Among the steroid hormones estradiol is a particularly potent transcriptional regulator controlling the activity of 438 genes with 132 genes up-regulated in its presence and 306 down-regulated (Frasor et al., 2003). Estradiol, through its two receptors the ERα and ERβ, with area specific distribution in the CNS (ERα: hypothalamus and amygdala; ERβ: hippocampus, entorhinal cortex and thalamus) is thought to influence autonomic activity, reproduction (ERα) and memory and motor functions (ERβ). Indeed rodent studies have demonstrated that estradiol administration induces female sexual receptivity through ERα (for a review see Osterlund & Hurd, 2001) but also hippocampal synaptogenesis through ERβ (McEwen, et al., 2001) and learning (Chestler & Juraska, 2000; Frye & Sturgis, 1998; Johansen, Birzniece, Lindblad, Olson & Backstrom, 2002; Shors & Leuner, 2003). Estradiol’s role in rodent learning involves, the enhancement of long term potentiation via n-methyl-d-aspartate (NMDA) binding (Shors, Falduto & Leuner, 2004; Smith & McMahon, 2005) and/or aceytltransferase induction (McEwen, 1998). Similarly, studies in postmenopausal women show estrogen administration improves verbal memory and well-being (de Noaves-Suarez et al., 2001; Maki, Zonderman & Resnick, 2001; Hogervorst et al., 1999). In pre-menopausal women estradiol concentrations during the follicular phase of the cycle correlate with better verbal memory but poor spatial memory (Hampson, 1990).

Of note, the two estrogen receptors express similar binding domains but distinctly different activation patterns with ERβ requiring 100-1000 greater
concentrations of estradiol to activate transcription than ERα (Osterlund & Hurd, 2001). Researchers propose that ERβ binding suppresses ERα expression and transcriptional activation. Behaviorally, the relationship between receptor expression and binding has not been investigated, but poses some interesting possibilities regarding estradiol’s role in emotional learning. Continued activation of the ERα and the ensuing sexual receptivity ultimately activates the ERβ in areas where learning is thought to occur and ultimately inhibits ERα mediated sexual receptivity. Pharmacological antagonism of ERα also blocks receptivity (Osterlund & Hurd, 2001). In states of elevated estradiol such as pregnancy, the balance between these two receptors could have evolved to align reproductive proclivities with fertility (ovulation) and to limit reproductive behavior once pregnant with the cognitive consequences simply an artifact of this process.

In recent years ligand-dependent extra-cellular receptors that mediate rapid, short-term responses have been identified and are closely linked with mood states. Most notably are those associated with the γ-aminobutyric acid (GABA) receptor complex, the NMDA glutamate receptors and dopamine (DA) receptors. Pregnenolone, pregnenolone sulfate, progesterone, allopregnanolone, DHEA and DHEAS all bind with and exert differential influence over the GABA_A receptor complex (Charalampopoulos et al., 2005; Gullinello & Smith, 2003; Sousa & Ticku, 1997; Valle et al., 1997). Progesterone, estradiol, DHEA and DHEAS modulate glutamate and DA and estradiol and DHEA modulate serotonin (5HT) (Birzniece et al., 2006; Cabrera et al., 2002; Cabrera & Navarro, 1996; Charalampopoulos et al., 2005; Compagnone & Mellon, 1998; Fink et al., 1999; Hou et al., 2003).
Regulation of GABA and glutamate activity because of their control over neuronal excitability may represent the most pervasive examples of the relationship between steroid hormones and brain function and subsequent changes in behavior. The GABA<sub>A</sub> receptor in particular exhibits distinctive binding/activity patterns with each of the aforementioned hormones based upon the chronicity of exposure and perhaps also the CNS location of the GABA cells (Birzniece et al., 2006). The GABA<sub>A</sub> receptor complex is composed of 18 subunits, currently divided into five functionally distinct families (Birzniece et al., 2006). The conformation of these subunits alters the behavior of the GABA cell by rendering the receptors more or less susceptible to endogenous GABA and other endogenous or synthetic compounds (Birzniece 2006; Fuji & Mellon, 2001; Hsu & Smith, 2002; Gulinello & Smith, 2003).

Although multiple hormones bind to and exert influence with the GABA<sub>A</sub> receptors, the influence of progesterone, DHEAS and to a lesser degree DHEA are the most clearly elucidated and will be the focus of the discussion. Progesterone, either alone or via its metabolite allopregnenelone, like the benzodiazepines (BDZ) and alcohol, is a potent sedative-hypnotic and anxiolytic. Similar to BDZ and alcohol, acute administration of progesterone increases GABA chloride (Cl-) channel open time to produce sedation, even anesthesia and respiratory failure (Arafat et al., 1988; Concas et al., 1998; Selye, 1941). These effects are mediated by binding with the α-1 subunit (Gulinello & Smith, 2003; Gulinello, Gong & Smith, 2001). The anxiolytic effects of these compounds are believed to be mediated by α-2, α-3, α-4 subunits (Gulinello & Smith, 2003; Gulinello, Gong & Smith, 2001). Chronic exposure to
progesterone, its metabolites, BDZ or alcohol up-regulates the activity of α-4 and α-6 subunits. When the α-4 and α-6 subunits are expressed in greater numbers than α-1 through α-3 subunits and in combination with other subunits, BDZ and progesterone do not bind as effectively to the receptor and GABA<sub>A</sub> Cl- channel open time is reduced significantly (Concas et al., 1998; Costa, Spence, Smith & French-Mullen, 1995). The net behavioral effect is CNS hyper-excitability and anxiogenesis.

Benzodiazepine research suggests that tolerance to chronic administration develops in phases with the gradual change in GABA<sub>A</sub> receptor confirmation and binding preferences. The sedative properties of the drug are lost initially (α-1) followed by the loss of anticonvulsant and anxiolytic subunits (α-2, α-3, α-4). Concomitantly, α-amino-3-hydroxy-5-methyl-4-isoazole proprionic acid (AMPA) receptor density increases and glutaminergic transmission is enhanced, particularly in the hippocampus and the frontal and occipital cortices (Izzo et al., 2000). It is reasonable to suspect that progesterone tolerance in pregnancy develops similarly.

Thus, based upon this research, chronic exposure to progesterone and its metabolites, as occurs during pregnancy would be expected elicit anxiety via conformational changes in the receptor, reduced GABA inhibition (Concas et al., 1998; Costa et al., 1995; Gulinello & Smith, 2003; Gulinello, Gong & Smith, 2001) and enhanced glutaminergic transmission (Cabrera & Bregonzia, 1995; Cabrera & Navaro, 1996; Cyr, Ghribi, DiPaolo, 2000). Moreover, as is the case with BDZ and alcohol withdrawal, the cessation of progesterone exposure following parturition, should precipitate some degree of mood instability characterized by agitation and anxiety. The behavioral manifestations of these changes alone (absent other major

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endocrine mediated responses) could represent the commonly reported and transient postpartum mood lability. As will be discussed in the subsequent sections, there is some research to support this hypothesis.

However, pregnancy is marked by significant endocrine changes that when combined seem to exert disproportionate influence on the GABAergic and glutaminergic systems. Briefly, Marrs (2006) reported a marked increase in postpartum concentrations of DHEAS that was associated with increased psychiatric distress. DHEAS is a potent GABA_A antagonist blocking GABA transmission with similar efficacy and from a proximally located receptor as that of picrotoxin, a potent convulsant (Sousa & Ticku, 1998). DHEAS also influences NMDA mediated release of norepinephrine (NE) and DA (Charalampopoulos et al., 2005). Against the backdrop of the expected rise and fall of progesterone and estradiol, large changes in DHEAS would fundamentally alter CNS excitability, particularly in the immediate puerperium when neither the compensatory enzymatic changes responsible for clearing the excess DHEAS will have occurred nor will the pre-progesterone exposure mediated conformational changes in the GABA_A receptor have returned.

Finally, it appears that the expression of both genomic progesterone (PR) and estradiol and probably also androgen receptors (AR) can be controlled independently of cognate ligand binding (for a review see Braunstein, 2004). Environmental stimuli, especially those involved with sexual and parenting behaviors, activate a number of intracellular signaling pathways including protein kinases A, G and MAPK absent hormone-receptor binding. Dopamine, insulin and other growth factors have been investigated thus far and have been shown to up-regulate and mediate steroid
hormone receptor regulated transcription in the absence of the cognate ligand without
inducing the associated hormone synthesis. The D1/D5 DA receptor agonists, in
particular, can substitute for progesterone in the facilitation sexual behavior in mice.
Other examples include NE induced neural PR and ER up-regulation and muscarinic
mediated ER up-regulation (Braunstein, 2004).

**Puerperal Hormones and Psychiatric Symptoms**

Based upon the supra-physiological concentrations of progesterone and
estradiol during pregnancy, the chronicity of exposure to these hormones and their
respective actions on individual neurotransmitter systems, but particularly
progesterone’s actions on GABA\textsubscript{A} receptor, one might expect signs of tolerance
towards the end of pregnancy, with withdrawal symptoms evident in the early
puerperium. Based upon models of addiction and withdrawal to synthetic compounds
that elicit similar changes in neurotransmitter and receptor availability, suggest these
symptoms would likely be marked by agitation and/or anxiety type symptoms.
Unfortunately, over the last 30 years relatively few investigators have explored the
connection between these reproductive hormones and psychiatric disturbances and
most have focused upon the measurement of depressive symptoms.

The results are equivocal but suggest a relationship between the magnitude of
change from pre- to postpartum concentrations of progesterone, estradiol and/or
estriol and the ambiguously defined baby blues. As was the case with the previously
cited non-endocrine investigations of postpartum mood, methodological differences
abound making direct comparison between individual projects difficult.
In one of the earliest attempts to connect reproductive hormones and mood, Nott et al. (1976) measured serum estradiol and progesterone in 27 primiparous and multiparous women three times at weekly intervals from 2-6 weeks pre-delivery and intermittently through 5-10 post-delivery. Their results indicated that higher pre-delivery estradiol was correlated with increased antenatal irritability and lower post-delivery estradiol was correlated with increased postpartum sleep disturbances. The magnitude of change from pre-delivery progesterone to post-delivery progesterone correlated with depression at 10 days postpartum but was negatively correlated with postnatal sleep disturbances.

O'Hara, Schechle, Lewis and Wright, (1991) and Metz et al. (1983), measured plasma progesterone and estrogen concentrations at various times both pre- and postnatally. O'Hara and colleagues found a significant positive relationship between antepartum free and total estriol levels and postpartum blues. Metz, et al. found no direct correlation between ovarian hormones and mood, but did show that the magnitude of fall in hormones was positively correlated with \( \alpha_2 \)-adrenoreceptor binding capacity, which was in turn correlated with measures of postpartum mood lability. The \( \alpha_2 \) adrenoreceptors are inhibitory autoreceptors located on NE cells in the locus ceruleus. When bound to the ligand, \( \alpha_2 \) limits the cell firing and neurotransmitter release. Increased binding capacity of these receptors would indicate a compensatory response by the cell to limit neurotransmitter release. The association observed by Metz et al. (1983) between increased \( \alpha_2 \) binding capacity and hormone magnitude of change and mood lability suggests a connection between puerperal hormones and NE production.
Kuevi, et al. (1983) reported a trend towards higher follicle stimulating hormone and lower estrogen and progesterone concentrations in women with the blues, particularly those women who showed a consistent state of 'blues' versus women who experienced brief periods of mood lability. Gard, Handley, Parsons and Waldron, (1986) reported a higher incidence of postpartum blues with the birth of a male child and/or a previous history of gynecological disorder.

The Cardiff study, (Harris et al. 1994) assessed salivary concentrations of progesterone and cortisol from 120 women over a period from two weeks pre-delivery through four weeks post-delivery. With almost 10,000 salivary samples collected, Harris and colleagues demonstrated a positive relationship in the magnitude of change between antenatal and postnatal progesterone and depression scores measured by EPDS, the Stein Scale for Maternity Blues and the Beck Depression Inventory. They found no relationship between cortisol and depression. Nappi et al. (2001) identified a significant negative correlation between serum allopregnanolone (progesterone metabolite) and blues when measured three days postpartum but was unable to identify an association between progesterone and blues.

The research presented thus far suggests that there is some relationship between hormone change and baby blues. Which hormone contributes to which type of symptom is unclear because of the lack of specificity in the psychological measures that were administered as well as differences in test time and in hormone collection method. A more informative approach to characterizing the nature of puerperal psychiatric symptoms and subsequent associations with hormones would include assessment of a broader range of symptoms and a larger complement of
hormones. This was accomplished by Buckwalter and associates (1999) who measured serum progesterone, estradiol, DHEA and testosterone concentrations at 36 weeks of pregnancy (n=19) and at 1-2 months postpartum (n=15). They found that higher DHEA levels during pregnancy were correlated with better mood scores while elevated postpartum testosterone was associated with negative mood. DHEA, unlike DHEAS exerts only nominal influence over the GABAergic cells but is reported to attenuate glucocorticoid induced glutamate cytotoxicity in rodent models (Herbert, 1998) suggesting that the balance between these DHEA and DHEAS is a factor in CNS excitability.

Hohlagswandter et al., (2001) also found elevated serum testosterone levels to be significantly associated with pre- and postpartum depression and with pre- and postpartum anger. More recently, Paoletti et al. (2006) measured serum DHEAS and cortisol levels in 14 healthy pregnant women across two menstrual cycles prior to pregnancy and throughout the pregnancy and compared those data to psychometric data from the SCL-90. They were unable to find any difference between non-pregnant and pregnant SCL-90 scores and thus concluded that puerperal mental illness does not exist.

Finally, Marrs (2006) measured salivary progesterone, DHEAS, testosterone, estrone, estradiol and estriol at 37 weeks pregnancy (n=32) and within 10 days postpartum (n=28) in a cohort of healthy primigravid women and found measurable psychiatric disturbances associated with androgenic steroid concentrations. Elevated prenatal DHEAS correlated positively with prenatal paranoia and psychoticism while prenatal testosterone correlated negatively with prenatal phobia, psychoticism,
somatization and the GSI. Diminished prenatal testosterone also heralded the onset and exacerbation of postnatal symptoms and was correlated with increased postnatal anxiety, hostility, psychoticism, somatization, obsessive compulsive behavior, interpersonal sensitivity, depression and the GSI. Following parturition both DHEAS concentrations and the frequency and severity of psychiatric disturbances increased. Postnatal DHEAS correlated positively with postnatal anxiety, phobia, paranoia, psychoticism, somatization and the GSI. Progesterone, estrone and estriol were not associated with psychiatric disturbances and associations with estradiol were limited and inconsistent.

Both the Marrs and the Buckwalter findings are consistent with the putative neuromodulatory actions of DHEA and DHEAS. Because DHEA is more consistently associated with neuroprotection and stress reduction, positive correlations between DHEA and improved mood are expected. Conversely, the actions DHEAS on GABA_A would predict CNS excitability producing a positive correlation between elevated DHEAS and symptoms of anxiety. The apparent disparity in testosterone findings are likely related to differences in matrix, serum versus saliva and the measurement of bound versus free hormone. While elevated total hormone concentrations may indeed be related to increased symptomatology, as was suggested by Buckwalter et al. (1999) and Hohlagswandter et al., (2001) the diminishment of free or bioactive testosterone observed by Marrs (2006), may be also be linked to psychiatric disturbances. These findings may suggest that changes in hormone binding rather than absolute circulating concentrations underlie these correlations.
The pattern of high DHEAS and low testosterone, combined with postpartal increase in DHEAS values observed in the Marrs study could also point to altered patterns of hormone metabolism wherein prenatal testosterone is simply an early marker of the ensuing changes. Serum DHEAS values, investigated in relation to the onset of labor, are reported to increase in the first two trimesters, remain stable in the third and return to non-pregnant values following parturition (Milewich et al., 1978; Soldin et al., 2005; Tagawa et al., 2004). In the Marrs study, salivary DHEAS concentrations were high in late pregnancy and increased by an average of 34% following parturition, with those participants exhibiting the largest increases, also suffering the most severe psychiatric disturbances. Moreover, four participants of the 28 who completed the testing, exceeded and many others approached the laboratory standards indicative adrenal pathology (>2500pg/mL) that typically merit further investigation.

With elevated DHEAS concentrations in general, testosterone concentrations are typically elevated as well. During pregnancy in particular, testosterone is presumed to increase significantly but fall to pre-pregnancy concentrations following parturition (Bammann, Coulam & Jiang, 1980). This appeared not to be the case in the Marrs study. Both pregnancy and postpartum testosterone concentrations were very low when compared to healthy non-pregnant women and were found to increase rather than decrease in five women following parturition, although as a group testosterone concentrations fell by 49%. In addition, low late pregnancy testosterone concentrations were associated with a myriad of psychiatric symptoms during
pregnancy but more importantly heralded the onset and exacerbation of postpartal psychiatric disturbances.

This hormone pattern, high DHEAS and low testosterone, is unique insofar as it not only conflicts with the published trends expected for these hormones when measured in serum, but because it was so strongly associated with psychiatric disturbance. Had these values been observed without consistent association to psychiatric disturbances, one might question their accuracy, but when combined with the symptomatology, they become evidence for a putative endocrine role in postpartum psychiatric dysfunction. Thus, low late pregnancy testosterone combined with elevated pre- and postpartum DHEAS concentrations not only represented an atypical pattern in hormone metabolism but were linked with significant psychopathology. When these data are combined with those of Buckwalter et al. (1999) and Hohlagswandter et al. (2001), adrenal androgen regulation becomes a key factor in peripartal mental health.

