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Cognitive and affective correlates of reproductive hormones

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COGNITIVE AND AFFECTIVE CORRELATES
OF REPRODUCTIVE HORMONES

by

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Bachelor of Arts
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1989

Master of Science
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2001

A thesis submitted in partial fulfillment
of the requirements for the

Master of Arts Degree in Psychology
Department of Psychology
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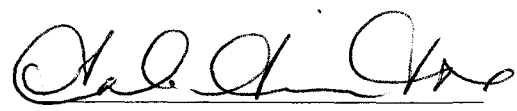
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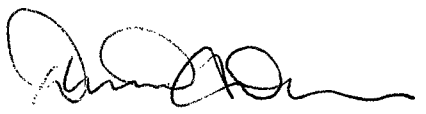
Cognitive and Affective Correlates of Reproductive Hormones

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


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ABSTRACT

Cognitive and Affective Correlates of Reproductive Hormones

by

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Approximately 80% of all women experience considerable mood lability in the days and weeks following parturition. Many researchers have attempted and failed to link postpartal mood changes to reproductive hormones and very little research examines perinatal cognitive ability. The goal of this research was to elucidate the pattern of cognitive and affective behaviors associated with the elevated hormones of pregnancy and the diminished hormones following parturition. The present study compared salivary progesterone, dehydroxyepiandrosterone (DHEAS), estrone, estradiol, estriol and testosterone with the results from a battery of neuropsychiatric assessments administered to thirty-two healthy, primigravid women at 37 weeks of pregnancy and within the first 10 days postpartum. Results from this study indicate that cognitive performance is impaired across multiple domains both during pregnancy and following parturition. Moreover, perinatal mood is adversely related to diminished late pregnancy testosterone levels followed by postpartal increases in DHEAS.

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CHAPTER 1

INTRODUCTION

Numerous animal studies indicate that steroid hormones exert both genomic and nongenomic influence on cellular communication and plasticity in the hippocampus, raphe nucleus, basal forebrain, frontal cortex, amygdala and the hypothalamus (Cabrera, Bregonzio, Laconi and Mampel, 2002; Hou, Yang and Voogt, 2003; Hsu and Smith, 2002; Johansen, Birzniece, Lindblad and Backstrom, 2002; Keefe, 2002; McEwen, 1998; Oades, 1978). While the genomic effects of steroid hormones on cell function have been widely researched, particularly in the cases of sexual differentiation and reproduction, nongenomic activity has only recently come to the forefront. In addition to regulating sexual differentiation and reproduction, researchers are finding that steroids also modulate everything from learning, memory, mood and cognitive states to stress response and seizure susceptibility, using both nuclear and non-nuclear non-transcriptional pathways (Backstrom, Zetterlund, Biom, and Romano, 1984; Baulieu and Robel, 1990; Cabrera and Navarro, 1996; Keefe, 2002; McEwen, 1998; McEwen, et al. 2001; Moss, Gu, and Wong, 1997).

Nowhere is this more evident than in progesterone's modulation of γ -aminobutyric acid (A) type (GABAA) chloride (Cl⁻) channels (Foley, et al. 2003; Johansen, et al. 2002; Takashima, Kawasaki, Kimura, Fujita and Sasaki, 2002) and dopamine (DA) release via n-methyl-d-aspartate (NMDA) glutamate receptors (Cabrera,

et al. 2002; Cabrera and Navarro, 1996; Cyr, Ghribi and DiPaolo, 2000). Progesterone and its metabolites are potent positive allosteric modulators of the GABAA chloride channel capable of producing dose-dependent effects ranging from sedation to anesthesia and even death (Arafat, et al. 1988; Concas, et al. 1997; Johansen, et al. 2002; Selye, 1946). Similar to the benzodiazepines, progesterone is a powerful sedative, hypnotic, anxiolytic and anticonvulsant when administered acutely (Arafat, et al. 1988; Backstrom, et al. 1984; Baulieu, 1990; Bitran, Hilvers and Kellog, 1991; Gulinello and Smith, 2003; Ghoneim, Henricks and Mewalt, 1984). Furthermore, as with benzodiazepines, chronic administration of progesterone produces both psychological and physiological tolerance and withdrawal symptoms including a marked increase in anxiety and irritability (Bloch, et al. 2000; Costa, Spence, Smith and French-Mullen, 1995; Ghoneim, Henricks and Mewalt, 1984; Gulinello and Smith, 2003; Hsu and Smith, 2003; Fujita, et al. 1999).

Numerous animal studies and some human studies suggest that like benzodiazepine, progesterone also impairs memory in a dose-dependent and time dependent manner (Arafat, et al. 1988; Costa, et al. 1995; Johansen, et al. 2002). Conversely, with chronic administration or exposure as tolerance develops memory improves (though not entirely to pre-administration levels) until withdrawal, where again there is a decremental decrease in memory function (Fujita, et al. 1999; Sundstrom, Smith and Gulinello, 2003).

Progesterone, via its metabolite allopregnanolone and in conjunction with estradiol, modulates the release of DA in both the nigrostriatal and mesolimbic pathways via binding to NMDA receptors (Cabrera, et al. 2002; Cabrera and Navarro, 1996; McEwen, 1998) and/or by regulating tyrosine hydroxylase levels (Hou, et al. 2003).

Progesterone and estrogen differentially bind to NMDA receptors in the hippocampus, dentate gyrus, nucleus accumbens and frontal cortex and regulate cellular excitability in a time and dose dependent fashion (Cyr, et al. 2000; McEwen, 1998). The ovarian hormones' influence on NMDA receptor activity in the hippocampus in general and on long-term potentiation in particular is arguably linked to learning and memory functions, while the role of progesterone on DA modulation in the nucleus accumbens and striatal region is thought to influence several aspects of mood and cognition.