Puerperal Hormones and Cognition

In as much as the vast hormone changes associated with pregnancy and parturition may elicit psychiatric distress, they may also alter cognitive function. Indeed, from the research presented earlier, pregnancy related cognitive impairment is widely expected and anecdotally accepted. Unfortunately, consistent empirical measurement and characterization of pregnancy related cognitive decline has thus far eluded investigators. Moreover, only three studies to date have actually measured puerperal hormones in conjunction with cognitive performance. The Vanston (2006)
study, which was discussed previously, found no evidence of impairment and no association between cognitive performance and hormones.

Both Buckwalter et al. (1999) and Marrs (2006) identified significant impairment in both pregnant and postpartum women across multiple cognitive domains but were unable to show consistent trends between individual hormones and specific cognitive modalities. However, the Marrs study did demonstrate a trend between higher hormone values in general and poorer cognitive performance overall. With so few investigations measuring puerperal hormones in conjunction with cognitive assessment, it is difficult to entirely discount the possibility of a hormone to cognition relationship, especially given the ample animal research that clearly demonstrates associations between hormones and learning (Chestler & Juraska, 2000; Frye & Sturgis, 1998; Johansen, Birzniece, Lindblad, Olson & Backstrom, 2002; Shors & Leuner 2003).

Summary

The general presumption about reproductive hormones is that they increase exponentially throughout the pregnancy and decrease rapidly following parturition. Accordingly, most postpartum research is based upon and supports this hypothesis (Darne, McGarigle & Lachelin, 1987; Harris, et al., 1993; Harris et al., 1994) including work by Marrs. The Marrs study found that progesterone estrone, estradiol and estriol were elevated in late pregnancy and generally declined following parturition. Estrone and estradiol concentrations increased in a few participants (one and three respectively) following parturition. Inasmuch as these changes are considered normal and have been associated, at least inconsistently, with the baby
blues some argue that pregnancy hormone changes are not directly responsible for the more serious symptoms of puerperal mental illness, but merely provide the backdrop for the re-emergence of a pre-existing condition and/or trigger an aberrant psychosocial response (Bloch et al., 2000). While it cannot be disputed that puerperal hormone changes might trigger the re-emergence of pre-existing conditions and might also elicit an ill-adapted stress response in some women, this hypothesis cannot explain the onset of serious psychiatric disturbances in previously healthy women immediately coincident with parturition.

A more accurate hypothesis, particularly in light of the unique pattern in adrenal androgen values reported by Marrs (2006), would be that the large changes in reproductive hormones either unmask a pre-existing endocrine condition and/or trigger an aberrant compensatory reaction in steroidogenesis. In either case, psychiatric symptoms might simply represent the outward manifestation of a disrupted internal chemistry. Of the questions that need to be addressed is whether either of those reactions is physiologically possible. Inasmuch as this pattern of circulating adrenal androgens has not been identified in other clinical disorders and adrenal androgens in general have not been considered to be a major determinant of pregnancy related psychiatric disturbances, a review of the literature pertaining to both the biological and pharmacological actions of these hormones is presented.
Biological and Pharmacological Actions of DHEAS and Testosterone

DHEAS and Testosterone Synthesis in Women

DHEA and its sulfated ester DHEAS, are synthesized primarily in the zona reticularis of the adrenal gland and, to a lesser extent, from ovarian granulosa and theca cells (Bonser et al., 2000; Burger, 2002). DHEAS is the most abundant adrenal androgen in human circulation (Hammer, et al., Rainey et al. 2002; Roberts, 1999) followed by cortisol and DHEA (Herbert, 1998). DHEA/DHEAS concentrations are elevated at birth, surge during adrenarche and reach their peak in early adulthood, declining substantially through senescence (Kroboth, 1999).

DHEA is the precursor for other adrenal androgens such as androstenedione and testosterone and after aromatization estrone and estradiol (Hammer et al., 2005; Roberts, 1999). During pregnancy, fetal adrenals produce vast quantities of DHEAS, from which estriol the most abundant estrogen of pregnancy, is derived (Challis & Lye, 1998). DHEA synthesized in the adrenal gland, is rapidly inactivated via conversion to its sulfate ester DHEAS (Bird et al., 1978; Burger, 2002; Hammer et al., 2005; Roberts, 1999).

Conversion of DHEA to DHEAS is dependant upon cytosolic enzymes called sulfotransferases, specifically identified as SULT2A1 (Hammer et al., 2005; Mensah-Nyagan et al., 1999). SULT2A1 are expressed in the adrenal glands, the intestines and the liver (Hammer et al., 2005). Circulating DHEAS is converted back into DHEA via the microsomal sulfatase (STS) (Hammer et al., 2005; Mensah-Nyagan et al. 1999). The sulfatase enzymes are widely distributed throughout the body and have been found in the testes, ovaries, adrenals, prostate, skin, central nervous system.
(CNS), fetal lungs, placenta, synovial fluid, endometrial tissue, peripheral blood lymphocytes, aorta, bone, kidneys and in breast cancer cells (Reed et al., 2005). Interestingly, STS activity is negligible in the adult liver (Hammer et al., 2005).

Conversion of DHEA to DHEAS and back varies across the life span, disease states and reproductive states (Kroboth et al., 1999; Salek, Bigos & Kroboth, 2002). Concomitant changes in androgen and estrogen production often follow suit. In non-pregnant women, approximately 64% of DHEAS is converted to the biologically active DHEA whereas only 13% DHEA is converted to DHEAS (Kroboth et al., 1999; Salek, Bigos & Kroboth, 2002). During pregnancy DHEAS production is significantly up-regulated with both maternal and fetal adrenal glands contributing substantially to its synthesis (Challis & Lye, 1998). The rates of DHEA>DHEAS>DHEA conversion during pregnancy are not known, however, conversion of DHEAS to DHEA during pregnancy is facilitated by the abundant expression of placental STS (Dibbelt & Kuss, 1991).

The fraction of testosterone produced by placental conversion of DHEAS relative to maternal input is unknown. However, data based upon ratios of maternal circulating levels to umbilical cord levels indicate that placental testosterone (Troisi et al., 2003) and fetal adrenal contributions (Dharia et al., 2004) are minimal with most aromatased to the estrogens. Accordingly, fetal and placental conversion of DHEAS are responsible for 50%, 50% and 90% of estrone, estradiol and estriol respectively (Challis & Lye, 1998) with remaining portions synthesized in maternal adrenal and peripheral tissue. According to Kroboth et al. 1999, the DHEA/ DHEAS
pathway accounts for up to 100% of active estrogens in menopausal women and 75% of estrogen synthesis in non-pregnant, pre-menopausal women.

**Pharmacodynamics of DHEA and DHEAS**

In addition to peripheral synthesis, DHEA and DHEAS are synthesized in the brain de novo and interact with each of the neurotransmitters (Baulieu, 1998). DHEAS is both a GABA<sub>A</sub> antagonist and dopamine DA agonist (Hansen, Fjalland & Jackson 1999). Like many sulfated steroids, DHEAS inhibits GABA<sub>A</sub> chloride channels (Mehta & Ticku 2001). DHEAS is also involved in both NMDA associated release of NE and DA, as well as tyrosine hydroxylase induction, particularly with long-term administration (Charalampopoulos et al., 2005).

The research on DHEA is less clear but suggests that DHEA has some capacity to inhibit GABA<sub>A</sub>, and enhance NMDA mediated NE release, if only acutely (Charalampopoulos, et al., 2005). This has lead researchers to postulate that DHEA requires conversion to DHEAS to exert its full neuromodulatory action (Charalampopoulous, et al., 2005). Other research suggests that DHEA and DHEAS differentially modulate GABA<sub>A</sub> according to brain region and time course of administration (Mehta & Ticku, 2001; Hanson, Fjalland & Jackson, 1999). Accordingly, DHEAS but not DHEA binds to GABA<sub>A</sub> site proximal to the picrotoxin binding site (Sousa & Ticku, 1997) whereas, DHEA, reportedly attenuates glucocorticoid and glutamate cytotoxicity (Herbert, 1998). Lu and colleagues (2003) reported that DHEA works synergistically with testosterone to prevent neuronal and cell death in rodent models by up-regulating ARs. The putative mechanism of neuroprotection is the testosterone-AR complex activation of the mitogen-activated
protein kinase / extracellular signal regulated kinase (MAPK/ERK) pathway (Nguyen, Yao & Pike, 2005). The MAPK/ERK is a signal transduction pathway responsible for cell growth and differentiation, inflammation and apoptosis. Conversely, DHEAS is not involved in AR receptor regulation (Mo, Lu & Simon, 2004).

If DHEA, but not DHEAS, offers neuroprotection against cytotoxicity and DHEAS but not DHEA chronically antagonizes the GABA \textsubscript{A} receptor, then the equilibrium between the two hormones becomes clinically relevant in both physiological and psychological disease states. Changes in enzyme availability, occurring during pregnancy, following parturition and perhaps even as breastfeeding begins or ceases, would necessarily alter the hormonal milieu and by association, central nervous system excitability. Although relevant evidence in the puerperium is limited, changes in the circulating concentrations of either DHEA or DHEAS observed in other endocrine pathologies reveal that both abnormally low and abnormally high circulating concentrations adversely impact both psychological and physiological well-being.

*Adrenal Androgens and Mental Health*

In conditions where DHEA/DHEAS are abnormally low such as in the elderly, individuals with Addison’s disease (Hunt et al., 2000), rheumatoid arthritis, systemic lupus erythematosus (Nordmark et al., 2005), human immunodeficiency virus (Schifitto et al., 2000) or adrenal insufficiency syndromes (Arlt, 2003; Arlt et al., 2005), supplementation improves mood, cognitive function and general well-being (Bloch et al., 1999; van Niekerk, Huppert & Herbert, 2001; Wolf, 2003; Wolf et al.,
Similarly, lower salivary DHEA levels have been noted in clinically depressed older adults (Michael, Jenaway, Paykel & Herbert, 2000).

In adrenal disease states where DHEAS levels are abnormally elevated (Dubrovsky, 2005) and in anabolic steroid use where excessive amounts of DHEA is taken as a supplement concomitant psychological disturbances and autonomic hyperactivity have been reported (Cafri, et al., 2005; Trenton & Currier, 2005). Moreover, a number of clinical case reports indicate that abnormally elevated DHEA and/or DHEAS concentrations elicit symptoms of anxiety, mania and psychosis that are in some cases resistant to traditional therapeutic approaches and abate only when hormone concentrations are brought in check (Dean, 2000; Howard, 1992; Jacobs et al., 1999; Markowitz, Carson & Jackson, 1999).

In patients with treatment refractory depressed psychosis, defined as resistant to psychotropic medication and electroconvulsive therapy (ECT), both DHEA and DHEAS levels were elevated compared to controls and predictive of ECT non-response (Maayan et al., 2000). Interestingly, the investigators found that neither pre-nor post-treatment DHEA and DHEAS changed significantly for either the responders or non-responders, perhaps suggesting a third factor associated with the behavioral outcome. It is also likely, that the substantial inter-individual variability commonly observed in hormone concentrations were concealed by comparison of mean data.

Individuals with treatment refractory anxiety disorder, associated with late-onset congenital adrenal hyperplasia exhibited elevated DHEAS values that were associated with increased anxiety scores on the Profile of Mood States questionnaire (Jacobs et al., 1999). Upon adrenal suppression treatment via either ketoconazole or
low dose glucocorticoids, anxiety scores decreased by 55%, concurrent with a 10% reduction of DHEAS, returning DHEAS concentrations to within normal physiological parameters. Depression scores were inconsistent and not related to DHEAS in this study.

In the schizophrenic disorders, researchers have demonstrated aberrant patterns in adrenal androgen concentrations, marked by elevated DHEA and/or diminished DHEAS. Michele et al. (2005) found plasma DHEA concentrations significantly increased in 23 schizophrenic patients versus 23 healthy controls. The data remained significant even when the groups were divided by gender. Males reportedly have higher circulating concentrations of DHEA (Roberts, 1999). Similarly, Ritsner and colleagues (2006) found significantly elevated DHEA concentrations in 21 male paranoid schizophrenics as compared to 14 healthy controls combined with significantly lower DHEAS and higher androstenedione concentrations in the patient group and normal concentrations of progesterone and testosterone. The researchers speculated that these patterns may represent a trait-like marker of impaired HPA or HPG activity that is characterized by decreased sulfotransferase and/or 17β-hydroxylase activity combined with increased 3β-hydroxysteroid dehydrogenase activity (Ritsner, Gibel, Ram, Maayan & Weizman, 2006).

Alternatively, a polymorphism in the enzyme that is responsible for the metabolism of many mixed oxidase reactions in the human liver the CYP3A4, yields a variation of the fetal enzyme CYP3A7 not normally present in adult livers that results in up to a 50% reduction in DHEAS concentrations (Smit et al., 2005). As
many of the medications commonly prescribed to patients with schizophrenia utilize CYP3A4 metabolism (Dahl, 2002) individuals possessing this polymorphism might present with anomalous reactions to medication in addition to the reduction in DHEAS concentrations.

The data on DHEA/DHEAS role in depression is mixed. Fabian et al. (2001) found that measurable decreases in both DHEA and DHEAS were associated with remission of clinical depression in the elderly. Whereas Michael et al. (2000) found that depression in the elderly was linked to lower levels of DHEA and DHEAS. The disparity between these results is possibly explained by methodological differences and/or by the kinetics of these hormones. DHEA has a very short half-life, (1-3 hours) (Roberts, 1999), is susceptible to diurnal rhythms, food and medication intake and has been reported to fluctuate wildly from hour to hour (Kroboth et al., 1999). Conversely, DHEAS has a longer half-life (10-20 hours) (Carlstrom, Karlsson & Von Schoultz, 2002) is more stable across time, but is susceptible to modulation by medication (Kroboth et al., 1999; Salek, Bigos & Kroboth, 2002), a common confounding variable in elderly populations.

Alternatively, the presence of depression in these populations could develop secondarily to a disrupted autonomic system, characterized by both somatic and psychiatric symptoms of anxiety. This was the case in Hsiao (2006) who measured DHEAS in a non-age restricted cohort of patients suffering an episode of clinical depression and found that DHEAS concentrations were significantly associated with the severity of co-morbid anxiety, but not associated with depression. Hsiao’s work is consistent with other studies, including Marrs (2006) and case reports that have

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shown elevated DHEAS is more closely associated the agitated states ranging from anxiety to mania and psychosis than with depressed states, even though depression may co-occur and may be significant. Likewise, the antagonistic actions of DHEAS at the GABA<sub>A</sub> receptor predict CNS hyper-excitability rather than depression.

Clinical Findings Associated with DHEA/DHEAS and Testosterone

In clinical disorders where DHEA/DHEAS concentrations are elevated, testosterone and estrogen concentrations are typically elevated as well. In women, elevated adrenal androgens result in a myriad of reproductive disorders often visually identified by hirsutism and virilization (Carr, 2001; Elsenbruch, 2003; Yildiz, 2004) with or without the concomitant diagnoses of polycystic ovarian syndrome (PCOS). PCOS, which is characterized chronic anovulation and variety of metabolic disorders, is thought to be caused by supra-physiological concentrations of DHEA/DHEAS, testosterone and estradiol and is commonly associated with both mild and severe psychiatric disturbances (Elsenbruch et al., 2003; Yildiz, 2004). Although it is not clear if the risk for psychiatric disturbance in women with PCOS is higher than that of the general population. Of note, there is a significantly higher incidence of PCOS in women with either bipolar disorder or epilepsy who are treated with valproic acid versus women treated with other compounds (Betts, Yarrow, Dutton, Greenhill & Rolfe 2003; Klipstein & Goldberg 2006). Whether valproic acid causes or simply triggers a pre-existing endocrine pathology remains to be elucidated. There are currently no endocrine evaluations reported for medication naïve patients.

In clinical disorders with low testosterone only, patients are noted to show decrements in mood and cognitive functioning (Arlt, 2003; Cherrier et al., 2001;
Wolf, 2003). It must be noted however, that research on low testosterone typically involves elderly males with hypogonadal function (Beuna et al., 1993; Burris, Banks, Carter, Davidson & Sherins, 1992; Carani et al., 1990). Of the research involving women, most is performed on postmenopausal women with reduced libido (Burger et al., 1984; Sherwin, Gelfand & Brender 1985; Vermeulan, 1976). Research on military performance, again with males, demonstrates that testosterone concentrations decrease over the course of intense military training in relation to increased cortisol production suggesting that low testosterone is a marker of hypothalamic-pituitary activation (Lieberman et al., 2005). Additionally, when under severe stress, elderly patients exhibit diminished testosterone levels concurrent to elevated cortisol (Dharia et al., 2004).

Finally, Akhondzadeh et al. (2006), reported that significantly lower testosterone concentrations were associated with symptom severity in male patients with schizophrenia (n=54) either in general when compared to healthy controls (n=25) and significantly lower testosterone concentrations were noted in those patients with predominantly negative symptoms (n=27) when compared to those with predominantly positive symptoms (n=33). Moreover, testosterone was inversely correlated with negative symptom severity. The researchers also found other endocrine abnormalities including significantly lower concentrations of follicle stimulating hormone (required for sperm formation) and lutenizing hormone (augments testosterone production) combined with significantly elevated prolactin (associated with impotence and loss of libido) concentrations in the negative symptom group when compared to the positive symptom and control groups.
Since dopamine inhibits prolactin, dopamine receptor blockade by neuroleptics often results in increased prolactin. However, all but three of the schizophrenia group were on the same medication, risperidone (n=51) and thus the difference in prolactin concentrations between the negative and positive symptom groups is not likely accounted for by differences in medication. Those changes could, however, be related to medication induced changes in other hormones that affect DA concentrations.

A study by Van den Berghe and colleagues (1995) found that DA suppresses DHEAS which in turn inhibits prolactin in critically ill patients. The complete circuit has yet to be elucidated, but lower DA as would be expected with neuroleptic treatment, could suggest higher DHEAS. If relatively less DHEAS is converted into DHEA and subsequently testosterone then this reaction could account for the lower testosterone concentrations in patients with negative schizophrenia. Additionally, lower DA would increase DHEAS concentrations while concomitantly increasing prolactin either via the relinquishment of the tonic inhibition the DA exerts over prolactin in the tuberoinfundibular pathway or via some other mechanism moderated by DHEA/DHEAS pathway. Alternatively, the decrease in FSH, LH combined with the increase in prolactin in patients with negative versus positive symptoms of schizophrenia could simply indicate a relative down-regulation of sexual/reproductive function consistent with diminishment of other behavioral capacities.

Physiological and Pharmacological Actions of Testosterone

The role of increased testosterone in aggressive behavior has been thoroughly investigated in both human and animal models, but a definitive neuroendocrine
mechanism has not been articulated (Albert, Walsh & Jonik, 1993; Archer 2004). Moreover, for as much as increased testosterone has been associated with aggression in criminal populations, clinically this is has not been the case (Pope, Kouri & Hudson 2007). Hypogonadal males given testosterone supplements rarely show aggression even as testosterone concentrations increase to supra-physiological values (Albert, Walsh & Jonik 1993). Although female hyperandrogenism is often associated with psychiatric disturbances, concomitant elevations in testosterone are not correlated with aggression (Weiner, Primeau & Ehrlmann 2004). The lack of relationship between testosterone and aggression in non-criminal populations makes sense in light of testosterone’s mechanism of action at the cellular level.

In very recent research, testosterone has been found to be a fairly potent calcium channel blocker in the coronary artery and also in uterine myometrial cells (Jones, Pugh, Jones & Channer 2003; Perusquia, Navarret, Jasso-Kamel & Montano, 2005). Subsequently, and contrary to popular belief, researchers are finding that diminished rather than elevated testosterone confers a markedly increased rate of coronary artery disease in men (Jones, et al., 2003). Further investigation suggests testosterone decreases myocardial ischemia via vasodilation specifically via L-channel calcium (Ca2+) blockade (Jones, English, Jones & Channer, 2004).

Similarly, in a study on uterine contractility, Perusquia and colleagues (2005) showed that testosterone and testosterone metabolites reduced uterine contractility in human pregnant and non-pregnant myometrial tissue (obtained via biopsy) even more so than progesterone. The purported mechanism of action was Ca2+ blockade but researchers also noted increased potassium influx causing cellular hyperpolarization.
as well as some cell membrane fluidity. Moreover, testosterone and its metabolites mediate these responses in the absence of identified nuclear androgen receptor binding (Jones et al., 2004).

In rodents testosterone acts through arginine vasopressin (AVP) and corticotrophin releasing hormone (CRH) to mediate glucocorticoid effects on neuronal response (for a review see Williamson, Bingham & Viau, 2005). Arginine vasopressin is believed to enhance CRH responsivity to acute stress. Enhanced CRH activates the pituitary hormone, adrenocorticotropin (ACTH). ACTH initiates the release of corticoids. Increased corticoids then feedback to inhibit the continued CRH/AVP synthesis to bring the system back into equilibrium. Williams et al. (2005) found androgen receptors co-localized on AVP neurons. Binding of testosterone effectively inhibits the stress related AVP up-regulation and expression which then inhibits corticoid output. In the absence of testosterone or in states of diminished testosterone, the negative feedback loop normally associated with this system is altered, AVP expression increases, which in turn increases CRH and the downstream release of corticoids. This reaction may be mediated by DHEA concentrations inasmuch as DHEA not only provides the substrate for testosterone synthesis, but also upregulates AR expression (Lu et al., 2003). Similarly, clinical research has shown that DHEA and cortisol are inversely related across multiple populations (Genazzani et al., 2003; Ueshiba et al., 2004). DHEAS on the other hand, has no effect on AR receptors (Mo, Lu, Hu & Simon, 2004).

Testosterone, however, also upregulates it own receptors. Unlike other hormones whose receptors down-regulate in the presence of ligand, ARs up-regulate...
(Patchev, Schroeder, Goetz, Rhode & Patchev, 2004) and thus more testosterone elicits more ARs while lower testosterone reduce the expression of ARs. The uniqueness of this positive feedback mechanism may have role in the presumptive associations between male dominance and/or aggressive behavior and testosterone concentrations with environmental factors reinforcing testosterone and AR activity.

Unfortunately, because testosterone is aromatized to estradiol and/or converted to dihydrotestosterone via 5α-reductase (the same enzyme that catalyzes the conversion of progesterone to allopregnanolone and/or shifts progesterone toward the cortisol pathway), it is difficult to dissociate purely androgenic from estrogenic CNS activity. Additionally, ARs and ERs show similar regional CNS distribution patterns and sequence homology to other steroid receptors as well as multiple levels of promiscuous interaction and target gene cross-regulation (Patchev et al., 2004). Moreover, both receptors demonstrate receptor-activated transcription in absence of hormone-receptor binding, but in the presence of either environmental stimuli and/or via binding with neurotransmitters (Braunstein, 2004). Nevertheless, when the molecular actions of testosterone are compared to those of estradiol, testosterone is generally inhibitory and estradiol is predominantly excitatory.

Summary

The research presented thus far provides clear evidence of an exceedingly complex relationship between neural and endocrine factors in the development of mental illness. Whether endocrine disturbances precede mental illness, develop concurrently or subsequently or are a result of medication remains to be elucidated. What is clear is that endocrine changes affect mental health.
Pregnancy and parturition offer researchers a unique model from which to study those associations. The hormone changes are vast and in some cases extreme. The abrupt withdrawal from the supra-physiological concentrations of reproductive hormones often coincides with the onset of psychiatric disturbances in previously healthy women. With such significant changes in reproductive hormones, compensatory reactions in other endocrine circuits are likely. Findings from Marrs (2006) may support this hypothesis. The low late pregnancy testosterone followed by the unexpected postpartal increase in DHEAS, not only represented a unique and previously unidentified pattern in puerperal hormones, but also, provides the first clear evidence of association between puerperal endocrine changes and the development of psychiatric symptoms in previously healthy women. Since there are no disorders currently documented that include this pattern of hormone values it is worth determining whether the profile is physiologically possible and by what mechanisms it might develop. While such a review is beyond the scope of the present research, consideration of the potential mechanisms that might produce elevated DHEAS and diminished testosterone provides useful insight regarding the uniqueness of the Marrs pattern and is included in the following section of this literature review.

Elevated DHEAS and Diminished Testosterone: Potential Mechanisms

Ideally, to investigate hormone synthesis patterns one would measure the entire pathway between the precursor (DHEAS) and product (testosterone), as well as measure the specific enzymes suspected of dysregulation. Barring that, however, it is possible to surmise which enzymes might contribute to a specific hormone profile.
based upon the presenting pattern of hormones compared with other known disorders associated with those enzyme deficiencies. Discussed below is a review of each the enzymes involved in metabolic process from DHEA/DHEAS through testosterone. In the initial sections, it is presumed that DHEAS and DHEA are in dynamic equilibrium and thus show parallel increases or decreases in circulating values. The equilibrium between these hormones is often presumed and has been validated in a number of clinical studies (for a review see Kroboth et al., 1999). There are a number of instances though where the equilibrium between these hormones is disrupted (Arlt et al., 2006; Reed et al., 2005) and thus in second part of this review those cases are considered.

Elevated or Normal DHEA Concurrent with Diminished Testosterone

Although, no disorders have been reported with high DHEAS and low testosterone, there are disorders marked by normal/high DHEA and low testosterone. Since DHEA and DHEAS concentrations are often highly correlated, the presumption is made that DHEA/DHEAS change uni-directionally. While that interpretation will be contended with regard to the Marrs (2006), it is worth investigating the disorders with high DHEA and low testosterone if only to remove them from the list of possible factors that could have contributed to the Marrs hormone profile and subsequent psychiatric disturbances. Listed below is a systematic review of enzymatic deficiencies potentially involved with high or normal DHEA and low testosterone. Please refer to Figure 2 for the following discussion.
17, 20 Lyase and 17a-Hydroxylase Activity

Two genetic variants of congenital adrenal hyperplasia (CAH) are associated with normal and/or elevated DHEA and diminished testosterone, each mediated through entirely different enzymes (Miller, 2005). Though not likely factors contributing to the hormone profile observed by Marrs (2006), these disorders provide a useful illustration of how enzymatic permutations fundamentally alter hormone metabolism. In the first variant of CAH, 17, 20 lyase activity is up-regulated while 17a-hydroxylase (17a-OH) activity is unchanged or diminished (Miller, 2005). This shifts the adrenal metabolic pathway away from the conversion of 17a-OH progesterone to androstenedione and towards the conversion of 17a-OH pregnenelone to DHEA (Miller, 2005). This shift initially produces less cortisol concurrent with increased DHEA. However, since DHEA is rapidly converted to DHEAS, rather than to downstream derivatives, the upregulation of 17, 20 lyase results in a reduction in testosterone concentrations. In this variant of CAH, called lipoid CAH, the primary mutation is not in the CYP450 17 but rather in the CYP450scc (side chain cleavage), steroidogenic acute regulatory protein (StAR), responsible cholesterol transport into the mitochondria where it is converted to pregnenelone and other steroid hormones (Miller, 2005). Males with this disorder are severely undervirilized, showing external female genitalia as well as life-threatening salt-wasting and cortisol deficiencies. Females, on the other hand, exhibit normal female anatomy and because the ovaries do not begin synthesizing steroids until puberty, StAR independent steroidogenesis remains functional until then (Miller, 2005). After puberty and with each subsequent
menstrual cycle, cholesterol esters accumulate, the adrenal cells engorge, and become less functional (Miller, 2005).

Researchers have termed the time-delayed “onset” of this disorder in females, the “two-hit model”. The first hit, a genetic mutation that is present at birth does not become fully activated until later when the second hit—puberty occurs (Miller, 2005). It is conceivable that pregnancy may be a “second hit” for some women in a yet unidentified endocrine reaction whose manifestations include psychiatric disturbances.

3β-Hydroxysteroid Dehydrogenase Activity

Another enzyme involved in the conversion of DHEA to testosterone includes 3β-hydroxysteroid dehydrogenase (3β-HSD). The 3β-HSD enzyme converts 17α-OH pregnenolone to 17α-OH-progesterone but also converts DHEA into testosterone. In another rare CAH variant, a mutation in the gene that encodes 3β-HSD globally inhibits the conversion of precursor hormones to products within each zone of the adrenal gland. This CAH variant is associated with salt-wasting (because of the enzyme’s involvement in the aldosterone pathway), genital ambiguity (because of the low testosterone) and hypogonadism (Carbunaru et al., 2004). It too can be ruled-out as a contributing factor the hormone profile observed in the Marrs study insofar as it would have been identified at birth.

However, researchers have speculated that a non-classical, late-onset variant of the 3β-HSD deficiency is present in women with PCOS particularly in those cases where insulin resistance is present (Carbunaru et al., 2004). Although a genetic mutation has not been identified, a consistent phenotype has been presented that
demonstrates compromised, but not totally inhibited 3\(\beta\)-HSD activity in the adrenal cortex with the concurrent hypersecretion of lutenizing hormone and increased ovarian production of testosterone. Thus, while hyperandrogenism is present in both the non-compromised 3\(\beta\)-HSD and compromised 3\(\beta\)-HSD versions of PCOS, testosterone concentrations in the compromised group were significantly lower (similar to those in the CAH variant discussed previously) and were thought to reflect up-regulated ovarian production rather than adrenal synthesis. Although this late-onset version of CAH can not be entirely ruled-out, the odds of this having been a factor in the Marrs (2006) study are low. Inasmuch as compromised 3\(\beta\)-HSD is associated with PCOS which is in turn associated with infertility and insulin resistance, it is unlikely that even undiagnosed participants would have been included in the study. However, this research illustrates that an enzyme need not be totally or globally deficient to elicit aberrant hormone synthesis patterns. Sometimes subtle changes in enzyme functionality produce clinical disruption.

17\(\beta\)-Hydroxysteroid Dehydrogenase Activity

The final enzyme involved in the conversion of DHEA to testosterone is 17\(\beta\)-HSD. The 17\(\beta\)-HSD enzyme convertsts DHEA to androstendiol and androstendiol to estrone. Since 17\(\beta\)-HSD deficiencies are typically associated with male pseudohermaphroditism, this enzyme deficiency can be ruled-out as having caused the low testosterone in the presence of high DHEA or DHEAS.

Whereas the complete abolition of a particular enzyme is not likely to have been a factor in the Marrs hormone profile, transient changes in enzyme activity
mediated by pregnancy or parturition and/or congenital deficits that only partially
compromise enzyme function, cannot be ruled out.

The relationship between DHEA and enzyme function is not fully understood
but suggests that DHEA regulates its own bioconversion and that of other hormones
both acutely and chronically via control of the local enzyme production (Labrie,
1997). For example, DHEA supplementation in both postmenopausal women and
elderly men increases testosterone and estradiol production while simultaneously
decreasing cortisol concentrations (Genzzani et al., 2006). It also influences the
production of other hormones through enzymatic up-regulation, such as
allopregnanolone (a progesterone derivative requiring 5α-reductase, the enzyme that
catalyzes the testosterone to dihydrotestosterone reaction) and 17α-
hydroxyprogesterone (17α -OHP) through the DHEA > 17, 20 lyase modulation
(Genzzani, et al. 2006; Roberts 1999). In the case of postmenopausal women,
researchers speculate that DHEA supplementation likely attenuates the age-related
debutances in 17, 20 lyase activity (Genzanni et al., 2006)

Interestingly, the exact opposite pattern with regard to DHEA and cortisol is
observed in both male and female patients with type 2 diabetes. In diabetics,
decreased 17, 20 lyase and increased 17α-OH expression are associated with
diminished DHEA and DHEAS concurrent with elevated ACTH and cortisol,
suggesting that 17α-OH expression is a key enzyme shifting DHEA synthesis either
towards (increased 17α-OH) or away from (decreased 17α-OH) cortisol production.
This pattern was reversed with diet, as was the insulin resistance (Ueshiba et al.,
2002).
From the research presented thus far it is evident that adrenal steroidogenesis is modulated both by substrate and enzyme availability, and both factors are intimately tied to DHEA concentrations. In the CAH variants discussed previously, DHEA concentrations were elevated or left unchanged but mutations in genes encoding the enzymes responsible for the conversion of DHEA into other metabolites drastically reduced the circulating androgen and estrogen concentrations. In postmenopausal women and elderly men, age-related declines in 17,20 lyase activity correspond to age-related declines in DHEA production as well as in androgen and estrogen synthesis. In diabetic patients these factors are compounded by increased 17α-OH expression and consequent cortisol up-regulation. Each of these factors is ameliorated with DHEA supplementation indicating that DHEA plays a prominent role in multiple metabolic pathways.

More importantly however, this research demonstrates that the onset of some endocrine disorders is delayed and may only come to fruition under certain circumstances. The two-hit model, similar to diathesis-stress model of mental illness, suggests that the phenotypic expression of some endocrine disorders requires both genetic and environmental contributions.

DHEA, DHEAS Disequilibrium

In the Marrs study (2006) DHEA concentrations were not measured but DHEAS and testosterone concentrations were. Barring disruptions in the 3β-HSD, 17,20 lyase and/or 17α-OH enzymes, the only remaining enzymes capable of creating high DHEAS and low testosterone are those involved with the bioconversion of
DHEA>DHEAS>DHEA, the SULT2A1 and STS enzymes. Disequilibrium between DHEA and DHEAS, where more DHEA is converted to DHEAS either by the up-regulation of SULT2A1 activity or down-regulation of STS activity would reduce the substrate availability needed for the conversion of downstream androgens and estrogens, but as was evidenced by the aforementioned research, might also alter the expression of other enzymes. Since there are no reports of SULT2A1 up-regulation (only down-regulation) the focus of this discussion will be on STS manipulation.

**Congenital Sulfatase Disorders**

The STS enzyme catalyzes the hydrolysis of the sulfate ester bond for multiple steroids including cholesterol sulfate, pregnenelone sulfate, DHEAS and estrone sulfate. The enzyme is encoded by a single gene located on the distal arm of the X-chromosome (Hernandez-Martin, Gonzalez-Sarmiento & Unamuno, 1999). Eighty to ninety percent of the mutations involve complete deletions whereas approximately 10-20% of cases involve partial or point mutations (Reed et al., 2005). Because the mutation is X-linked, the associated disorders develop only in male children of female carriers. The most common of these disorders is X-linked ichthyosis (X-LI) which develops in approximately 1-6000 male children (Bradshaw & Carr, 1986). The gestational signs of X-LI are elevated DHEAS and diminished estriol caused by placental a STS deficiency (Bradshaw & Carr, 1986). Androgen concentrations are not typically measured.

Mothers of male infants with this disorder typically have longer pregnancies as well as difficult and/or non-progressive labor related to the limited estradiol conversion from estrone sulfate. Males born with X-LI develop dark scaly patches of
skin due to diminished cholesterol sulfate to cholesterol conversion in the skin.