Since human pregnancy is marked by both a rapid and sustained increase in ovarian steroid levels and an equally rapid decline following parturition (Buckwalter, et al. 2001; Russell, et al. 2001; Harris et al. 1994), it is the ideal model from which to study the connection between hormones, mood and mental state. Indeed, many studies have linked the precipitous fall in hormones to the elevated rates of anxiety, depression and psychosis seen postpartum and during menstruation (Harris, et al. 1994; Meakin, et al. 1995; Nott, et al. 1976; Sundstrom, et al. 2003; Weick, 1989). However, most human studies have found only weak associations among circulating ovarian hormone levels and mood and/or mental state (Buckwalter, et al. 1998; Harris, et al. 1994) This is particularly interesting in light of the animal research that has clearly and consistently shown a relationship between ovarian hormones, memory and behavior (Johansen, et al. 2002; Keefe, 2002). Additionally, electrophysiological data (Backstrom, et al. 1984; Becker, Creutzfeldt, Schwibbe and Wuttke, 1982; Hsu and Smith, 2003) further supports a relationship between ovarian hormones and cell activity as do cell culture and immunochemistry studies (Biggio, et al. 2001; Hsu, et al. 2003; Takashima, et al. 2002). In human studies, however, especially in the postpartum mental disorder paradigm, there

is little evidence beyond what is anecdotally accepted that indicates a clear and consistent connection between endocrine changes and alterations in either mood or cognition. This suggests a lack of clarity in the physiological indices of endocrine mediated cognitive and affective changes, a lack of sensitivity in the testing methods utilized, or both.

The failure to consistently connect steroid hormones to mood or cognition in human models is likely due to testing methodology. Most studies suffer from extremely small sample sizes, use vastly different measurement tools from one project to the next, and assay hormone levels only a limited number of times. Consequently, without a sufficient number of subjects, the projects lack the sensitivity to detect any changes. Furthermore, without repeated hormonal assays at regularly defined intervals over an extended period of time, it is difficult to control for all of the confounding variables associated with hormonal regulation (natural circadian rhythms, food intake, sleep, stress, etc.). However, when sample size is sufficient and multiple hormone tests are taken over an extended period of time at designated intervals, as in the case of the Cardiff Study (n, 120; Harris, et al. 1994), a trend emerges suggesting that there is an association between antenatal progesterone levels and postpartum mood symptoms. A similar but less consistent trend emerges linking estradiol to postpartal negative mood (DeNovaes, Almeida, Joffe and Cohen, 2001; Nott, et al. 1976; Keuvi, et al. 1983). Unfortunately, there is a relative paucity of research addressing the relationship between other prominent steroid hormones and mood and even fewer studies that have investigated the relationship between perinatal steroid hormones and cognition.

O'Hara and colleagues (1991) found an association between antepartal estriol and postpartum blues while Harris et al., (1994) found no significant relationship between

cortisol and perinatal depression. Buckwalter, et al. (1999) measured dehydroxyepiandrosterone (DHEA) and testosterone as well as progesterone and estradiol and showed higher DHEA levels were associated with better mood during pregnancy, while elevated testosterone was associated with increased negative mood postpartum.

Of the few studies that address the relationship between hormones and cognition, the results are mixed, again because of vast differences in testing methodology. Jarrahi-Zadeh and colleagues (1969) assessed 85 women both pre- and postpartum using a variety of subjective and objective instruments. They found an increased frequency of perceived deficit in memory during pregnancy that did not correlate highly with objective ratings. However, pregnant women as a group performed significantly more poorly on objective tests than when not pregnant; this was particularly evident in tasks that required concentration and motor speed. This was later confirmed by Sharp and colleagues in 1993 who, using a similar subjective/objective measurement design, found that 81% of the 48 women tested rated their memory during pregnancy as impaired. Furthermore, objective tests of memory performance found that pregnant women did indeed perform more poorly on verbal recall tasks as compared to controls. Neither Jarrahi-Zadeh (1969) nor Sharp (1993) attempted to link hormones to changes in cognition.

Other studies looking at cognitive changes associated with pregnancy include Eidelman et al. (1993) who looked at memory deficits during the immediate postpartum period (days 1-3) and found that though memory deficits did appear on day one they resolved within three days postpartum. Crawley, et al. (2001) showed that memory deficits were only subjectively perceived by women during pregnancy and were

objectively immeasurable at any time period either during pregnancy or after delivery. Recently de Groot, Adam and Hornstra (2003) found that selective attention was impaired antenatally at 36 weeks but resolved at 32 weeks postpartum. Neither Eidelman et al. (1993), Crawley et al. (2001) nor de Groot et al. (2003) measured or compared hormone levels to cognitive function, and each used substantially different instruments as dependent measures.

To date, Buckwalter and associates (1999) have been the only researchers to measure cognitive deficits associated with pregnancy and to attempt to link those deficits with hormone levels. Among the battery of neuropsychological assessments utilized, only verbal memory was significantly impaired during pregnancy and remained so one month postpartum. All other modules tested revealed no statistically significant deficits but did show trends of impairment in a number of areas. Furthermore, none of the cognitive tests correlated to any of the hormones assayed nor were they correlated to changes in mood. However, the changes in mood were correlated to particular hormones, which suggest at least a tenable link between hormones and mood. Most notably, elevated DHEA was associated with improved mood during pregnancy and elevated testosterone was associated with negative mood postpartum. However, as with the other studies mentioned, this study suffered from a small sample size ($n=19$) and took only two hormone samples. Moreover, Buckwalter, et al. (1999) and all of the other studies mentioned thus far (except the Cardiff study), measured hormone levels via serum or plasma. As will be discussed in detail in Chapter 2, neither serum nor plasma is a desired medium for measuring what is considered to be the biologically active component of the hormone. Salivary assays, such as those that were used in the Cardiff Study, measure the

biologically active portion of the hormone and thus provide a more sensitive assessment tool.

Finally, like all of the studies that preceded it, the Buckwalter et al. (1999) study used a standard battery of neurocognitive instruments that, while adept at measuring the gross cognitive deficits associated with traumatic or vascular injury, are relatively incapable of detecting what are likely to be subtle changes in function. Moreover, aside from measuring verbal memory which has been shown to be influenced by high levels of progesterone, this and all of the other studies failed to choose tools that measure other cognitive domains theoretically associated with chronically high levels of ovarian hormones.