Cryptorchidism, which is marked by testicular mal-descent, is not considered a congenital disorder related to STS activity, but appears to be more prevalent in male X-LI babies (20-30%) than would be expected in the general population (Reed et al., 2005). The prevalence of crytorchidism is also 1-6000 and is thought to develop because of diminished testosterone synthesis or androgen receptor insensitivity during gestation (Bradshaw & Carr, 1986). Since diminished STS limits the substrate availability required for testosterone biosynthesis, researchers have begun to investigate partial or point mutations on STS gene that may be linked to cryptochidism (Reed et al., 2005).

Although no male infants were reported by Marrs (2006) to have had these disorders at 10 days postpartum, it can not be ruled out that the participants in this study were not carriers of this particular genetic mutation and that elevated DHEAS was not some how related to diminished sulfatase activity. Female carriers of this genetic mutation, depending upon the degree and location of the mutation may or may not develop the ichthyosis skin condition themselves. It was previously believed that acquired ichthyosis resulted from a de novo mutation in the STS gene. Re-examination of the mothers and grandmothers of male children with this disorder suggests the presence of mutation is correlated with the degree and severity of female symptom development (Cuevas-Covarrubias, Valdes-Flores, Orozco & Diaz-Zagoya, 1999). Researchers believed that the STS activity in female carriers of this mutation is not impaired. When it was actually measured however, STS activity in female carriers was significantly less than in normal females (Epstein & Leventhal, 1981). But only
one such comparison of STS activity in carriers versus non-carriers has been published to date with only five participants.

It has also been suggested that female carriers of this genetic mutation exhibit an increased incidence of "psychoreactive" disorders (Hernandez-Martin, Gonzalez-Sarmiento & Unamuno, 1999). Unfortunately, the original article claiming the psychoreactive responses was unavailable for review and there is very little data on the health status of female carriers. The extant research is focused entirely upon the identification and classification of male patients. The possibility exists, however, that female carriers of this mutation, likely exhibit diminished STS when compared to their non-carrier counterparts and that up-regulation in pregnancy related DHEAS production saturates the enzymes capacity catalyze hydrolysis thus un-masking a previously latent disorder.

Endogenous Factors Regulating Sulfatase Activity

In addition to the congenital disorders associated with STS deficiency, recent investigations have identified a number of endogenous and exogenous factors that decrease STS activity and thus impair DHEAS>DHEA conversion. These include interleukin \( \beta \), estradiol and/or estradiol withdrawal and some synthetic progestins. Progesterone, testosterone, estradiol, other synthetic progestins, retinoids, vitamin D3, tumor necrosis factor \( \alpha \) and interleukin 6 (IL-6), on the other hand, have all been found to increase STS expression (Reed et al., 2005). Because of its potential to diminish the circulating concentrations of androgens and estrogens, STS activity in hormone dependant cancers has been explored extensively in recent years. Data from this line research, although potentially confounded by oncogenesis, provide important
clues regarding mechanisms of STS inhibition as well as the subsequent hormone and psychological changes associated therewith.

_Cancer Research_

Using human corticoadrenal carcinoma cells, Gell and colleagues (1998) investigated the role of estradiol in DHEAS production in cell culture and found that estradiol increased DHEAS production in a dose-dependant manner while simultaneously decreasing 3β-HSD activity and cortisol production. Moreover, estrogen receptor antagonism did not impede DHEAS production. Researchers speculated that because of the increase in DHEAS and concomitant decrease in 3β-HSD activity and cortisol, estradiol mediated the hormone concentrations through the 3β-HSD enzyme. However, they did not measure DHEA or androstenedione, the two hormones most likely to be altered by increased DHEAS concentrations and concomitant changes in enzyme activity.

An alternative and more parsimonious explanation might be that estradiol inhibits STS activity as part of a local negative feedback loop. By inhibiting STS activity estradiol would limit the concentration estrone available for synthesis to estradiol and also limit the amount of DHEA, androstenedione and testosterone. The reduction in 3β-HSD activity might simply reflect a natural downregulation in activity based upon the diminished availability of precursor or it could be mediated by a third factor linked to cancer steroidogenesis. This hypothesis was partially supported by Pasqualini and Chetrie (2001), who found estradiol inhibited estrone sulfatase activity in breast cancer cells. In addition, multiple labs that have since developed dozens of potent synthetic STS inhibitors by modifying the basic structure
of the estradiol molecule (for a review see Nussbaumer & Billich, 2004).

Unfortunately, many of these compounds irreversibly inhibited STS and had very low $E_{D50}$ (4) and were thus not acceptable for human use. Dozens of molecular manipulations yielded many reversible STS inhibitors that were safer but far less effective (Nussbaumer & Billich, 2004).

The first STS inhibitor to reach phase 1 clinical trials was STX 64 (667 Coumate) (Stanway et al., 2006). Prior to clinical trials, Coumate administration in male rodents demonstrated that STS inhibition resulted in increased DHEAS which was associated with unprovoked aggression (Nicholas et al., 2001). STS inhibition also enhanced long term learning in rodent models (Flood, Farr, Johnson, Li & Morley, 1999).

In the phase 1 clinical trial, Coumate (5mg and 20mg) was administered to 13 postmenopausal women with either locally advanced or metastatic breast cancer in a non-random, open-label, dose-escalation study over a period of six weeks. The outcome measures included serum concentrations of DHEAS, DHEA, androstenedione, androstendiol, testosterone, estrone, estrone sulfate, estradiol as well as STS presence in peripheral blood lymphocytes (PBL) and in the tumor cell. With STS inhibition, DHEAS concentrations increased significantly while DHEA, testosterone and estradiol concentrations decreased. These changes paralleled drug dosage with higher doses linked to larger changes in circulating hormone concentrations (Stanway et al., 2006).

As expected, the ratio of DHEAS/DHEA increased substantially (320%) following drug administration. Estrone sulfate and the ratio of estrone sulfate to
estrone increased as well but not as dramatically as DHEAS. Sulfatase activity was dramatically inhibited in both the PBLs and within the tumors. Of interest the adverse events associated with drug administrations included Grade 2 or moderate (on scale of 0-none to 5-death) fatigue, hot flushes, mood alterations (details not listed), arthralgia (STS are found in synovial fluid) and headache. Since psychiatric disturbances were not measured as outcome variables, it is difficult to discern the exact nature and scope of the mood alterations experienced by participants in this trial, but it is important to note that psychiatric disturbances did occur. Thus, in addition to its potential efficacy as a cancer treatment, Coumate administration produced a hormone profile similar to the one observed in Marrs (2006) with high DHEAS and low testosterone that was associated with mood instability and/or negative behavioral changes (rodent) (Nicholas et al., 2001) providing preliminary evidence that compromised STS activity could be associated with puerperal psychiatric disturbances in some women.

**Sulfatase and Pregnancy**

This possibility was explored by Maayan and colleagues (2005) using a rodent model of pseudo-pregnancy/withdrawal. Investigators exposed three groups of rats to a period of hyper-physiological levels of estradiol or vehicle followed by an abrupt withdrawal in order to proximate the pregnancy/postpartum experience. The rats were ovariectomized to eliminate peripheral synthesis capabilities. Following withdrawal both peripheral serum and cortical concentrations of DHEA, DHEAS, pregnenelone, pregnenelone sulfate levels were assessed as was STS activity. There were no differences between the groups in peripheral serum DHEA or DHEAS, nor
were there differences in serum pregnenolone or pregnenelone sulfate. This would be expected because ovariectomy removed all peripheral synthesis capabilities. There were however, significant differences in cortical DHEAS and STS concentrations between the experimental and control groups. DHEAS concentrations were substantially higher and STS concentrations were lower in the experimental group. The authors speculated that rapid estradiol withdrawal, as occurs following parturition, altered the equilibrium between cortical DHEA and DHEAS concentrations via decreased STS activity. However, since the investigators did not measure STS activity during the pseudo-pregnancy when the rodents were exposed to supra-physiological concentrations of estradiol, it is impossible to determine whether the STS impairment was mediated by elevated estradiol as was suggested by the aforementioned cancer research or by the subsequent of withdrawal of the reproductive hormone as was speculated by Maayan et al. (2005).

Based upon these cancer studies, it seems more likely that STS inhibition is tied to estradiol concentrations rather than to estradiol withdrawal. This would suggest that the compromised STS activity observed following parturition by Maayan et al. (2005) reflected the diminished STS of late pregnancy and not necessarily a postpartum decline. The time-course of systems re-regulation following parturition could be related to oft reported 3-4 day postpartal clearance of the estradiol and other reproductive hormones (Illingworth & McNeilly, 1998) and/or to the inherent time course of STS transcription. There are no data on cortical or peripheral STS transcription rates, but data from cultured human skin fibroblasts suggest that STS synthesis takes at least two days to complete and that the STS half-life is four days
(Conary et al., 1986). This time course, along with the extended clearance of puerperal hormones and the already limited STS activity in the adult human liver (Hammer et al., 2005), would suggest that maternal STS activity is probably low in late pregnancy, but is compensated for by placental contributions (Carr, 1998). Following parturition, however, when the placenta is removed and as estradiol and the other previously elevated hormones decline, there would likely be some delay before STS activity returned to pre-pregnancy levels. This could result in a postpartal increase in DHEAS and the degree to which DHEAS concentrations increased would correspond to the severity of psychiatric symptoms as was postulated by Marrs (2006).

Admittedly, the research is lacking and this hypothesis remains to be tested. However, in light of the hormone profile and associated psychiatric symptoms observed in the Marrs study, diminished STS activity provides a plausible hypothesis for the development of these symptoms. Whether the proposed changes in STS activity are merely reactions to the puerperal endocrine environment or represent some previously unidentified congenital deficiency is currently unknown and will remain so unless and until a proper genetic study is undertaken.

However, a longitudinal analysis of postpartum hormones and psychiatric disturbances could yield additional clues to the etiology and course of postpartum psychiatric disturbances and its association with endogenous endocrine factors. The degree to which these hormone factors change over time should correspond to improvements or decrements in psychiatric symptoms. More specifically, if the observed endocrine patterns noted in the Marrs study represent a primary
endocrinopathy that is simply un-masked by pregnancy, further disturbances in endocrine regulation and continued psychiatric distress are expected. Whereas if the postpartal increase in DHEAS concentrations represent reaction to the abrupt changes in the reproductive hormones, DHEAS and other hormone values should return to normal and psychiatric symptoms are expected to diminish.
CHAPTER 3

METHODS

Participants

The twenty-eight healthy, primigravid women who completed the Marrs (2006) study were re-contacted and recruited for this longitudinal follow-up study. The Marrs (2006) study assessed cognitive, affective and hormonal variables associated with pregnancy and parturition at both 37 weeks of pregnancy and within 10 days postpartum. The present study looked at those same variables at four, eight and twelve months postpartum.

Only healthy, primigravid women without histories or current evidence of drug or alcohol use or abuse or neurological or psychiatric disorders and who were not taking medications that would confound with either psychological or hormone measures were used as participants in Marrs (2006). In the present follow-up study, there were no exclusionary criteria and all of the women involved in the Marrs (2006) research who agreed to participate were included. Medications, illnesses, breastfeeding and subsequent pregnancies were documented at the four, eight and twelve month postpartum data collection times.

Of the 28 participants in the previous research, 14 women agreed to participate in this follow-up. However, participation across the study was inconsistent with different women being available for testing at each of the follow-up times.
Twelve women were tested at four months, eight women were assessed at both eight and twelve months and only five women were tested at all three test times.

In order to equate the number of participants at each test time for purpose of data analysis, it was decided that participant data would be included in the final analyses for those women for whom there was no more than one set of missing variables (a single missed testing session). Nine participants met this requirement. For those nine participants, the single set of missing data were estimated using the series median of individual participant values. Data were estimated for one participant at four months, two participants at eight months and one participant at 12 months.

Enrollment and Testing

Upon completion of the pregnancy and postpartum testing in Marrs (2006) study participants were appraised of the possibility of a follow-up study and asked if they would be interested in participating in the subsequent research. All 28 agreed to be contacted. Approximately two-weeks before each participant reached four, eight and twelve months postpartum, each participant was contacted by telephone. (Prior to study approval from the hormone laboratory, four participants had passed the four-month test date and were not contacted initially until their eight-month assessment). This study was approved by the University of Nevada, Las Vegas Institutional Review Board (Appendix A)

Upon agreement to participate, new informed consents were mailed and signed, salivary specimen collection kits and instructions (Appendix B) were mailed and testing appointments were set for the participants. Additional consent forms were
signed in the presence of the researcher at the first appointment. Testing occurred at four, eight and twelve months postpartum +/- one week for each participant in the participant’s home. Data collection occurred over a 15 month period.

The morning of each testing session, pre-prandial, un-stimulated, salivary specimen were collected by the participant and stored at room temperature until the testing session. At each testing session, the following instruments were administered in order: the Symptom Checklist 90-Revised (SCL-90-R), the California Verbal Learning Test-II (CVLT-II) part one, Paced Auditory Serial Attention Test (PASAT), the CVLT-II part two, the Rey Complex Figure Test (CFT) copy, the Finger Tapping Test (FTT), the Purdue Pegboard, the Verbal Fluency Test, CFT-recall and the Design Fluency Test.

Breaks were given to the participant as requested and when needed to allot for down-time between tests. Testing at each session took approximately two hours. To compensate for practice effects on cognitive measures, alternate test forms were administered for the CVLT-II and the Rey CFT at each testing session.

Steroid Hormone Analysis and Neuropsychiatric Measures

Steroid Hormone Analysis

Non-stimulated saliva specimen were collected for the quantification of progesterone, DHEAS, testosterone, estradiol and estriol. Estrone, which was quantified in Marrs (2006), was not quantified in the present study due to laboratory financial considerations. However, since estrone did not appear to be a factor affecting dependent variables in Marrs (2006), its impact on the present study was
expected to be minimal. The morning of each test session, before eating drinking or
brushing her teeth, participant saliva was collected by expectoration over a 30-minute
period between 8:30 and 9:00 AM. Participants who were breastfeeding were further
instructed to avoid breastfeeding within two hours of the collection interval to prevent
feeding-stimulated hormone release that might confound results. Specimen were
shipped by two-day courier to the analytical facility (AllVia Diagnostic Laboratory,
Phoenix, AZ) where they were stored at -20°C for <24 hours, then thawed and
analyzed for progesterone, DHEAS, estradiol and estriol concentrations by enzyme-
linked immunosorbent assays. Testosterone was measured using luminescence
immunoassay. The lower and upper bounds of quantification and inter-day variance
for each hormone were established prior to analysis of participant samples. The lower
and upper limits of quantification were as follows: Progesterone 10-3000 pg/mL;
DHEAS 100-12,000 pg/mL; testosterone .3-760 pg/mL; estradiol .1-100 pg/mL;
estriol 1-4000 pg/mL.

Neuropsychiatric Measures

Intelligence

Intelligence was estimated in Marrs (2006) using the Barona Index and those
scores were utilized in this investigation as part of the demographic data and for
comparison with appropriate age and IQ-matched normative data.

Psychiatric Symptoms

Nine clusters of psychiatric symptoms were assessed using the SCL-90-R.
The SCL-90-R is a 90-item psychiatric self-report inventory designed to measure the
severity and intensity of psychiatric symptoms in both inpatient and outpatient
populations (Derogatis, 1994). Participants rated the severity of distress experienced during the prior seven-day period using a 0-4 Likert-type scale (0=no distress-“not at all” to 4=extreme). Symptoms measured included: anxiety, hostility (aggression, irritability, etc.) phobic anxiety, paranoid ideation, psychoticism, somatization (perceptions of pain or other physical disturbances), obsessive-compulsive behavior, interpersonal sensitivity (feelings of personal inadequacy), depression and the global severity index (GSI), a composite score that reflects the overall symptom severity. The GSI is calculated as a sum of all responses divided by 90 (the total number of responses).

*Cognitive Functioning*

Marrs (2006) identified cognitive impairment across the puerperium that was marked by particularly low verbal and spatial memory performance. To assess changes in cognitive performance across the postpartum year, the present study utilized the same neurocognitive measures as were administered in Marrs (2006) at each test time. The tests administered included: the CVLT-II, PASAT, Rey CFT, the verbal and spatial fluency tests, the Purdue Pegboard test and the finger-tapping test.

The CVLT-II assessed short and long-term memory as well as learning strategy and conceptual organization using five trials of 16 words in four conceptual categories (Lezak, 1995; Spreen & Straus, 1998). Results were evaluated based upon total recall, short and long delay recall, proactive interference and semantic clustering (Lezak, 1995; Spreen & Straus, 1998). Both Marrs (2006) and Buckwalter et al. (1999) found significant verbal memory impairment in both pregnant and postpartum women. Activation studies show that the CVLT activates the left inferior prefrontal
cortex, the left dorsal lateral prefrontal cortex, the orbitofrontal cortex and the left hippocampus (Savage et al., 2001).

The PASAT was used to assess the rate of information processing, sustained attention and vigilance. The PASAT consists of a taped presentation of randomly presented numbers. In each trial, the subject was asked to add pairs of numbers together in sequence with the second number added to the first, the third number added to the second, etc. There are four trials each with increasingly more difficult presentation rates (Lezak, 1995; Spreen & Straus, 1998). The PASAT is believed to be especially sensitive to subtle changes in attentional abilities. Marrs (2006) found mild to moderate impairment in attentional capacities which may have contributed to poor performance on the CVLT-II.

The CFT measured visual spatial and constructional ability as well as visual memory, planning, organizational and problem solving (Lezak, 1995; Spreen & Straus, 1998). Participants were asked to copy a complex figure and after a delay and without prior warning were asked to produce it again from memory. The figure was scored based upon accuracy and recall (Spreen & Straus, 1998). The CFT is argued to be adept at identifying frontal cortex dysfunction (Cummings & Trimble, 1995). CFT scores in Marrs (2006) were particularly low when compared to normative means.