Recall from the discussion above that progesterone is a potent positive allosteric modulator of GABAA CI- channels. Like benzodiazepine it is a powerful sedative, anxiolytic, anticonvulsant and, at strong enough doses, can be an anesthetic (Arafat, et al. 1988; Concas, et al. 1997; Johansen, et al. 2002; Selye, 1946). Also like benzodiazepine, progesterone though its extensive metabolites has an extended half-life (Baulieu, Robel, 1990; Keefe, 2002; McEwen, 1998); and it is capable of producing both psychological and physiological withdrawal symptoms (Bloch, et al. 2000; Costa, et al. 1995; Fujita, et al. 1999; Ghoneim, et al. 1984; Gulinello and Smith, 2003; Hsu and Smith, 2003). Furthermore, progesterone like the benzodiazepines shows a strong affinity for GABAA receptors in the hippocampus, and has been found in the raphe nucleus, nucleus accumbens, striatum, amygdala, frontal cortex and the hypothalamus (Bixo, Andersson, Windblad and Backstrom, 1997). Given as well that that progesterone enhances the release of DA in the striatum (Cabrera, et al. 2002; Cabrera and Navarro, 1996) and

nucleus accumbens, it is easy to infer a pattern of behaviors congruent with chronic progesterone exposure/withdrawal.

The sedative properties of progesterone predict changes in concentration, attention, motor and/or cognitive slowing. Its anxiolytic properties should reduce anxiety during pregnancy but increase anxiety after delivery, during the withdrawal phase. Its affinity to GABAA receptors in the hippocampus should affect learning and memory (McEwen, 1998), especially where processing speed is involved, while its presence in the raphe nucleus might alter arousal and excitability (Klink, Robichaud and Debonnel, 2002; Oades, 1978). The increase in circulating DA during pregnancy, particularly in the nucleus accumbens should increase motivational or pleasure-seeking activities as an addictive drug might. The precipitous decline in DA after delivery, however, should cause a bevy of withdrawal type symptoms, including increased anxiety. Since one of the major projection pathways from the nucleus accumbens is to the frontal cortex, the decline in both GABA and DA should have adverse effects on planning, organization and executive function as well as affect regulation, particularly with regard to social judgment and motivation via its connections with the amygdala and other limbic structures. In fact, when one compares the personality and cognitive changes associated with prefrontal cortex injuries to those associated with postpartum depression, a strikingly similar although more subtle, pattern emerges, particularly when one considers the executive dysfunction and mood lability reported by many pregnant and postpartum women. Yet there is no convincing evidence linking steroid hormones to changes in human cognition and affective regulation either during or after pregnancy.

With the above in mind, it is the purpose of this study to explore the connection among multiple steroid hormones and cognitive and affective functioning in pregnant and postpartum women. The present research utilized a battery of neuropsychological instruments sensitive to subtle changes in both cognitive and affective functioning, as well as salivary hormone assays capable of measuring the biologically active component of the hormones. The range of hormones measured was expanded to include not only progesterone and estradiol, but estrone and estriol, as well as DHEAS and testosterone. By increasing the sensitivity of the psychological assessment tools and the hormonal assays, it is predicted that a clear link between steroid hormone levels and cognition and steroid hormone levels and affective regulation will be rendered.

To summarize, the goals of this research are to identify: 1) cognitive and emotional changes associated with chronically elevated levels of steroid hormones during pregnancy, 2) cognitive and emotional changes associated with the rapid withdrawal of hormones postpartum, and 3) to identify biological markers of perinatal mood dysfunction.

CHAPTER 2

LITERATURE REVIEW

Animal studies have clearly and consistently shown a link between hormones and memory and, as much is possible, between hormones and affective behavior. But the data in human studies is inconclusive for a number of reasons. First, experimental design in animal studies is typically more tightly controlled and technical procedures are more invasive than is ethical with human subjects. Secondly, human studies more often than not have extremely small samples, often precluding the possibility of finding significant results. Thirdly, measures of cognitive and affective behavior are relatively limited in animal studies compared to the number of measures available in human research; thus very rarely do any two human studies use the same instruments. Fourthly, because the relationship between hormones, mood and cognition is a topic outside the purview of most disciplines, there is a paucity of human research compared to what is available in the animal literature. Finally, the lack of research and the interdisciplinary nature of the topic have created a real vacuum of understanding. Not only are there relatively few experts in steroid endocrinology, compared to the vast numbers in peptide endocrinology, but there are even fewer who are interested in the connection between hormones mood and cognition. Likewise, those who study mood and cognition very rarely consider the possibility that steroid hormones might influence the expression of either.

Given the lack of human research on the role of hormones, cognition and affective regulation, it might be useful to provide a fair amount of background information prior to reviewing the psychological literature. Indeed, a significant portion of this section will focus on the neuromodulatory role of steroid hormones in addition to the physiological components of the system itself. Since some of the most exciting research challenges many commonly held beliefs regarding steroid synthesis and intra-nuclear mechanisms of action, a basic review of these processes is also provided. After all the background information is presented, a thorough review of relevant literature is given, with emphasis on integrating information gleaned from animal studies and the overview of steroid endocrinology with data from human models.

The Endocrine System and the HPO Axis

The endocrine system utilizes hormones as a means of communication between the cells and tissues. Its primary purpose, together with the nervous system, is to maintain biological homeostasis. To that end, hormones are secreted directly into the circulatory system by the hypothalamus and the pituitary to various target glands including the adrenal, the thyroid, the testis and the ovaries. Through a series of both positive and negative feedback and feed forward loops, called circuits or axes, the endocrine system regulates hormone synthesis and secretion which in turn regulates energy metabolism, reproduction and growth (Niewoehaner, 1998). The hypothalamus is the primary integrator of the endocrine system and in conjunction with the pituitary modulates the hormonal secretion and synthesis that regulates the action of the autonomic nervous

system and the functioning of virtually all bodily organs (Martin, 1996; Niewoehner, 1998).