The verbal and spatial fluency tests were designed to measure lateralized executive functioning. During the verbal fluency task subjects were asked to name as many words as they could in a particular category in one minute. They were also asked to name animals within a minute. Verbal fluency assesses left frontal cortex
functioning. For the spatial fluency task subjects were asked to draw multiple novel figures within a certain time frame. The spatial fluency test assessed right frontal cortex functioning (Cummings & Trimble, 1995). Both tasks are difficult for individuals with dorsal lateral prefrontal cortex injuries.

The Purdue Pegboard assessed fine motor dexterity and motor processing speed as well as right-left dominance. Subjects were asked to take pegs from a cup and place them in the pegboard, first with the dominant hand, then the non-dominant hand, and finally with both hands. Each trial takes thirty seconds and is scored by number of pegs placed during each time period (Spreen & Straus, 1998).

The finger tapping test measured fine motor speed and right-left dominance. Subjects must tap a key with the index finger of each hand as quickly as possible for five trials of 10 seconds each. Scores were computed for each hand and a mean for the five trials was produced (Spreen & Straus, 1998).

Data Analysis

The primary goal of this study was to evaluate the longitudinal trends and relative associations between postpartum hormones, psychiatric symptoms and cognitive performance across the first postpartum year. To assess the trends in hormone concentrations, psychiatric symptoms and cognitive performance, data from each group of variables were compared at five test times: 37-weeks of pregnancy (T1), <10 days postpartum (T2), four-months postpartum (T3), eight-months postpartum (T4) and one-year postpartum (T5) where data for T1 and T2 were
collected in Marrs (2006) and data for T3, T4, and T5 were collected in the present study.

Data were analyzed using a series of repeated measures within-subject univariate analyses of variance (ANOVA). Assumptions of sphericity for each symptom scale, hormone value and cognitive variable were assessed using Mauchly’s W statistic and when violated, significance levels were adjusted using the Greenhouse-Geisser method. Differences between test times were calculated using simple effects contrasts.

Performance on cognitive tests is susceptible to change over time due to both the imprecision of the instrument and/or practice effects (Wilson, Watson, Baddeley, Emslie & Evans, 2000). Thus, delineating functional change in individual scores requires the accommodation of those factors. A common procedure for dealing with this is to utilize reliable change indices (RCI). An RCI establishes the range of expected scores across time to determine the number of points on each cognitive test required in either direction for change scores to be considered to have not occurred by chance. Typically a confidence interval of either 90% or 95% is used. However, upon review of the RCIs established by Wood, Delis, Scott, Kramer & Holdnack (2006) for the CVLT-II in a healthy control group (there are no RCIs established for the other instruments used in this study) it was determined that the number of points required to merit the designation “improved” would exceed the total points possible for this instrument after a couple of trials and would not likely provide a useful reference. Thus, measures of change were based upon statistical difference and comparisons made to normative standards published for age, IQ and/or education-matched
controls. Interpretation of change in these circumstances must be made cautiously and with the understanding that practice may have accounted for a large percentage of any observed improvement.

To assess the relatedness of hormones to psychiatric symptoms and cognitive performance Pearson's bivariate correlations were calculated. Because of the small sample, data were not normally distributed and resisted transformation. It was decided in advance that if normality assumptions were not met, parametric statistics would still be used with the caveat that significance levels be interpreted cautiously. As was case with Marrs (2006), those participants with the most severe symptoms also typically exhibited the most extreme hormone values and, thus, represented the clinical cases of most interest. To have removed these cases from data analysis would have obfuscated the relational trends between non-normal hormone profiles and psychiatric symptoms.

In Marrs (2006) post-hoc analysis of data revealed two distinct groups of women, those who were considered symptomatic (T-score >60 on any one symptom cluster of the SCL-90-R) and those who were asymptomatic. Because of the small sample in the present study, statistical analysis of these two groups was not possible. However, descriptive analyses of symptomatic versus asymptomatic participants were conducted using the same criteria as Marrs (2006).

The large number of analyses performed necessarily increased the type 1 error rate which might or might not have been counterbalanced by the limited power associated with such a small sample size. Typically adjustments to the significance level are made. It was decided in advance not to do this, so that all symptom trends
would be identified, again with the caveat that significance should be interpreted cautiously. It was also decided in advance, that while the complete battery of cognitive tests would be administered, only those factors found to be most impaired in Marrs (2006) and that continued to show impairment when pregnancy and postpartum data were re-analyzed for this subset of nine women, would be analyzed in the present study.
CHAPTER 4

RESULTS

Participant Data

The average age of study participants was 31.6 years (SD 3.1), education was 15.8 years (SD 2.45) and the full scale IQ as estimated from the Barona index administered in Marrs (2006) was 112.4, (SD 5.7). Pregnancy and health related data for the nine participants who were followed across the postpartum year are given in Table 1. Mean gestational length for these participants was 278 days (SD 2.7) and each of the nine women had vaginal deliveries. Seven of these nine participants gave birth to boys, compared to 50% of the total group of participants in Marrs (2006).

At the four month postpartum test time seven participants were breastfeeding and four participants had begun menstruation. Three participants were taking oral contraceptives and two participants were taking anti-depressants. At this test time four participants were working part-time, three of whom worked in the home. Comparatively, of the nine women who declined to participate in the research, but who returned our calls, seven were working outside the home full-time.

At the eight month postpartum test time, two women were still breastfeeding. Six women had at least one menstrual cycle prior to this test session. The same four participants that were working at four months were continuing to work part-time at eight months and the same three participants who were previously taking oral

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contraceptives were still taking oral contraceptives. Both participants previously on anti-depressants had ceased taking the medications.

At 12 months postpartum, only one participant was known to be breastfeeding. Participant E was unavailable for testing and it was not known whether she was still breastfeeding. The same three participants were taking oral contraceptives and no other medications were reported. Each of the seven participants known not to be breastfeeding at this time reported having mostly regular menstrual cycles. Participant H was later found to be five weeks pregnant at this test time. Her progesterone, DHEAS, testosterone and estriol values did not differ significantly from those of the other eight participants. Her estradiol values were significantly greater than those of the other participants at the 12 month testing session, but were lower than either her own four month or eight month estradiol values, when she was known not to be pregnant. Thus, her data were included in the analyses.

Psychological Data

*Longitudinal Trends in Postpartum Mental Health*

Postpartum psychiatric distress has been described and investigated largely under the rubric of three popularly but loosely defined depressive disorders developing sometime within the first postpartum year. Accumulating evidence suggests that postpartum psychiatric symptoms are not limited to depression and develop in the immediate puerperium. The current research examined the breadth, onset time and time course of these disturbances over one year in a cohort of nine women. In order to characterize fully the spectrum of psychiatric symptoms across
the postpartum year, the SCL-90-R was administered at four (T3), eight (T4) and twelve (T5) months postpartum as the primary outcome measure. SCL-90-R data previously collected during week 37 of pregnancy (T1) and 10 days postpartum (T2) (Marrs 2006) for these nine women were included in the longitudinal trend analyses.

**Symptom Checklist 90-R**

The SCL-90-R manual (Derogatis, 1994) provides normative T-scores for both psychiatric and non-patient populations. All data comparisons in this study were made to the normative scores for the female non-patient population. Each of the symptom domains has a mean T-score of 50 with a standard deviation of 10. A T-score of 60 is equivalent to a percentile rank of 84, suggesting that scores one standard deviation above the mean are indicative of relatively high distress levels. Listed in Table 2 are mean T-scores, standard deviations and percentage of participants who were considered symptomatic for each of the symptom domains measured by the SCL-90-R at each of the five test times.

As can be seen in Table 2 mean participant scores were close to or slightly above normative means in each of the symptoms clusters at each test time suggesting that the participants as a whole experienced mild to moderate distress. However, obtained standard deviations and examination of individual scores belies this generalization by exhibiting a large range of individual scores and symptom severity. Looking at the percentage of women who were considered symptomatic (SCL-90-R T-score >60) at each test time demonstrates for some symptoms a larger percentage of participants suffered from psychiatric distress than was inferred from the mean scores. This is illustrated in Figure 3 which plots the percentage of symptomatic
women at each test time. Conversely, at each test time there were women for whom pregnancy was a wonderful experience and who's SCL-90-R T-scores remained below 50 across all test times.

During pregnancy symptoms of distress were present in at least half of the women tested. The depression, somatization and obsessive compulsive scales showed the highest percentage of symptomatic women at this test time. Ten days following parturition, the percentage of symptomatic women increased for all but the paranoia, somatization and obsessive compulsive scales. Four participants demonstrated symptoms of obsessive compulsive behavior at both test times. Additionally, in the immediate postpartum, one-third to over one-half of the women tested were symptomatic in each of the anxiety symptom clusters (anxiety, phobia, obsessive compulsive behavior and somatization). Four women showed evidence of sub-threshold psychotic disturbances absent concurrent elevations in paranoia and eight of the nine women tested scored >60 in the depression scale, representing the largest measure of psychiatric distress. Overall, five women were significantly distressed in enough clusters to merit GSI scores >60.

At four months postpartum, both the frequency and severity of psychiatric symptoms diminished with only one participant exhibiting a GSI score > 60 and two additional participants showing signs of mild distress with intermittent elevations in individual symptoms scales. Psychiatric distress increased again at eight months postpartum with four participants exhibiting signs of depression, three participants exhibiting obsessive compulsive behavior, two participants showing elevated psychoticism scores and two participants showing elevated GSI scores. Depression
scores wane again at one-year, but the GSI remains consistent with two participants reaching the cutoff of >60. It is interesting to note that by eight months postpartum only two participants were still breastfeeding and seven participants had resumed menstruation.

In order to determine if the symptom changes described above were statistically significant a series of repeated measures ANOVAs were run. As shown in the top row of Table 3 all of the symptoms showed significant improvement across time except for anxiety, paranoia and interpersonal sensitivity which showed no change. It should be noted, however, that paranoia was not a significant contributor to psychiatric distress at any test time.

A trend analysis was performed to detect the direction and shape of these trends in postpartum symptom change. Significant linear and cubic trends were identified for a number of symptom clusters. With the exception of somatization, which followed a consistent downward trend from pregnancy through the postpartum year, each of the other symptom clusters exhibited some degree of curve in the trend line, typically denoted by spikes in symptom severity both at 10 days postpartum and again at four months postpartum, although symptoms increased to a much lesser degree at the four month test time. The second and third rows of Table 3 show which of these obtained trends reach statistical significance.

To determine when the largest change in symptom severity took place, paired comparisons were made between each test time. These results are reported in Table 3 as well and illustrated in Figure 3. The largest number of significant changes in symptom severity and frequency occurred between the immediate postpartum and
four month test times with statistically significant differences occurring in all symptom clusters except anxiety, paranoia and interpersonal sensitivity, which improved but did not meet statistical significance. Thereafter, few statistical differences are obtained between successive test times. This indicates that recovery from symptoms experienced during pregnancy and immediately postpartum is largely resolved by four months postpartum. Similarly, it suggests that symptoms appear to peak in the immediate postpartum.

Summary

By way of overview it would appear that postpartum psychiatric disturbances develop in late pregnancy, escalate in the immediate postpartum and diminish greatly by four months postpartum. Symptoms may wax and wane over the course of the postpartum year, and may develop in association with other life events, but postpartum symptoms appear to be temporally related to childbirth. Thus, the investigation postpartum symptoms in childbearing women should be conducted in proximity to the precipitating event rather in the months and year that follows. Moreover, in contrast to the current nomenclature and nosological distinctions that are rather narrowly focused upon depression, postpartum psychiatric disturbances seem to be characterized by a range of symptoms.

Cognitive Performance

Previously, Marrs (2006) observed moderate cognitive impairment across multiple domains both during pregnancy and in the immediate postpartum. Cognitive performance was particularly poor in both verbal and spatial memory with percentile
rankings from only the single digits to the low double digits when compared to age and IQ-matched normative data. The purpose of this study was to determine if and when during the first postpartum year, cognitive performance returned to normal and to track these potential longitudinal trends across the first postpartum year.

Longitudinal Trends in Cognitive Performance

Evaluation of T1 and T2 cognitive tests for this group of nine women showed significant impairment in verbal memory at both test times. However, spatial memory did not appear to be impaired at 10 days postpartum as had been the case in Marrs (2006). Similarly, performance on other cognitive tests such as the PASAT, the verbal and spatial fluency tests were not impaired at either the pre- or postpartum testing session for the current participants. Performance on the Purdue pegboard, however, was below average at both of these test times whereas the finger tapping test was not suggesting that manual dexterity may have been an issue during pregnancy and in the immediate postpartum.

So as to minimize Type I error and maximize statistical power only verbal memory performance was analyzed across the three postpartum testing sessions carried out in this research. However, a descriptive overview of each of the cognitive test results obtained across the first postpartum year is provided next.

As demonstrated by Table 4, and illustrated in Figure 4, performance on most of the cognitive tests administered in this research showed a slight upward trend from the end of pregnancy to the postpartum period which, for the most part, was characterized by stable above average performance across all postpartum test times. One exception was spatial memory, as measured by the recall portion of the CFT,
spatial memory showed substantial improvement from pregnancy to postpartum but declined again at four months and again at twelve months. The apparent improvements in spatial memory correspond to the administration of Taylor's alternate CFT form. Comparability studies have found that while the copy scores of each of the CFT forms is equal in healthy young adults, the Rey CFT standard form is more difficult and typically merits a five point difference in scores (Spreen & Strauss 1998). When those points are accounted for, the data reveal that there was no substantial improvement in the recall portion of the spatial memory task. Considering that each woman was exposed to the Rey CFT standard form on three different occasions, practice effects would have been expected. Indeed, in healthy young adults an improvement of 10% or more per trial is expected (Spreen & Strauss, 1998). In the present research the overall improvement across the three administrations of the standard form was less than 10%.

Unlike CFT scores from Marrs (2006) where the copy portion of the CFT was equally as impaired as the recall portion, copy scores in the present study were generally above the mean at each test time but did show slight downward trend across test times. The difference in copy scores may be related to the small sample size in the current study.

Performance on the Purdue pegboard was below average both during pregnancy and following parturition but showed improvement across the remaining test times. If both the finger tapping test and the pegboard had been impaired, motor slowing would have been suspected. Since the Purdue pegboard demands significant
fine motor dexterity it is possible the pregnancy related swelling contributed to the poor performance.

As noted above, verbal memory was impaired at 37 weeks of pregnancy and in the immediate postpartum period. Table 5 and Figure 5 show that when compared to age and IQ-matched (based upon an estimated full-scale IQ of 112) normative data, immediate, short and long delay verbal memory scores ranged from the <1st to the 25th percentile during pregnancy and <1st to the 32nd percentile in the immediate postpartum (Spreen & Strauss 1998). Normative data by age and IQ were not available for the semantic clustering or learning slope variables. Accordingly, the percentile ratings reported here for these measures may be higher than what have been expected for this group based upon their performance on the recall scales. Semantic clustering, the degree that words were categorized by meaning in the recall measures, was above average at both T1 and T2, whereas the learning curve scores fell considerable below average at both of these test times. Scores for this subset of women were consistent with those for the entire group in Marrs (2006).

For the most part verbal memory improved across the postpartum year with percentile rankings approaching or exceeding normative means. The lower scores sometimes observed at 10 days postpartum and again at eight months postpartum corresponded to the administration of the alternate test form although test designers posit high correspondence between performance on the standard and alternate forms (Dellis et al., 2000).

Irrespective any potential performance discrepancies between the standard and alternate forms, verbal memory scores improved in each of the dimensions measured.
except for proactive interference, Trial B, which remained below 15% throughout the postpartum. Trial B is a distracter list of words administered after the fifth trial of the primary list, in the immediate recall portion of the exam and before either of the delayed recall trials begins. It measures the degree to which previously learned information hinders the acquisition of new information. While some proactive interference is expected in non-clinical populations, the consistently low scores for trial B observed across pregnancy and postpartum indicate a potential deficit in working memory (Jonides & Nee, 2006). Consistent with that possibility, the obtained learning slope scores, which measure the number of new words learned per trial were relatively low and stable across most postpartum test times.

Deficits in working memory are suspected when the number of words learned in Trial 1 is greater than the number of words learned in Trial B as measured by a difference in z-score of >1.5 points (Donders, 2006). This criterion was met at three test times and just missed the cutoff at four months and at eight months where the difference between the scores was 1.49 and 1.32 points, respectively. Interestingly, in comparison to other individuals with similar difficulties in proactive interference, overall recall scores (CVLT-II, Trial 1-5 total) were significantly better for participants in the present study whose scores ranged from 52-62 total words recalled across all test times versus a mean of 49 total words recalled (n=955) (Donders, 2006). Similarly, mean semantic memory z-scores for this participant group were very high, ranging from 0-3.59 across all test times and likely contributed to the greater number of words recalled.
Repeated measures analyses (Table 6), revealed significant main effects for time for each of the primary measures of verbal memory except for Trial B which was not significant and long delay recall which approached significance at p>.056. Semantic clustering also improved significantly over time but the learning curve did not. The trend analysis indicated significant linear trends for each of the primary measures except long delay recall.

Change between test times was analyzed further using a series of repeated measures ANOVA contrast tests. As is exhibited by Tables 6, verbal memory scores improved in a mostly linear fashion across time. Improvement between test times was not always statistically significant. However, improvement between T1 and T5 was significant in most of the verbal memory measures, excluding Trial B, the learning curve and long delay recall.

Inasmuch as neither a control group nor a reliable change index was used to counter the effects of practice in short and long term verbal memory test performance, these results must be interpreted cautiously. It is impossible to discern whether true improvement or improvement mediated by repeated exposure was observed in the present study. However, the lack of improvement in both the learning slope and in performance on trial B suggests the possibility that improvement in the other aspects of verbal memory may have come from practice.

**Associations between Verbal Memory and Psychological Distress**

Unlike in Marrs (2006) where psychiatric symptoms were inconsistently and sometimes positively associated with cognitive performance, in the present study several scales on the CVLT-II were consistently and negatively associated with SCL-
90-R symptoms, predominantly at T1, T2 and T3. For example, anxiety was negatively correlated with immediate recall trial 1 and recall total at one year postpartum (r=-.716, p<.05; r=-.688, p<.05, respectively). It had previously been associated with poor delayed recall during pregnancy (r=-.669, p<.05). Hostility was associated with poorer immediate recall trial 1 and trial B during pregnancy but not in subsequent testing session (r=-.713, p<.05; r=-.913 p<.001, respectively).

Somatization was a factor in both the long delay recall trial at T2 (r=-.671, p<.05), T3 (r=-.730, p<.05) and on semantic clustering ability during pregnancy only (r=-.709 p<.05). Obsessive compulsive behavior was related to poor performance on the immediate recall total (r=-.679, p<.05), short delay free recall (r=-.666, p<.05) and the long delay recall trial (r=-.723, p<.05) at four months postpartum. Increased interpersonal sensitivity was also associated with performance on the long delay trial (r=-.691, p<.05) at T3 as was depression at T2 and T3 (r=-.753, p<.05; r=-.691, p<.05, respectively). Finally, the GSI was associated with poor long delay recall abilities at T2 (r=-.682, p<.05) and T3 (r=-.813, p<.01).

Summary

The most robust findings concerning cognitive performance during pregnancy and postpartum obtained herein were that deficits in spatial and verbal working memory originally identified during pregnancy persist through the first postpartum year. Moreover, psychiatric distress impaired verbal memory performance. At least it was the case that each of the significant associations obtained between verbal memory and distress were negative and most prominent during pregnancy, the immediate postpartum and four-months postpartum. As verbal memory improved,
whether by practice or not, and psychiatric distress was ameliorated, the correlations between the two dissipated.

Hormone Data

Results from Marrs (2006) demonstrated a strong relationship between the adrenal androgens DHEAS and testosterone and psychiatric disturbances. Prenatal testosterone was associated negatively with prenatal psychiatric distress, but also heralded the onset and exacerbation of symptoms following parturition. Concurrently, elevated DHEAS was associated positively with both pre- and postpartum distress. Following parturition as DHEAS concentrations increased so too did the severity of psychiatric distress. The current study investigated the time related trends in these hormones relative to psychiatric distress and cognitive function.

Patterns of Change

The inter-individual variance in hormone values observed in this study was enormous, with standard deviations as large as or greater than mean values for some hormones. These mean values and standard deviations are shown for each hormone measured at each test time in Table 7 along with reference ranges for non-pregnant, non-postpartum women. It should be noted that reference ranges for salivary hormone values have not been established for either pregnant or postpartum women and these reference ranges should be interpreted with caution. Mean data for each hormone are plotted against test time in Figure 6.

Immediately following parturition mean progesterone, estradiol and estriol decreased by 95%, 46% and 97% respectively. Mean DHEAS concentrations almost
doubled following pregnancy showing a 99.24% increase at the first postpartum test time and testosterone values increased by 10%.

Between the immediate postpartum and the subsequent three testing sessions the pattern of hormone change varied among the hormones. As may be gleaned from Table 7 mean postpartum progesterone, estradiol estriol concentrations generally fell within the normal range of expected values for non-pregnant women, non-postpartum women and remained fairly consistent across the postpartum year.

Mean postpartum testosterone concentrations fell within the normal range of expected values, but skewed toward the lower end of the normal range at four months postpartum and then approached the median normative values for the remaining two test times. Inter-individual variability was particularly large for postpartum testosterone with concentrations ranging from as low as .4 pg/mL for Participant A at T2, to as high as 80 pg/mL for Participant E at T4. Individual hormone values and percent changes between successive test times are given for each participant in Table 8.

DHEAS showed the most unique pattern in that mean values increased from pregnancy to postpartum and showed no tendency to decrease across the postpartum year. Moreover mean DHEAS values were at the high end of the reported reference ranges. Mean DHEAS concentrations across the postpartum year ranged from 1725 pg/mL to 2125 pg/mL compared to the 200-2500 pg/mL reference range. At each of the four postpartum test times, at least two participants approached or exceeded the clinical reference ranges. Overall four different women met or exceeded clinical cutoffs for this hormone at least once during the year. As may be seen by reference to
Table 8, participant E exceeded the cutoff on four occasions and Participant G, exceeded the cutoff on two occasions. Participants D and H exceeded the clinical cutoff on one occasion each.

DHEAS concentrations >2500 pg/mL are clinically indicative of adrenal dysfunction and typically merit further diagnostic investigation. Moreover, elevated DHEAS values are generally co-associated with elevated testosterone (Bulun & Adashi, 2003) which did not occur in this research. Participants with supra-physiological concentrations of DHEAS were notified by the investigator and encouraged to seek further testing. Only Participant E whose DHEAS values reached >7200 pg/mL chose to do so.

Special note is taken that the mean postpartum estriol values, while relatively stable across the postpartum trended toward the high end of the non-pregnant, non-postpartum reference ranges. Mean postpartum estriol concentrations observed in this study ranged from 12-14 pg/mL compared to the laboratory reference range of .5-16 pg/mL (Table 7). Whereas individual postpartum values ranged from as low as 4.2 pg/mL to as high as 26.6 pg/mL, five different women on nine different occasions exceeded the clinical cutoff (Table 8).

Estriol is the primary metabolite of fetal DHEAS during pregnancy. Fetal adrenals produce large quantities of DHEAS, which are then metabolized into estriol by the fetal liver via 16α-hydroxylation. With the occasional supra-physiological DHEAS values observed in the present study, one might expect increased conversion of DHEAS to estriol in the maternal liver. Correlations between hormones at each of
the test times are given in Table 9. As can be seen therein a significant correlation
between DHEAS and estriol occurs only at T4.

Further examination of the hormone to hormone correlations shown in Table 9
reveals that while DHEAS was significantly correlated with testosterone at four, eight
and twelve months postpartum, testosterone concentrations were not correlated with
estradiol concentrations at any of the test times, but were correlated significantly with
estriol during pregnancy and postpartum and again at T4. The lack of association
between testosterone and estradiol is surprising insofar as testosterone and estradiol
are thought to be highly correlated, particularly in hyperandrogenic conditions (Bulun

*Longitudinal Trends in Postpartum Hormones*

A series of repeated measures ANOVAs were performed to assess the
statistical differences in mean hormone concentrations across test times. Multiple
contrast measures were utilized to determine differences in mean hormone
concentrations between each test time and polynomial trend analyses were performed
to assess the shape and significance of trends across time.

As illustrated in Table 10 there were significant main effects for time for
progesterone and estriol with most of the effect accounted for by the significant
changes from pregnancy to the immediate postpartum (p<.000 for each). Neither
DHEAS nor estradiol showed significant main effects but did follow significant linear
and cubic trends, respectively, and showed some significant changes between
individual test times, particularly at T1 and T5.
Mean DHEAS values between test times did not show significant differences, probably because of the previously noted substantial inter-individual and intra-individual (between test times) variability observed for this hormone. Nevertheless, the unique pattern obtained for this hormone merits its further consideration.

DHEAS values measured in serum, are reported to be high in early pregnancy diminish in late pregnancy and return to non-pregnant concentrations following parturition (Soldin et al., 2005; Tagawa et al., 2004). At one year postpartum, serum DHEAS concentrations are expected to be within non-pregnant reference ranges (Soldin et al., 2005). There are no published data on salivary DHEAS concentrations either during late pregnancy or at any time during the first postpartum year. However, the balance between serum values, which represent the fraction of hormone bound to protein (DHEAS is tightly bound to albumin) and the salivary concentrations, which represent the free fraction of hormone, that which is not bound to circulating proteins, are highly correlated and reportedly maintained in dynamic equilibrium (Bolaji, 1994; Lu et al., 1999; Meulenberg & Hofman, 1989; Vinning & McGinley, 1987). Thus, it would be expected that the trends in salivary hormones observed in this study compared to others would be similar those obtained previously in serum. This appeared not to be the case. With the exception of a slight decrease at eight months postpartum, mean DHEAS concentrations increased from pregnancy through the first postpartum year. It has also been reported that elevated DHEAS concentrations are typically associated with elevated testosterone and estradiol (Kroboth et al., 1999). This appeared not to be the case in the present study.
Hormone to Symptom Associations

In Marrs (2006), the adrenal androgens DHEAS and testosterone were uniquely and significantly associated with the full spectrum of psychiatric disturbances measured by the SCL-90-R. Elevated puerperal DHEAS and diminished late pregnancy testosterone were associated with pre- and postpartum symptoms whereas progesterone and estriol were not associated with any symptoms and estradiol was only correlated with a few dimensions. To determine what role these hormones played in psychiatric symptomatology across the year, correlations between hormone values and psychiatric symptoms were calculated for the current participants at each test time.

Results from the correlation calculations are listed in Table 11. Correlations between hormones and psychiatric symptoms during pregnancy and postpartum were not significant. However, immediate postpartum DHEAS was significantly correlated with increased postpartum anxiety, paranoia, psychoticism and the GSI. Progesterone and estriol were not associated with symptoms at either of these two test times and estradiol was not correlated with any symptom at any test time.

At four months postpartum, progesterone, DHEAS and testosterone were all significantly and positively associated with a variety of psychiatric symptoms as shown in Table 11. Most notable were the hormone to mood correlations for anxiety, phobia, paranoia, psychoticism, obsessive compulsive behavior and depression. Estriol was also significantly correlated with depression at this test time.

At eight months postpartum significant positive hormone to psychiatric symptom correlations were found only for DHEAS, testosterone and estriol. As
shown in Table 11, DHEAS was correlated with phobia, paranoia and psychosis and testosterone was correlated with phobia. It is notable that the largest number of correlations at eight months postpartum was found for estriol which was correlated positively with anxiety, phobia, paranoia, psychoticism, obsessive compulsive behavior and depression.

Finally, at twelve months postpartum, only progesterone was associated with psychiatric symptoms. Progesterone was correlated with phobia, paranoia, psychoticism and somatization as again shown in Table 11. It must be noted that hormone values and SCL-90-R scores for participant E were estimated for this test time using the median value of her hormone values and scores from previous sessions and thus correlations presented here must be interpreted with caution.

**Hormone to Verbal Memory Associations**

In Marrs (2006) the relationship between individual hormones and tests of cognitive performance was inconsistent but did indicate that elevated hormone concentrations were associated generally with poorer performance across multiple measures. In the present study, no statistically significant associations were identified between measures of verbal memory and any hormone at any of the three postpartum test times.

**Summary**

The hormone data presented herein suggest that inter-individual variability is considerable and that trends changes in hormones across the postpartum period can be concealed by analysis of mean data alone. Nevertheless, the obtained mean data do demonstrate that progesterone, testosterone, estradiol and estriol are elevated during
late pregnancy, decline after parturition, and stabilize across the postpartum year. On the other hand, mean DHEAS values trended upward across the postpartum year.

Each of the hormones measured was correlated positively with psychiatric symptoms at some time during the postpartum year except for estradiol, which was not correlated with any symptoms at any test time. DHEAS was significantly correlated with symptoms at T2, T3 and T4 showing the largest number of significant correlations of any of the hormones measured. This was followed by progesterone which was associated with symptoms at T3 and T5 while testosterone and estriol were associated with symptoms at T3 and T4. The present study obtained no significant hormone to cognitive performance correlations at any test time.

Case Histories

Two women within this cohort, Participants D and E, suffered significant psychiatric distress in the immediate postpartum to merit a more detailed description of their individual symptoms, hormone patterns and results from the neuropsychological assessments. Participant D was 29 years old at the time of the first testing session, married, pregnant with a male child, right-handed and employed professionally, with 16 years of education. Participant E was 26 years old, married, pregnant with a female child, left-handed, with 16 years of education. She had been employed professionally until five months of pregnancy when persistent nausea had precluded her continued employment.
Participant D

Participant D reported a normal but extended pregnancy. She delivered approximately two weeks after her scheduled due date with labor induction required. Her labor was approximately 18 hours. At T1, she showed some signs of psychological disturbance with elevated SCL-90-R T-scores in the following symptom clusters: somatization, 62; obsessive compulsive, 72; depression, 62; and GSI, 63. It was noted that during this testing session, her affect was unusually flat, with little to no expression of either positive or negative emotion.

Performance on the battery of neuropsychological exams was marked by below average short and long term verbal recall (45\textsuperscript{th} and 32\textsuperscript{nd} percentiles, respectively), very poor control of proactive interference (Trial B, 16\textsuperscript{th} percentile) as measured by the CVLT-II and poor spatial memory (9\textsuperscript{th} percentile) as measured by the CFT. Attentional capacity as measured by the PASAT was at or just below the 50\textsuperscript{th} percentile across all four trial speeds. Motor processing and fine motor skills as measured by the FTT and Purdue were within normal ranges and performance on both the verbal and design fluency tests was at or just below the 50\textsuperscript{th} percentile.

Following parturition, Participant D experienced severe anxiety and panic attacks. She exhibited autonomic instability without concomitant thoughts of harming her child. Her SCL-90-R scores increased considerably. Her T-scores were as follows: anxiety, 76; hostility, 61; phobia, 66; psychoticism, 69; somatization, 78; obsessive compulsive behavior, 70; depression, 72; and her GSI was 70. Again, and even with such active psychiatric disturbances her affect was unusually flat. Concurrent with these symptoms DHEAS and testosterone concentrations went from
640 pg/mL and 48 pg/mL respectively at T1 to 4555 pg/mL and 25 pg/mL respectively, following parturition. Postpartum cognitive performance improved minimally and/or remained consistent with performance during pregnancy, although her CVLT-II total immediate recall declined somewhat from the 45th percentile during pregnancy to the 42nd percentile postpartum. Spatial memory remained poor at the 9th percentile.

At approximately three weeks postpartum she sought help from a physician and was prescribed escitalpram oxalate (Lexapro), a selective serotonin reuptake inhibitor (SSRI) commonly prescribed for depression but also for generalized anxiety disorder. By two months postpartum the participant reported feeling better and by four months postpartum had begun to taper her medication. At four months postpartum, her symptoms had subsided with only the somatization scale reaching T-score above 60 (T=62). Her DHEAS and testosterone concentrations returned to within normal ranges and her affect had returned to normal. Cognitive performance across all tests improved slightly or remained consistent with previous performance except for spatial memory which declined further to the 8th percentile.

At eight months postpartum, it was revealed that Participant D’s son had recently undergone a procedure to correct testicular mal-descent. Testicular mal-descent sometimes referred to as cryptorchidism occurs in 1-6000 births and is thought to be caused by low gestational testosterone and/or testosterone receptor insensitivity (Bradshaw & Carr, 1986). The surgery was successful and the child was doing well. No other health related issues were reported. Symptom T-scores at this time were slightly elevated: psychoticism, 60; obsessive compulsive behavior, 62;
interpersonal sensitivity, 63; and depression, 62. Her GSI was 58. DHEAS increased by 482 pg/mL from the previous test time but was within the normal range. Other hormone values were also within the normal range. Cognitive performance continued to improve. CVLT-II scores were all above the 50th percentile and spatial memory scores improved to the 25th percentile.

At 12 months postpartum no SCL scores were above 60, DHEAS concentrations fell ~300 pg/mL. All other hormones remained within normal ranges. Cognitive performance remained stable, except for spatial memory which declined to the 10th percentile.

Participant E

Participant E had a difficult pregnancy and suffered from significant nausea and vomiting throughout the entire pregnancy. At T1 she was showing signs of distress with elevated SCL-90-R scores across several domains. Her T-scores were as follows: anxiety, 73; hostility, 55; phobia, 76; paranoia, 60; psychoticism, 65; somatization, 72; obsessive compulsive behavior, 73; interpersonal sensitivity 69; depression, 72; and her GSI was 73. Despite the difficulties she reported being excited about the birth and was particularly interested in having the nausea dissipate. Her cognitive performance was below average during pregnancy, ranging from the 16th percentile in Trial 1 and Trial B, long delay recall measures to the 32nd percentile for short delay and the 47th percentile for total immediate recall in the CVLT-II. Her attentional capacity and cognitive processing speed was somewhat below the mean but her motor processing and fine motor skills were at or above normative mean performance. Unlike Participant D who showed significant impairment in spatial
memory, Participant E performed above average on this measure scoring in the 79th percentile.

Following parturition Participant E suffered significant anxiety and was immediately plagued by violent and aggressive thoughts typically involving the death or injury of her infant or herself. The severity of her distress increased significantly as is seen with the increase in SCL-90-R symptom T-scores: anxiety, 80; hostility, 61; phobia, 76; paranoia, 57; psychoticism, 71; somatization, 80; obsessive compulsive behavior, 80; interpersonal sensitivity, 67; depression, 74; and her GSI was 75. Concurrent with the psychiatric distress, participant D experienced significant changes in circulating androgens. Pregnancy DHEAS and testosterone concentrations were 596 pg/mL and 19 pg/mL respectively. Postpartum DHEAS jumped to 2799 pg/mL while testosterone concentrations rose to 33 pg/mL.