The hypothalamus along with the pituitary and the ovaries form a circuit called the HPO axis. Together they regulate the menstrual cycle and support pregnancy. During the menstrual cycle, the hypothalamus stimulates the pituitary's release of luteinizing hormone (LH) and follicle stimulation hormone (FSH) by releasing the gonadotropin-releasing hormone (GnRH). The release of hypothalamic GnRH causes the pituitary to release FSH and LH. As the follicle develops, 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 levels peak immediately before ovulation; this peak signals the decline of GnRH and LH levels at ovulation on about day 15 of the cycle. This part of the cycle is called the follicular phase. After ovulation, during the luteal phase, estradiol levels wane, while progesterone levels increase until day 21-23 when the corpus luteum forms. A couple of days later, the endometrium sheds and menstruation begins (Schwartz, 2000; Starr and McMillan, 1997). Estradiol reaches a second peak, simultaneously with the progesterone peak at days 21-23 (Kaplan, Pesce and Kazmierczak. 2003). If there is a viable follicle and fertilization occurs, estradiol continues to increase (along with estriol and estrone) and there is a surge in LH. After implantation, the fetoplacental unit begins secreting human chorionic gonadotropin hormone (B-hCG) which will maintain the corpus luteum and endometrium throughout the pregnancy. Elevated estradiol levels then suppress FHS secretion (Neal, 2002; Schwartz, 2000).

During a normal menstrual cycle plasma estrogen levels range from approximately 143-694 pmol/l in the follicular phase to 176-1134 pmol/l in the luteal phase (Griffin and Ojeda, 2000; Thompson, Sergejew and Kulkarni, 2000). During pregnancy total estrogen levels increase to 15,000 pmol/l (Illingworth and McNeilly, 1998) and immediately following delivery they fall very close to zero (Illingworth and McNeilly, 1998). Progesterone levels range from .6-2.6 nmol/l in the follicular to 13.2-75.2 nmol/l in the luteal phase (Griffin and Ojeda, 2000; Thompson, et al. 2000). Progesterone levels can rise to over 800 nmol/l during pregnancy and fall to as low as 2.7 nmol/l following delivery (Harris, et al. 1994; Illingworth and McNeilly, 1998).

It is important to notice three aspects of this system. First, even during the normal menstrual cycle, women generally experience at least a 2-fold increase in both estrogen and progesterone, which is significant in and of itself. But during pregnancy the increase for both hormones is exponential. Secondly, as with all hormones, ovarian hormones are released into the blood-stream where they must travel great distances to reach their target. Since there are estrogen and progesterone receptors located throughout the central nervous system (CNS), it is likely that a good percentage of these hormones bind with receptors in areas other than the hypothalamus and thus may be involved in functions other than reproduction. Thirdly, if ovarian hormones bind with other receptors in brain regions not directly associated with reproduction, then it stands to reason that the cyclical shift in hormones might have behavioral and/or cognitive correlates. Some evidence suggests that this is the case. For example, the rise and fall of estrogen is associated with both a cyclical potentiation and downregulation of dendritic growth and synaptogenesis in rat hippocampal cells both in culture and in vivo. Subsequent behavioral tests given

during different times of the rat estrus cycle mirror the pattern of growth and downregulation with increased efficiency in the Morris water maze test during periods of high estrogen and increased deficits during the high progesterone period (McEwen, et al. 2001). Human studies in the premenstrual syndrome paradigm suggest that there are both emotional and cognitive changes associated with the female menstrual cycle. Studies have shown that in the late luteal phase of the menstrual cycle, when progesterone levels are falling, anxiety increases rather significantly in some women (Poromaa, Smith and Gulinello, 2003). Cognitive researchers have shown that high levels of estrogen correlate with diminished performance on tests of spatial ability (Hampson, 1990) and improved performance on tests of verbal memory (Maki, Zonderman and Resnick, 2001; Hogervorst, Boshuison, Reidel, Willeken and Jolles, 1999).

Finally, catamenial epilepsy as well as other forms of epilepsy, are either initiated and/or exacerbated both during the follicular phase of the menstrual cycle when estrogen is elevated and in the late luteal phase of menstruation when progesterone levels drop significantly (Morrel, 1999). Electrophysiological data confirms that during the follicular phase, women show an increase in spike frequency, particularly in the hippocampus and in other regions of the temporal lobe where epileptogenesis is thought to evolve (Backstrom, et al.; 1984; Backstrom, 1976; Becker, Cruetzfeldt, Schwibbe and Wuttke 1982). Overall, researchers suggest that estrogen acts as an excitatory agent while progesterone is considered inhibitory.

Given the fact that hormones are released into circulation and travel great distances to reach their target combined with the possibility for hormone binding in regions not associated with reproduction, one would expect an abundance of evidence

linking changes in circulating hormones to changes in behavior and cognition. The above studies, particularly McEwen et al. (2001) and their work on estrogen and synaptogenesis and the epilepsy research certainly suggest that hormones modulate brain function in some fairly significant ways, but there is very little research in this area. Therefore, before discussing additional evidence linking the rise and fall of ovarian hormones to behavioral and cognitive changes, particularly during pregnancy where the changes are substantial, it might be helpful to review hormone synthesis, metabolism and neuromodulatory capabilities.

Peripheral Ovarian Steroid Synthesis and Metabolism

Synthesis

Standard tables of steroid hormone synthesis show the pathway listed in Figure 1. All steroid hormones are synthesized from cholesterol. Cholesterol is synthesized from acetate in the liver as well as from other cells throughout the body utilizing starches and/or fats. In the ovaries and adrenals, cholesterol is transformed into pregnenelone, the precursor for progesterone. The by-product of pregnenelone's conversion to progesterone is pregnenelone sulfate (PS), not listed in figure, but a potent neuromodulator in its own right.

The fate of progesterone is tissue and enzyme dependent (Hillier, 1998). Progesterone biosynthesis in the ovaries leads to production of 17- OH-progesterone, androstenedione, testosterone, and the three (there are twenty in all) primary estrogens estrone (E1), estradiol (E2), estriol (E3). Progesterone in the adrenals leads to the synthesis of deoxycorticosterone, corticosterone, aldosterone and eventually cortisol

(Hillier, 1998). The female and fetal adrenals also produce DHEA which is then converted first to DHEAS (sulfate) and then to estrone and estradiol (Russell, et al. 2001). Progesterone is also synthesized by glial cells in the central nervous system and by Schwann cells in the periphery, both in the absence of ovarian function (Keefe, 2002; Hillier, 1998).