In addition to the violent images, participant E suffered from periods of autonomic instability (greater than twice daily) that were marked by increased heart rate, chest pain, leg pain, difficulty breathing and night sweats for which she sought medical attention. Various tests were run and all were negative. Detailed information was not disclosed to this investigator. At 10 days postpartum she developed mastitis, concurrent with a high fever and was prescribed the antibiotic Diaclox. She was encouraged repeatedly by this investigator to seek treatment for her psychological distress, but she declined to do so. Phone conversations with the investigator indicated no remission in either physiological or psychological symptoms over the course of the first month postpartum. At approximately one month postpartum, she sought medical treatment and was prescribed citalpram hydrobromide (Celexa) but
did not receive counseling. She remained on Celexa for approximately one month, at which time she was prescribed Lexapro. Postpartum cognitive performance improved or remained stable across all domains except for spatial memory, which declined significantly from pregnancy to the 10 day postpartum testing session.

At four months postpartum, Participant E was still taking Lexapro and suffering from psychiatric symptoms but she reported that the occurrence of autonomic instability had diminished from twice daily to 2-3 times per week. The participant also reported that the medication had helped with her “motivation to get out of bed.” Although the autonomic instability had largely diminished she still suffered from night sweats. Moreover, the occurrence of obtrusive thoughts and subsequent compulsive avoidance behavior had remained the same or had increased. She reported being plagued by images of her daughter being mauled by dogs, of being stabbed, and of having the cable from the breast pump strangle her daughter. Again she was encouraged to seek treatment and refused, claiming that her symptoms had largely been minimized by the physician that had prescribed her the medication. Her SCL-90-R T-scores at this time were: anxiety, 77; hostility, 61; phobia, 76; paranoia, 67; psychoticism, 69; somatization, 66; obsessive compulsive behavior, 68; interpersonal sensitivity, 68; depression, 68; and GSI, 72.

Concurrent with the elevated SCL90-R T-scores, some supra-clinical hormone values were observed with the concentrations of DHEAS being almost three times above normal clinical ranges at 7212 pg/mL while her progesterone was at 700 pg/mL. She was encouraged to follow-up with her physician regarding endocrine function. It is not known which endocrine tests were completed but the patient
reported no abnormalities were identified. Cognitive performance remained stable or improved minimally. Verbal memory was at or just above average in all domains except for Trial B, proactive interference which remained at the 16th percentile. Spatial memory performance remained at the 42nd percentile.

At eight months postpartum, participant E’s psychiatric symptoms were still elevated though not as severely as at previous test times. She had stopped taking Lexapro at approximately five months postpartum and had not received counseling. Her DHEAS were still above the clinical cut off at 5731 pg/mL, more than twice the upper range of normal non-pregnant concentrations. In addition to the psychiatric distress, she reported an unusual skin condition marked by excessively scaly skin on her wrists, feet, ankles, knees and torso. Dermatological treatment had not provided relief. Based upon her hormone values, she was again encouraged to follow-up with her physician: the results of which are unknown as she dropped out from the study after this test time. Cognitive performance at eight months postpartum showed no significant changes from the previous test times and remained within or just below average.
CHAPTER 5

DISCUSSION

Trends in Postpartum Symptomatology

The purpose of the study was to examine prospectively the longitudinal trends in postpartum psychiatric disturbances, cognitive performance and hormone values in a cohort of healthy, primigravid women. This study represents the first longitudinal, cohort investigation of these variables. Findings from this study confirm some, and dispute other, commonly held hypotheses regarding pregnancy and postpartum that had hereto not been tested. Perhaps the most important of these involves the onset and course of psychiatric disturbances relative to puerperal hormone changes.

Postpartum mental illness has heretofore been classified along the spectrum of mood disorders, predominantly based on unipolar depression not linked to organic factors. The DSM-IV allows for the onset of postpartum disorders within 30 days of parturition, but researchers regularly include cases as far out as one year post-delivery (Andrews-Fike, 1999; Gavin et al., 2005; Mowery & Lennon, 2001; Pfuhlmann et al., 1998; Sing & Kauer, 1999; Wisner, Peindl & Hanusa, 1993; Wisner, Peindl & Hanusa, 1995).

Data from Marrs (2006) and the present study support the time-limited onset put forth by the DSM-IV, by demonstrating that new cases of postpartum psychiatric distress are not likely to originate beyond four months post-delivery. Even though
symptoms may wax and wane somewhat over the postpartum year, the most significant psychiatric symptoms emerge in the days following parturition and largely dissipate in all but the most serious cases by four months postpartum.

This general finding is consistent with data from a recent Danish registry study by Munk-Olsen et al. (2006) who reviewed the records of 1171 women over the course of 30 years and demonstrated that women were at significantly greater risk of needing either in-patient and/or out-patient psychiatric care in the first 19 days following parturition than at any other period in their lives. Similarly, Stowe et al., (2003) found that 66% of all cases of postpartum depression develop within three weeks postpartum and Klompenhouer and van Hulst (1991) who found that 70% of all cases of postpartum psychosis develop within 10 days of parturition.

Findings from Marrs (2006) and the present study suggest that the limited range of psychiatric symptoms considered by the DSM-IV and investigated by most researchers needs to be expanded. Although depression was certainly present in both Marrs (2006) and the current study and was, in both cases the most frequently ascribed to symptom cluster, depression was not the most debilitating symptom indicated by the obtained SCL-90-R T-scores. Rather, at four, eight and twelve months postpartum the mean T-scores for phobia, psychoticism and obsessive compulsive behavior scores generally exceeded depression T-scores. This may have been related to the type of questions that load on the depression scale. After all many depressive “symptoms” might be expected as a consequent of childbirth and even of child care and not indicative of true psychiatric dysfunction. Be that as it may, the data obtained in this study do indicate that anxiety type symptoms, including
autonomic instability, phobia, obsessive behavior and some degree of psychoticism are at least as evident as depression in the postpartum. This finding is consistent with the few studies that have investigated co-morbid anxiety symptoms postpartum and found anxiety symptoms to be prevalent in both the immediate and late postpartum period (Austin, 2004; Reicher-Rossler & Fallahpour, 2003; Ross et al., 2002; Wenzel et al., 2005).

Thus, it is suggested that postpartum psychiatric distress hinges more on the anxiety than depressive disorders (Austin, 2004; Ross et al., 2002; Wenzel, Gorman & Stuart, 2001; Wisner et al., 1999). When the individual scores from the present study are considered, it is apparent that only elevated anxiety components persisted beyond four months postpartum. With the two most serious cases of postpartum psychiatric distress, Participants D and E, depression T-scores did not exceed anxiety symptom T-scores at any postpartum test time, and the primary complaint reported by both participants was anxiety with autonomic instability.

What distinguished these two participant’s cases from each other, was the presence of violently aggressive and obtrusive images and the degree of psychoticism in Participant E. Although both participants experienced similar levels of anxiety and autonomic instability, only Participant E experienced the intrusive images and, perhaps, as a consequence this extended her symptoms through eight months postpartum. Jennings et al 1999 found that violent, intrusive thoughts were more prevalent in postpartum women and contributed significantly to the severity of their symptomatology. Thus, while depression certainly played a role in postpartum...
psychiatric distress, it was neither the most prominent nor the most persistent
symptom and may in fact have been secondary to other symptoms.

In light of these findings, future research should be directed toward the
development of a postpartum-specific assessment tool that addresses both the breadth
and the depth of psychiatric symptoms, is capable of distinguishing between
postpartum and non-postpartum psychiatric distress and is administered in closer
proximity to the precipitating event.

Trends in Postpartum Cognitive Performance

Cognitive deficits are an anecdotally accepted consequence of pregnancy that
have thus far eluded empirical explanation. Research shows that upwards of 80% of
pregnant women perceive that they have memory deficits during pregnancy (Brindle
et al., 1991; Jarrahi-Zadeh et al., 1969; Sharp et al., 1993). However, very few studies
have empirically demonstrated pregnancy related cognitive deficits.

Investigations by Buckwalter et al. (1999) and Marrs (2006) demonstrated
significant verbal and spatial memory deficits during pregnancy and the immediate
postpartum when compared to age, IQ and gender matched normative data but did not
obtain consistent significant correlations between individual hormones or
found no differences in cognitive performance between pregnant and non-pregnant
women and no correlations between mood symptoms (as measured by the Profile of
Mood States) and any aspect of cognitive performance.
Review of the data from the present and the previous study (Marrs, 2006) indicates that some level of cognitive impairment may occur during pregnancy and persist through the immediate postpartum. Although in the present study, any deficits that occurred typically resolved in the course of the year-long postpartum period observed. Verbal and spatial memory, as measured by the CVLT-II and CFT respectively, were most notably impaired during pregnancy.

When compared to normative data, the mean data for spatial memory obtained from the current participants showed no impairment in spatial memory measured at 10 days postpartum and at eight months postpartum but did show impairment at four and twelve months postpartum. Further review of CFT performance demonstrated that improvement occurred at those test times when the Taylor alternate form was administered. Researchers speculate that the Rey CFT is more difficult than other alternate CFT forms and that scores on the standard form are at least five points lower than those observed on the alternate forms (Spreen & Strauss, 1998). When mean scores on the alternate forms were adjusted for the five point difference, impaired performance across all test times was observed. These obtained and adjusted low scores across trials were particularly noteworthy insofar as only minimal practice effects were exhibited. Despite having been exposed to the same figure on three different occasions, recall scores improved by less than 10% per trial.

Verbal memory scores were substantially depressed during pregnancy and the early postpartum. However, except for Trial B, the measure of proactive interference, verbal memory scores generally showed a significant linear increase across the one year postpartum period. Bolstering performance on the recall measures were semantic
memory skills. Semantic memory scores across all trials, but especially at four, eight and twelve months postpartum were significantly higher than individual verbal memory recall measures.

The increasing trends in recall scores and semantic clustering across the postpartum contrast with the uniformly poor learning slope measure and Trial B. Trial B measures the individual’s ability to adequately suppress irrelevant information influences the amount of information that can be retrieved from working memory (Jonides & Nee, 2006). A discrepancy of greater than a 1.5 point difference in z-score between Trial 1 and Trial B (Trial 1 > Trail B) is suggestive of impairment (Donders, 2006). This criterion was met during pregnancy, postpartum and again at twelve months postpartum and suggests the possibility of impairment in working memory.

Trends in Postpartum Hormones

Puerperal hormone concentrations are reported to increase during pregnancy, decrease following delivery, and return to “normal” in the ensuing months as the cyclicity of reproductive hormones returns (Illingworth & McNeilly, 1998). This hypothesis has generally been confirmed for the reproductive hormones such as progesterone, estrone, estradiol and estriol, but not for the androgenic hormones such as DHEAS and testosterone. There is, however, a paucity of data regarding the reproductive hormones in the months following parturition and basically no data regarding postpartum trends the non-reproductive adrenal androgens. Accordingly, the impact of these hormones on postpartum mental health is unclear.
Marrs (2006) showed that progesterone, estrone, estradiol and estriol were elevated in late pregnancy and decreased significantly by the 10 day postpartum testing session. DHEAS and testosterone concentrations did not follow this pattern. Testosterone concentrations were low in late pregnancy contrary to published reports (Bammann, Coulam & Jiang, 1980), while DHEAS concentrations were somewhat elevated in late pregnancy and then rose dramatically following parturition, again contrary to published reports (Milewich et al., 1978; Soldin et al., 2005; Tagawa et al., 2004). Moreover, both the low late pregnancy and the elevated puerperal DHEAS concentrations were significantly associated with the breadth and severity of psychiatric symptoms.

Thus, it was postulated in the present study, that the degree to which DHEAS returned to within normal non-pregnant concentrations would coincide with improvement in psychiatric symptomatology. Inasmuch as only low late pregnancy and not postpartum testosterone concentrations were associated with psychiatric symptoms in Marrs (2006), testosterone was not expected to be a factor in the present study. It was also postulated that if DHEAS concentrations remained above the normal clinical values, psychiatric symptoms would persist. Moreover, to the degree that DHEAS and by association DHEA might affect the metabolism of other steroid hormones, chronically elevated DHEAS concentrations were expected to elicit unspecified changes in the circulating values of other steroids hormones.

The findings from this study, although preliminary and necessarily limited by the small number of participants, support each of these hypotheses. In the present study, DHEAS was the single largest contributor to postpartum distress across all test
times with almost twice as many significant associations as any other hormone measured. In the case of the anxiety type disorders such as anxiety, phobia, paranoia, psychoticism and obsessive compulsive behavior, DHEAS accounted for upwards of 80% percent of the variance in symptom severity. Although statistical significance must be interpreted cautiously herein light of the small participant sample, these data suggest that DHEAS plays an integral role in postpartum mental health.

Analyses of individual cases, illustrate both the impact of acutely elevated DHEAS on psychiatric well-being and the persistence of psychiatric and physiological distress associated with chronically elevated DHEAS. In current study, DHEAS concentrations increased dramatically following parturition in seven of the nine participants and for five of those seven, elevated GSI scores indicated psychiatric distress. Of those five participants, DHEAS values of two participants exceeded the upper limit (>2500 pg/mL) of what is considered normal for non-pregnant women.

The two participants, D and E, whose DHEAS values exceeded the clinical cutoff in the immediate puerperium, were the most severely distressed of the group and reported experiencing symptoms at least through the first couple of months following delivery. Unfortunately, testing did not begin again until four months postpartum. However, by four months postpartum, DHEAS concentrations in Participant D and the other participants had returned to within normal ranges. Participant D’s DHEAS remained within the normal limits for the duration of the study and her symptoms largely dissipated, whereas the DHEAS values of other
participants increased beyond the reference range intermittently and in parallel with symptom elevations.

DHEAS concentrations in Participant E, however, continued to increase and by four months were at >7200 pg/mL, well beyond what is considered normal. In conjunction, her psychiatric symptoms persisted and other hormone values began showing signs of irregularity. Namely, progesterone concentrations moved beyond the normal luteal phase values (>600pg/mL) even though she had not yet begun to menstruate. At eight months, although her DHEAS concentrations had decreased somewhat, they were still well above the normal range and her testosterone and estriol, had moved significantly above normal non-pregnant values at this time.

Concurrent with these hormone changes and possibly in large part because of them, significant correlations between progesterone and psychiatric symptoms appeared at four months and again at twelve months postpartum. In Marrs (2006) progesterone was not associated with psychiatric symptoms at either test time and so it was unexpected for progesterone to be significantly correlated with distress in the present study. It is possible that the correlations between progesterone and symptoms at twelve months were spurious. Participant E was not available for testing at this time and thus, both her hormone values and symptom scores were estimated.

Inasmuch DHEAS, and by association DHEA, impact the synthesis of many hormones via enzymatic regulation (Labrie et al., 1997; Genazzani et al., 2003; Ueshiba et al., 2002), it is speculated that elevated DHEAS observed at four months postpartum, was associated with the increase in circulating progesterone. The
consequent development of significant correlations between progesterone and symptoms may support this hypothesis.

As the reservoir for DHEA, increased DHEAS values, often correspond to increased DHEA, testosterone and estradiol and have been found to influence other hormone values such as allopregnanolone concentrations (Genzanni et al., 2006). Allopregnanolone is the primary metabolite of progesterone. It is speculated that DHEA up-regulates 17, 20 lyase activity and shifts metabolism towards the progesterone pathway (Genzanni et al., 2006) presumptively increasing progesterone concentrations as well as concentrations of this metabolite. Barring complete abrogation of STS activity, for which there is no evidence of in the current study, high concentrations of DHEAS would be expected to increase DHEA values to some degree. The spike in progesterone and concurrent associations with symptoms could reflect this shift.

With elevated DHEAS, testosterone and estradiol concentrations are expected to increase. This has been established with PCOS and hyperandrogenic women where DHEAS, DHEA and the entire aromatase pathway is up-regulated significantly (Carr, 2001; Elsenbruch, 2003; Yildiz, 2004). This appeared not to occur here, with mean concentrations for both hormones falling at the lower end of the non-pregnant, non-postpartum, reference ranges. However, since there are no established salivary reference ranges for postpartum and lactating women, and data on menstrual cycle phase was not collected in the present study, it is impossible to discern how these factors might have influenced the observed hormone values.
Nevertheless, with elevated DHEAS, elevated testosterone and estradiol are expected. Review of the individual hormones values reveals that the women with the highest DHEAS values also had the highest testosterone values. Even though their testosterone values fell squarely within the non-pregnant range at 15-23 pg/mL, these values were ~100% greater than those of the other participants. Consequently, DHEAS and testosterone were significantly correlated at this and the subsequent test times.

Testosterone which had been negatively associated with onset of symptoms in Marrs (2006) was positively associated with a myriad of symptoms at four months postpartum. The directional shift in this correlation was particularly striking insofar as mean circulating concentrations of testosterone at four months postpartum were 50% lower than those observed during pregnancy when testosterone was associated negatively with symptoms. As was speculated with progesterone, the testosterone to behavior correlations may be more related to the associations between DHEAS and symptoms and DHEAS and testosterone than to actual associations between testosterone and symptoms, especially in light of the difference in testosterone values between pregnancy and postpartum.

It is also possible that factors in pregnancy versus postpartum pharmacokinetics account for the absolute difference in testosterone values that are now associated with symptoms. The amount of testosterone required to elicit a cellular or behavioral response during pregnancy could appear higher than what is required postpartum because of the increased plasma volume during pregnancy. The relative difference between the two values may actually represent similar
concentrations of hormone per unit of volume, if that could be calculated. This would suggest that there is a range of effective hormone values per unit volume that when breached elicits compensatory reactions in other hormones or enzymes, of which psychiatric symptoms are simply the outward manifestation. What this range is and how it relates to the other hormones is unclear.