Unlike the other steroid hormones, progesterone is further metabolized in the ovaries, adrenals and other tissues as well as in the central nervous system producing very active metabolites. Research shows that at least six of progesterone's 20 metabolites directly modulate neurotransmission (Table 1). Some of the more potent metabolites of progesterone found in animal studies include pregnanediolone, 3α and 5α -tetrahydroxydioxycorticosterone, (derived from corticosterone pathway) and allopregnanolone, (3α -OH-pregnan-20-one). Pregnanediolone is the end product of progesterone metabolism and allopregnanolone is formed from the 5α -reduced metabolite 5α -DHP or P3 (Bixo, et al. 1997). Arafat et al. (1988) found 5α -Pregnan- 3α -ol-20-one (P4) and 5β -Pregnan- 3α -ol-20-one (P6) to be the most abundant progesterone metabolites found in human plasma when measured via gas chromatography-mass spectrometry. Animal studies suggest that allopregnanolone, (3α -OH-pregnan-20-one), is the most abundant and potent progesterone metabolite. It is not clear if allopregnanolone was measured in the Arafat et al. study.

Measures performed on extracted human postmortem brain tissue showed significant levels of progesterone, allopregnanolone and 5α -DHP throughout the cerebral cortex, particularly in the hypothalamus, limbic system, brainstem, basal ganglia and cerebellum (Bixo, et al. 1997). The amygdala, the cerebellum, hypothalamus and nucleus

accumbens show the highest concentrations of progesterone, while the substantia nigra and the basal hypothalamus show the most allopregnanolone and 5 α -DHP. Bixo et al. suggested that the discrepancy in distribution may be related to the fact that progesterone is metabolized in two separate steps, progesterone to 5 α -DHP in neurons and 5 α -DHP to allopregnanolone in astrocytes.

Hormone Production

The production rate for estradiol in a normal cycling woman ranges from 100-600ug p/day depending upon the day of the cycle and the weight of the woman, with obese women producing up to two times the amount of estrogen (Faigle and Schenkel, 1998). The most potent of the estrogens are estradiol and estrone followed by estriol, which is consistent with their metabolic pathways.¹ However, during pregnancy estriol is most abundant (Kaplan, Pesce and Kazmerczak, 2003; Solomon and Fuchs, 1971).

The production rate of progesterone in non-pregnant women ranges from 15-20mg p/day in the luteal phase and falls to less than 5% of those values during the follicular phase (Faigle and Schenkel, 1998). Plasma levels range from 5- 20ng/ml depending upon the stage of the cycle. Progesterone's peripheral half-life is extremely short, approximately 30 minutes, but its metabolism produces several highly potent derivatives, which effectively extend the actions of the steroid. There are, however, indications that CNS levels of progesterone and its metabolites are maintained at steady and in some cases higher levels than those measured in circulation, even in the absence of ovarian or adrenal synthesis (Baulieu, 1991; Papadopoulos, et al. 1991).

¹ Reverse oxidation of estradiol results in estrone (17 β HSD), which is then hydroxylated and produces 2-hydroxyestrogens (catecholestrogens) and 16 α - hydroxyestrogen. 16 α - hydroxyestrogen reduction by 17 β HSD yields estriol (Hillier, 1998).

During pregnancy both the mother and the fetoplacental unit produce estrogen and progesterone². The placenta alone cannot convert pregnenolone to either progesterone or estrogen, so pregnenolone is transferred from the placenta to the fetus where it is synthesized into progesterone and then to the estrogens (Beling, 1971). During the first six weeks of pregnancy, maternal or ovarian production of progesterone predominates. Between the sixth and eighth week, the fetoplacental unit becomes the primary source of progesterone (Challis and Lye, 1998). Fifty percent of maternal estrone and estradiol are synthesized by the fetal adrenal gland and 50% is synthesized from maternal DHEA. Up to 90% of maternal estriol is produced by the fetus via hydroxylation of DHEAS in the fetal liver (Challis and Lye, 1998). Estriol is the primary estrogen during pregnancy, and is thought to ensure continued uteroplacental blood flow. Abnormally low estriol generally indicates fetal distress (Kaplan, et al. 2003). Plasma levels of estriol range from 16-23ug/100ml during the last three weeks of pregnancy (Kaplan, et al. 2003).

Both the mother and the fetoplacental unit produce estrogen and progesterone from the beginning of pregnancy up to 6-8 weeks of gestation, after which the fetoplacental unit takes over. The rate of fetoplacental progesterone production (as measured by radio labeling progesterone in the placenta) near the end of pregnancy can be as high 322mg for a singleton and up to 522mg for twins (Solomon and Fuchs, 1971). After delivery of the placenta, production of progesterone by the fetoplacental unit ceases and maternal production does not resume fully for several weeks.

² Of interest, pregnenolone, the precursor for both progesterone and estrogen is converted to pregnenolone sulfate in large amounts by the placenta. Pregnenolone sulfate, is a potent neuromodulator of both the GABA and DA systems (Valle, Gingras, Le Moal, Mayon and Piazza, 1999).

Protein Binding and Hormone Measurement

Both the estrogens and progesterone are highly bound to proteins in the blood. The estrogens are highly bound to albumin (estradiol - 60%, estrone - 80% and estriol - 91%) and sex hormone-binding globulin (estradiol - 3.7%, estrone - 16%, estriol - 1%). The amount of free hormone, considered the biologically active portion of the hormone is relatively small (estradiol - 1.8%, estrone - 3.6%, estriol - 8.1%) (Longcope, 1998). Progesterone is also bound to circulating proteins and albumin. Progesterone is primarily bound to cortisol binding globulin and albumin and some glycoproteins, especially during pregnancy. The percentage of free progesterone, thought to represent the biologically active fraction, is 1-10% of total plasma concentration (Steimer, 2004).

Protein binding is important for a number of reasons. In most of the human research, hormones are assayed via plasma or serum, which measures hormones bound to protein. Hormones bound to protein are not biologically active (Griffen and Ojeda, 2000), that is, they are not free to bind to receptors and initiate changes in the cell. On the other hand, unbound hormone represents that portion of the circulating hormone that is biologically active. Unbound hormone can either bind to receptors or be metabolized into component parts and thus is thought to represent a more direct measurement of hormone activity (Lu, et al. 1999).

The most common measure of hormone is via radioimmunoassay (RIA) using serum samples. RIA uses the binding of radio-labeled antigens (Ag) (hormone) to antibodies (Ab) by an unlabeled antigen to measure the Ag:Ab reaction. Since unlabeled hormone inhibits binding of the radiolabeled hormone, the amount of radioactivity measured is inversely proportional to the amount of hormone in the sample: lower

concentrations of radioactive hormone equal higher concentrations of unlabeled hormone (Griffen and Ojeda, 2000). Another technique is the enzyme-linked immunosorbent assay (ELISA) also called the enzyme immunoassay (EIA). This project is using the ELISA method. ELISA utilizes the same basic technique as the RIA except that it introduces an enzyme labeled Ag to the equation. The Ag:Ab reaction is then measured by the color change of the enzyme. ELISAs have several benefits over RIAs, namely ELISA produces no radioactive waste and is easier and less expensive to perform.

Steroids and the Brain

Classic Nuclear Receptors

After synthesis in the ovaries, metabolism in the liver, progesterone and progesterone derivatives enter systemic circulation where, because of high lipid solubility, they easily cross the blood brain barrier. Upon crossing the blood brain barrier, ovarian hormones travel to the hypothalamus where they modulate hypophysiotrophic factors such as the release of the pituitary hormones like GnRH, thereby completing the feedback loop in reproductive management (Baulieu and Robel, 1990).

Steroid hormones are believed to exert their influence on the cell via binding to receptors in the cytoplasm. Once in the cytoplasm they are transported into the nucleus where the hormone receptor complex activates transcription factors and triggers RNA-dependent protein synthesis (Keefe, 2002; Jennes and Langub, 2000; Moss, et al. 1997). Estrogen and progesterone work synergistically to regulate reproductive function. The presence of estrogen in the cell increases the number of progesterone receptors and the presence of progesterone decreases the number of estrogen receptors (Keefe, 2002).

Until recently, genomic activity in the hypothalamus, which regulates reproduction and sexual differentiation, was considered the sole purpose of ovarian hormones. However, new research shows that not only are there estrogen and progesterone receptors located throughout the brain, but post-mortem human studies have found significant levels of both hormones in areas of the brain where no nuclear receptors have been identified (Bixo, et al. 1997). These findings are supported by postmortem animal studies using light microscopic immunochemistry and autoradiography techniques (McEwen, et al. 2001). This indicates that the ovarian hormones, particularly progesterone, may be involved in functions other than reproduction and sexual differentiation and may exert their influence via non-genomic means. It also suggests that sexual differentiation extends beyond simple reproductive physiology and into neural dimorphism³, perhaps underlying the differential etiologies in many disorders. Indeed, many researchers contend that gender dimorphism in central nervous system structures is far more widespread than is currently understood and that "we should consider all regions dimorphic until proven otherwise⁴," (Payne, 1996). If this is the case then one must ask 1) what brain regions are affected by ovarian hormones? 2) By what mechanism is action elicited? 3) What are the concomitant effects on behavior?

³Several brain regions show gender-specific dimorphism in morphology and functioning. For example the male (rat) raphe nucleus shows a lower density of receptors but fires at a much higher rate than do the neurons in the female raphe nucleus (Fink, et al. 1998). Furthermore, female rats show higher levels of synthesis and turnover than male rats.

⁴In an interesting study by Wood and Shors (1998) researchers found that estrogen mediated stress induced classical conditioning in female but not male rats. Stress (tail shock) facilitated the conditioned eye blink responses in the male rats but impaired acquisition in the female rats. When estrogen was removed from the equation via ovariectomy (OVX), acquisition of the conditioned response improved in female rats. Conversely when estrogen was added back to the OVX rats, acquisition was again impaired.

Endocrine Targets in the Brain

Animal (rodent) research has found estrogen in multiple regions throughout the brain where few or no classic estrogen receptors exist. These areas include CA1 region of the hippocampus, the dorsal raphe nucleus and the basal forebrain (McEwen, 1998). In the hippocampus, for example, both estrogen and progesterone exert profound influence on cell function. Morphologic studies with female rats found that estrogen treatment initiated dendritic spine growth and synaptogenesis on the pyramidal neurons in the hippocampus (McEwen, et al. 1997). Moreover, the growth was cyclical and ephemeral and closely followed the estrus (menstrual) cycle. The new dendrites and synapses were broken down during the later half of the luteal phase of the cycle only to return again during follicular phase (McEwen, et al. 1997).

The critical factor in synaptogenesis and dendritic growth was the rise and fall of estrogen in relation to progesterone. During the follicular phase, estrogen levels increase and spine-formation begins. When the progesterone level begins to increase in relation to estrogen, spine formation is rapidly potentiated, but as estrogen levels off and progesterone levels continue climbing, spine formation is quickly downregulated. When progesterone levels decline or are removed, complete downregulation of synaptic growth occurs within 8-12 hours; when estrogen is the only variable being added and removed, spine downregulation occurs much more slowly, over the course of days after its withdrawal ⁵ (McEwen, et al. 1997).

In addition to its activity in the hippocampus, progesterone has been measured in a variety of regions throughout the CNS. For example, a postmortem study of five

⁵ Studies with male rats showed that estrogen administration failed to induce as much dendritic growth as was seen in female rats. Researchers suggested that the likely distinguishing factor was testosterone.

women measuring 17 brain regions and serum progesterone, 5 α -pregnane-3,20-dione (5 α DHP) and 3 α -hydroxy-5 α pregnane-20-one (allopregnanolone) levels found high levels of progesterone in the amygdala, cerebellum, frontal cortex, hippocampus and hypothalamus. The highest levels of 5 α -DHP and allopregnanolone were found in the substantia nigra and hypothalamus. What was particularly interesting was that progesterone levels correlated with 5 α -DHP and not allopregnanolone, but 5 α -DHP correlated with allopregnanolone (Bixo, et al. 1997). This supports the idea that central nervous system conversion of progesterone to allopregnanolone involves two separate steps and may occur in different regions of the brain. Other studies have suggested that the conversion from progesterone to 5 α -DHP takes place in the neurons while the conversion of 5 α -DHP to allopregnanolone occurs mainly in the astrocytes (Martini, Melcangi and Maggi, 1993).