Estradiol, which is a direct metabolite of testosterone, was not correlated with testosterone at any test time nor was it correlated with any other hormone. As in Marrs (2006) estradiol was not correlated with symptoms. Mean estradiol values fell within the normal non-pregnant, non-postpartum range, although the inter-individual variability was great and may have been related to menstrual phase variation. Its lack of association with testosterone may suggest an alternate metabolic pathway, perhaps the bioconversion of estrone > estradiol. However, this pathway typically favors the estradiol to estrone conversion versus the estrone to estradiol conversion (Stanczyk, 1998).

Estriol concentrations which had not been associated with symptoms either during pregnancy or following parturition were significantly and positively associated with a myriad of symptoms at eight months postpartum even though circulating values were some 98% less than during pregnancy. Again, the change in plasma volume may have contributed somewhat to the relative change in estriol. However, unlike pregnancy testosterone which is thought to represent mostly maternal synthesis (Triosi et al., 2003), estriol is largely of fetal origin (Challis & Lye, 1998). Indeed, expression of the hepatic enzyme 16α-OH that converts DHEAS to estriol is reported to be extremely low in adulthood (Lacroix, Sonnier, Moncion, Cheron & Cresteil,
1997; Leeder et al., 2005; Stevens et al., 2003). So it is particularly intriguing that postpartum estriol concentrations observed in this study were not only at the high end of non-pregnant clinical reference ranges but were also associated with symptoms. Like the elevated progesterone, elevated estriol may represent a compensatory reaction related to elevated DHEAS i.e. up-regulated hepatic enzymes to increase metabolic clearance with the ensuing correlations between this hormone and symptoms simply denoting that change.

The cause of the postpartal increase in DHEAS remains to be investigated, but data from this study, when combined with the findings from the various cancer studies cited previously and the work by Maayan et al. (2005) point to diminished STS activity. Research on STS inhibitors for the treatment of hormone dependent cancers, indicates that STS inhibition not only elicits an increased ratio of sulfated to non-sulfated hormones, combined with a decrease in downstream androgens such as testosterone and estradiol (Gell et al., 1998; Pasqualini & Chetrite, 2001; Stanway et al., 2006), but also, mediates behavioral changes in rodent models (Nicholas et al., 2001) and psychiatric distress in human patients (Stanway et al., 2006).

Maayan and colleagues found that withdrawal from elevated estradiol in rodent pseudo-pregnancy was associated with diminished STS activity and a consequent increase in cortical DHEAS, whereas Pasqualini and Chetrite 2001 demonstrated that elevated estradiol alone, could effectively diminish STS activity. Based upon those findings, it is postulated that the continued increase in estradiol concentrations through pregnancy negatively impacts STS activity, but because of abundant placental STS (Dibbelt & Kuss, 1991), the affects are not observed fully.
until after parturition. The resultant increase postpartum DHEAS may simply reflect a transient diminishment of STS activity that over time, will return to non-pregnant levels.

It also possible, that for some women the physiological condition of pregnancy unmasks a previously latent endocrine pathology. This hypothesis was presumptively supported by the medical conditions of Participant D’s son and Participant E herself. Both participants disclosed the presence of disorders that if genetically verified, are consistent with congenitally impaired STS activity.

Participant D’s son had been born with a disorder called cryptorchidism or testicular mal-descent, a condition that is present in 1-6000 male births. Participant E, who had a female child, developed a skin condition strikingly similar to the X-linked ichthyosis that is associated with STS deficiency in male children and occurs in 1-6000 births as well. Both conditions may be caused by similar genetic mutations that impair STS activity (Bradshaw & Carr, 1986). Female carriers of this mutation do not express the aforementioned disorders, but have been reported to acquire similar skin-related conditions (Reed et al., 2005). Some evidence suggests that female carriers express significantly less STS activity than women who do not carry this mutation (Epstein & Leventhal, 1981). Unfortunately, there is only one published report where STS activity was measured in the female carriers’ of the mutation and there are no published reports regarding any other potential behavioral or physiological manifestations. Nevertheless, the co-manifestation of STS related medical conditions, elevated DHEAS and psychiatric symptoms points to compromised STS activity in the etiology of postpartum psychopathology. Whether the enzyme changes
are transient as much of the data in this study suggest or chronic, as was potentially
exhibited by participant E requires additional investigation.

Because multiple factors are capable of up- and/or down-regulating STS
activity, including estradiol, it is not clear how the menstrual cycle affects the balance
between DHEA and DHEAS. The intermittent increases in individual DHEAS values
observed in this study, combined with the consequent symptom elevations could
reflect menstrual cycle variations in STS. It might be that upon investigation of these
factors, STS activity is found to mediate the severity of premenstrual syndrome by
way of increased DHEAS. Inasmuch as women with premenstrual distress are
reported to have a higher incidence of postpartum psychiatric disturbances (Bloch et
al., 2005), it is possible that STS activity contributes to both disorders. Further
examination of the associations between DHEAS and/or STS and female
psychopathology might reveal such an association.

Conclusion

While a preliminary investigation with a limited number of participants,
results from this study provide several important insights regarding the onset, course
and hormonal correlates of peripartal psychiatric disturbances and cognitive
functioning. Results from this study show that psychiatric disturbances are more
prevalent and more severe in the immediate postpartum than in the months following
parturition. A large number of the psychiatric disturbances are associated with
elevated DHEAS, which in turn appears to influence the equilibrium of other
hormones. In some women the distress is transient and abates as DHEAS values
return to within normal reference ranges. In others, the increase in postpartal DHEAS
is more drastic and chronic with corresponding symptoms that are more severe and persistent. Whether transient or chronic, postpartum psychiatric symptoms develop in association with puerperal hormone changes and cannot be relegated to the realm of psychosocial stressor.

Data from this study also demonstrated that puerperal cognitive deficits, although not associated consistently with puerperal hormone changes or mood changes do exist, and appear to involve some aspect of working memory. Deficits in both verbal and spatial memory were observed during pregnancy. Review of the longitudinal trends in these cognitive dimensions suggests many aspects of verbal memory improve, but that difficulties with proactive interference persist through the year. Spatial memory does not appear to improve. Collectively, these data suggest that motherhood negatively impacts working memory.
Table 1: Participant Data

Participant pregnancy and health status across test times.

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Average length of gestation 278 days. V: vaginal. No record of breastfeeding status for Participant E at T5 or Participant F at T4. *Participant E was taking medication until approximately five months postpartum. Diaclox is antibiotic. Lexapro and Celexa are anti-depressants. Yasmin and Levora are oral contraceptives. Participant H was 5 weeks pregnant at T5.
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SYM: percent symptomatic (T score >60); ANX: anxiety; HOS: hostility; PHOB: phobia; PAR: paranoia; PSY: psychoticism; SOM: somatization; OC: obsessive compulsive behavior; IS: interpersonal sensitivity; DEP: depression; GSI: global severity index.
Table 3: Longitudinal trends in pregnancy and postpartum symptoms

Repeated measures, contrast and trend analyses for SCL-90-R scores across the year.

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<th>PAR</th>
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<th>SOM</th>
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T1: 37 weeks pregnant; T2: <10 days postpartum; T3: four months postpartum; T4: eight months postpartum; T5: twelve months postpartum; ANX: anxiety; HOS: hostility; PHOB: phobia; PAR: paranoia; PSY: psychoticism; SOM: somatization; OC: obsessive compulsive behavior; IS: interpersonal sensitivity; DEP: depression; GSI: global severity index.
Table 4: Longitudinal trends in pregnancy and postpartum cognitive performance

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<td>94%</td>
<td>32%</td>
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</table>

IM: immediate; centiles derived from age and IQ-matched normative data reported in Spreen and Strauss (1998). IQ-matched normative data not available for semantic clustering and learning slope (Delis et al., 2000). Alternate forms were used at 10 days and 8 months postpartum.
Table 6: Longitudinal trends in pregnancy and postpartum verbal memory

Repeated measures, contrast and trend analyses for CVLT-II across test times.

<table>
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<tr>
<th></th>
<th>IM Recall 1</th>
<th>IM Recall 1-5</th>
<th>IM Recall B</th>
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<td>T3 vs T4</td>
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<td>T4 vs T5</td>
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<td>0.007</td>
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IM: immediate; CFT: complex figure test; T1: 37 weeks pregnant; T2: <10 days postpartum; T3: four months postpartum; T4: eight months postpartum; T5: twelve months postpartum.
Table 7: Mean hormone values

<table>
<thead>
<tr>
<th>Hormone values across all test times and reference ranges.</th>
<th>37 Weeks Pregnant</th>
<th>&lt;10 Days Postpartum</th>
<th>4-Months Postpartum</th>
<th>8-Months Postpartum</th>
<th>12-Months Postpartum</th>
<th>Reference Ranges*</th>
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<tr>
<td></td>
<td>Mean pg/mL</td>
<td>Mean pg/mL</td>
<td>Mean pg/mL</td>
<td>Mean pg/mL</td>
<td>Mean pg/mL</td>
<td>Follicular Luteal pg/mL</td>
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<td>1276.18</td>
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<td>8.01</td>
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<td>8.69</td>
<td>14.57</td>
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<td>9.05</td>
<td>14.30</td>
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<td>.5-16</td>
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</table>

*Reference ranges for non-pregnant, non-postpartum women. The follicular phase occurs during the early part of the cycle until ovulation between days 14-16 and corresponds with a peak in estradiol. The luteal phase occurs during days 20-22 and corresponds with a peak in progesterone.
### Table 8: Individual hormone values

**Individual hormone values and changes across test times.**

<table>
<thead>
<tr>
<th>Testosterone pg/mL</th>
<th>Participant</th>
<th>37 weeks</th>
<th>&lt;10 Days</th>
<th>Percent Change</th>
<th>Postpartum</th>
<th>Percent Change</th>
<th>4-Months</th>
<th>Percent Change</th>
<th>8-Months</th>
<th>Percent Change</th>
<th>12-Months</th>
<th>Percent Change</th>
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<td>77.3</td>
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<td>-24.97%</td>
<td>64.4</td>
<td>11.03%</td>
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<th>Postpartum</th>
<th>Percent Change</th>
<th>4-Months</th>
<th>Percent Change</th>
<th>8-Months</th>
<th>Percent Change</th>
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<th>Postpartum</th>
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<th>4-Months</th>
<th>Percent Change</th>
<th>8-Months</th>
<th>Percent Change</th>
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<tr>
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Table 9: Hormone to hormone correlations

Hormone to hormone correlations.

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*p<.05, **p<.01, ***p<.001.
Table 10: Longitudinal trends in pregnancy and postpartum hormones

Repeated measures, contrast and trend analyses for hormone values across test times.

<table>
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<tr>
<th></th>
<th>Progesterone</th>
<th>DHEAS</th>
<th>Testosterone</th>
<th>Estradiol</th>
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<td>Trend Type</td>
<td>Linear</td>
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<td>Cubic</td>
<td>Linear</td>
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<td>Significance</td>
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<td>0.049</td>
<td>0.044</td>
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<td>T1 vs T2</td>
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<td>T2 vs T3</td>
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<td>0.490</td>
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<td>T3 vs T4</td>
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<td>0.022</td>
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<tr>
<td>T4 vs T5</td>
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<td>T1 vs T5</td>
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<td>T2 vs T5</td>
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<tr>
<td>T3 vs T5</td>
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<tr>
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<td>T5 vs Previous</td>
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<td>0.005</td>
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T1: 37 weeks pregnant; T2: <10 days postpartum; T3: four months postpartum; T4: eight months postpartum; T5: twelve months postpartum.
Table 11: Hormone to symptom correlations

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<th>ANX</th>
<th>HOS</th>
<th>PHOB</th>
<th>PAR</th>
<th>PSY</th>
<th>SOM</th>
<th>OC</th>
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ANX: anxiety; HOS: hostility; PHOB: phobia; PAR: paranoia; PSY: psychoticism; SOM: somatization; OC: obsessive compulsive behavior; IS: interpersonal sensitivity; DEP: depression; GSI: global severity index; *p<.05, **p<.01, ***p<.001.
Figure 1: Maternal fetal-placental steroidogenesis

Figure 2: Adrenal and peripheral steroidogenesis

Figure 3: Percentage of symptomatic women

Anxiety and Depressive Symptoms

Psychotic Symptoms

Associated Symptoms

Severity of Symptoms

ANX: anxiety; PHOB: phobia; OC: obsessive compulsive behavior; DEP: depression; PSY: psychoticism; PAR: paranoia; HOS: hostility; SOM: somatization; IS: interpersonal sensitivity; GSI: global severity index.
Figure 4: Longitudinal trends in pregnancy and postpartum cognitive performance

Spatial Memory

- CFT Copy
- CFT Recall

Attention and Cognitive Processing

- PASAT 2.4
- PASAT 2.0
- PASAT 1.6
- PASAT 1.4

Executive Function Word and Design Generative Ability

- FAS
- Animal Design
- Free Design
- Design Fixed

Motor Processing Speed

- FTT-P
- FTT-NP
- PPT-P
- PPT-NP

CFT: complex figure test; PASAT: paced auditory serial addition test; FTT-P: finger-tapping test preferred hand; FTT-NP: finger-tapping test non-preferred hand; PPT-Purdue pegboard test preferred hand; PPT-NP: Purdue pegboard test non-preferred hand.

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Figure 5: Longitudinal trends in pregnancy and postpartum verbal memory

CVLT-II: California Verbal Learning Test-II; IM: immediate.
Figure 6: Longitudinal trends in pregnancy and postpartum hormones
APPENDIX A

OFFICE FOR THE PROTECTION OF HUMAN PARTICIPANTS APPROVAL
DATE: June 23, 2004

TO: Dr. Douglas P. Ferraro
    Psychology Department

FROM: Dr. Michael Stitt, Chair
    UNLV Social/Behavioral Sciences Institutional Review Board
    via the Office for the Protection of Research Subjects

RE: Protocol Title: Cognitive and Affective Correlates of Reproductive Hormones
    OPRS# 0406 - 1251

This memorandum is notification that the UNLV Social/Behavioral Sciences Institutional Review
Board reviewed and approved the subject protocol. Research on the project may proceed once you
receive a hardcopy of this memo from OPRS. This approval is effective from June 23, 2004, the date
of IRB approval, through June 2, 2005 a period of one year from the initial IRB review.

Should the use of human subjects described in this protocol continue beyond June 2, 2005, it will be
necessary for you to request an extension and undergo continuing review. Should you initiate any
changes to the protocol, it will be necessary to request additional approval for such change(s) in
writing through the Office for the Protection of Research Subjects.

If you have questions or require any assistance, please contact the Office for the Protection of
Research Subjects at OPRSHumanSubjects@ccmail.nevada.edu or call 895-2794.
NOTICE TO ALL RESEARCHERS:

Please be aware that a protocol violation (e.g., failure to submit a modification for any change of an IRB approved protocol) may result in mandatory remedial education, additional audits, re-consenting subjects, researcher probation, suspension of any research protocol at issue, suspension of additional existing research protocols, invalidation of all research conducted under the research protocol at issue, and further appropriate consequences as determined by the IRB and the Institutional Officer.

DATE: May 18, 2005
TO: Dr. Douglas Ferraro, Psychology Department
FROM: Office for the Protection of Research Subjects
RE: Notification of IRB Action
Protocol Title: Cognitive and Affective Correlates of Reproductive Hormones
Protocol #: 0406-1251

This IRB action will reset your expiration date for this protocol. The protocol is approved for a period of one year from the date of IRB approval. The new expiration date for this protocol is May 12, 2006.

PLEASE NOTE:
Attached to this approval notice is the official Informed Consent/Assent (IC/IA) Form for this study. The IC/IA contains an official approval stamp. Only copies of this official IC/IA form may be used when obtaining consent. Please keep the original for your records.

Should there be any change to the protocol, it will be necessary to submit a Modification Form through OPRS. No changes may be made to the existing protocol until modifications have been approved by the IRB.

Should the use of human subjects described in this protocol continue beyond May 12, 2006, it would be necessary to submit a Continuing Review Request Form 60 days before the expiration date.

If you have questions or require any assistance, please contact the Office for the Protection of Research Subjects at OPRS@unlv.nevada.edu or call 895-2794.
APPENDIX B

STUDY INSTRUCTIONS
Thank-you for participating in this study. Your participation will yield important information about postpartum mental illness.

Instructions for Saliva Collection

1. Upon rising on the morning of testing, before eating, drinking, breastfeeding* or brushing teeth, place specimen vial to bottom lip and spit into vial.
2. Fill vial with at least 8 ml of saliva.
3. Close vial.
5. Label vial with your 6-digit identification code (first initial, last initial, mm/yy of birth date, ex: AB0264), date and time of specimen collection.
6. Place vial in zip-lock baggie and refrigerate.
7. Specimen will be picked-up during your scheduled session.

Helpful Hints

*If you feel that you have to breastfeed prior to specimen collection, please wait 2 hours before attempting to spit into the vial. Please note on the label the time of breastfeeding and the time that the specimen was collected.

If you have difficulty producing the desired amount of saliva, imagine sucking on a sour lemon, or cut open a lemon (but don't eat it). The thought or sight of a sour lemon will initiate salivation.

Some women prefer to wrap a paper towel around the vial while spitting so as to collect any excess saliva.
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University of Nevada, Las Vegas

Dissertation Title: Longitudinal Trends in Postpartum Mental Health, Cognition and Steroid Hormones

Dissertation Examination Committee:
Chairperson, Dr. Douglas P. Ferraro, Ph. D.
Committee Member, Dr. Daniel Allen, Ph.D.
Committee Member, Dr. Jennifer Ramsey, Ph.D.
Graduate Faculty Representative, Dr. Michelle Elekonich, Ph. D.