Neurosteroids

If progesterone and estrogen are present in the brain in regions not traditionally associated with reproduction then the question becomes, what are they doing there? Moreover, if there are no nuclear estrogen or progesterone receptors in these areas by what means do these hormones influence cell function, if at all?

Recall from above that in addition to the peripheral synthesis of ovarian hormones both neurons and glial cells can and do synthesize some steroid hormones. These steroids, called neurosteroids can be synthesized in the brain de novo and irrespective of peripheral steroid synthesis (Baulieu, 1991). Neurosteroids are divided into two classes, active and inactive. Inactive neurosteroids are steroids that are synthesized in the nervous system but are not active on neural tissue (Stofel-Wagner, 2001). Active neurosteroids or

neuroactive neurosteroids are synthesized in the nervous system and actively modulate neural tissue. Pregnenelone (progesterone precursor), pregnenelone sulfate (conversion by-product), progesterone and at least six of its derivatives are considered neuroactive neurosteroids. The adrenal steroid DHEA, its sulfated ester DHEAS (estrogen precursor), and 17 β -estradiol are neuroactive steroids but it is not clear whether they can be synthesized in the nervous system de novo.

Both neurosteroids and neuroactive steroids exert their influence on neurotransmitter systems via genomic and non-genomic means (Stofel-Wagner, 2001). Recall that traditional genomic theory holds that the molecule diffuses across the membrane, binds to a receptor and the hormone receptor complex moves into the nucleus where it activates gene transcription and some sort of response. Genomic activity is thought to take hours to days to complete. However, some hormones, particularly progesterone and DHEAS, are able to elicit neural and behavioral changes within seconds to minutes of exposure. This led researchers to explore the possibility that neurosteroids bind to membrane receptors, rather than cytoplasmic or intranuclear receptors, and modulate cell behavior via other means. In fact, this has proved true. Estrogen is capable of modulating synaptogenesis and dendritic growth in hippocampal CA1 pyramidal cells without any recognized nuclear receptors (McEwen, 1998), while progesterone and its derivatives bind to ligand channels and initiate both simple ionotropic and G-protein coupled responses depending upon the chronicity of exposure.

Neurosteroids and Neurotransmitters

Neurosteroids modulate each neurotransmitter system to some degree or another. Research shows that the estrogens, DHEAS and progesterone are particularly potent neuromodulators. Below is a review of the more significant effects of the estrogens, progesterone, DHEAS and testosterone on the central nervous system.

Estrogen

Research shows that estrogen, in addition to initiating dendritic growth and synaptogenesis in the hippocampus, modulates cholinergic neurotransmission from the basal forebrain to the hippocampus via acetyltransferase induction (McEwen, 1998). In female rats estrogen increases the expression of serotonin type 2a (5HT2A) receptors and the 5HT transporter in the dorsal raphe nucleus (DRN) by as much as 50% (Fink, et al. 1998), suggesting a possible role of estrogen in the treatment of depression. In fact, some clinicians have effectively reduced the incidence of postpartum depression in women with previous histories of the disorder by administering estrogen in the weeks following delivery (de Noaves-Soares, et al. 2001). In perimenopausal women, estrogen replacement therapy appears to ameliorate symptoms of depression (de Novaes-Soares, et al. 2001) as well as improve verbal memory (Maki, Zonderman and Resnick, 2001; Hogervorst, et al. 1999; Hogervorst, Yaffe, Richards and Huppert 2002; Kampen and Sherwin, 1994; Sherwin, 1994).

In postmenopausal women, estrogen administration increases the 5HT2A density in the anterior cingulate, olfactory and frontal cortices as well as in the DRN (Moses, et al. 2000). Estrogen also regulates DA transmission in the tuberoinfundibular (TIDA) region of the hypothalamus (Hou, et al. 2003) and is correlated with tyrosine hydroxylase

mRNA expression in the brainstem as well as in both the nigrostriatal and mesolimbic DA pathways (McEwen, 1998).

The cognitive correlates of the rise and fall of estrogen have been studied extensively in both human and animal models. In postmenopausal women estrogen replacement therapy improved memory function, particularly verbal memory (Hogervorst, et al. 1999; Hogervorst, et al. 2002; Kampen and Sherwin, 1994; Maki, Zonderman and Resnick, 2001; Sherwin, 1994). In normally cycling women, higher levels of estradiol during the late follicular phase corresponded to higher scores on tasks involving verbal and fine motor skills, but lower scores on spatial tasks. Conversely during menstruation when levels of both progesterone and estrogen are low, spatial skills improved (Hampson, 1990). In a small study looking at the effects of a GnRH agonist (estrogen antagonist) on memory, it was found that 7 of 16 women reported moderate to marked memory impairment during the final weeks of treatment. Prospective memory was most impaired (Newton, Slota, Yuzpe, Tumman, 1996). This is further supported by estrogen replacement therapy (ERT) in postmenopausal women where verbal memory was significantly improved in women receiving ERT compared to those who did not (Hogervorst, et al. 1999; Hogervorst, et al.; Maki, et al. 2001; Sherwin, 1994).

Progesterone

Progesterone, in addition to potentiating many of the changes associated with estrogen, actively modulates GABAergic, dopaminergic and glutaminergic transmission and does so primarily through nongenomic means. It is these changes that appear to be most closely linked to the affective and cognitive deficits associated with pregnancy and postpartum and for that reason are discussed in detail below.

GABA

GABA is the primary inhibitory neurotransmitter of the central nervous system with diffuse projections throughout the brain. Located in interneurons, GABA has two types of receptors: the simple ionotropic GABAA receptor and the G-protein coupled GABAB receptor. Progesterone and several of its metabolites are potent positive allosteric modulators of the GABAA Cl⁻ channels (Bitran, et al. 1991; Puia, Ducic, Vincini and Costa, 1992). Like benzodiazepines, progesterone binds to membrane receptor sites, this increases the receptor's affinity for endogenous GABA and increases the frequency of channel openings, thereby increasing the influx of GABA itself (Nestler, Hyman and Malenka, 2000; Smith, 2001).

During short-term administration, progesterone via allopregnanolone is considered a more effective modulator of GABAA than any of the BDZs (Arafat, et al. 1988; Backstrom, et al. 1984; Bitran, et al. 1991; Baulieu, 1990; Ghoneim, et al. 1984; Gulinello and Smith, 2003). Acute administration of progesterone or its derivative allopregnanolone is highly sedative and produces dose dependent decrements in learning and memory in most animal models.

Chesler and Juraska (2000) found that combined estrogen and progesterone administration in ovariectomized rats produced deficits in Morris water maze acquisition but that neither produced deficits when administered alone. The Morris water maze is presumed to measure aspects of spatial/reference, working and long-term memory. Frye and Sturgis (1995) found that the progesterone metabolite allopregnanolone increased the latency and decreased the number of correct choices in the Y maze test. Johansen et al. (2002), found that male rats injected with allopregnanolone performed significantly

worse on the Morris water maze test than did those injected with vehicle only. Guilinello and associates (2003) found that female but not male rats show an elevated startle response after progesterone withdrawal, but without differences in sensorimotor gating.

Unfortunately no such study exists comparing acute progesterone administration and human cognitive deficits. But because of its similarity in actions to the benzodiazepines (BDZ) we can infer the types of deficits that might occur. Ghonneim, et al. (1984) tested immediate and free recall in 120 subjects after administration of diazepam (placebo, 1mg, 2mg, 3mg). Each group was tested three times after consuming the drug. The results showed a consistent decline in performance as the dose increased. Furthermore, at the higher dosage not only was the magnitude of the decline in performance greater, but the recovery duration was extended as well. Weingartner, et al. (1992) found that triazolom administration impaired recognition and free recall but not other aspects of explicit memory.

In a study measuring the sedative properties of orally administrated progesterone, Arafat et al. (1988) found significant impairment of mental state in women two hours after oral administration of 200mg and 400mg of micronized progesterone. Using gas chromatography-mass spectography, researchers were able to measure the metabolites formed from serum samples and found that the women who experienced the most severe sedation formed the highest number of metabolites. But not all women formed all metabolites, suggesting a possible sensitivity to progesterone in some women but not others. Furthermore, given the severity of the sedation in some women, had the researchers tested cognitive function, they might have found similar decrements in memory as those described in the BDZ literature.

If progesterone and BDZ impair memory in acute doses, what happens during chronic exposure, particularly when the levels are rapidly and continuously increased over the course of an extended period of time, such as during pregnancy? The answer to this question involves a more thorough understanding of the GABAergic system.

GABA Subunit Composition and Mood, Memory and Mental State

Recall from above that progesterone binds to a receptor site located on the GABAA CI- channel, and that binding increases the cell's affinity for endogenous GABA as well as increasing the channel open time. Acute administration of a single dose of progesterone elicits a rapid response that dissipates rather quickly if no further dosing occurs. However, because progesterone metabolism includes an extensive list of very active metabolites continued dosing or exposure not only extends the steroid's half-life, but induces changes in cell morphology consistent with physiological tolerance (Gulinello and Smith, 2003). Unlike the other cells that respond to activity changes via receptor up or down-regulation, the GABA cell responds by changing the conformation of the receptor itself (Hsu and Smith, 2002; Izzo, 2000; Puia, Ducic, Vincini and Costa, 1992).

GABAA receptor composition is mediated by the arrangement of a complex combination of subunits. There are at least 16 and up to 19 subunits (Fuji and Mellon, 2001; Smith, 2001) currently identified that are grouped into seven functionally distinct families (Nestler, et al. 2000), which depending upon conformation, alter the behavior of the GABA cell. For example, the sedative-hypnotic effects of BDZs are mediated by binding to the α -1 subunit, while the α -2, α -3, α -5 subunits are thought to mediate the anxiolytic effects of the drug (Biggio, Follesa, Purdy and Concas, 2001; Poromaa, Smith

and Gulinello, 2003). Conversely, α -4, and α -6 subunits are insensitive to BDZ and are thought to elicit anxiogenic behavior when present in greater numbers than the α -1, α -2, α -3 and α -5 subunits (Biggio, et al. 2001; Poromaa, et al. 2003; Wafford, et al. 1996). Subunits α -4 and α -6 are the least abundant GABAA subunits in the brain under normal circumstances; but under conditions of prolonged stress, chronic alcohol or BDZ use, or after chronic progesterone/allopregnanolone exposure, α -4 and α -6 appear to come online in greater than normal numbers (Foley, et al. 2003; Gulinello and Smith, 2003; Poromaa, et al. 2003). The presence of these subunits makes GABAA receptors completely insensitive to the sedative and anxiolytic properties of BDZ (Gulinello, Orman and Smith, 2003) and in fact their presence is considered anxiogenic in most animal models (Foley et al. 2003; Gulinello, et al. 2003). In human alcohol withdrawal (supported primarily by animal research), researchers speculate that the increased presence of α -4 and α -6, mediate many of the anxiety/irritability related symptomology (Hsu and Smith, 2003; Smith, 2001; Smith, et al. 1998). Animal studies with pregnant or pseudo pregnant rats also show an increased presence of the α -4 and α -6 subunits during the late phase of pregnancy and immediately following parturition, suggesting the possibility that withdrawal from chronic progesterone elicits most of the mood/anxiety behaviors associated with the immediate postpartum period (Gulinello and Smith, 2003; Smith, 2001).

If GABAA receptor subunit composition mediates the mood symptoms associated with chronic exposure/withdrawal to progesterone, might it also mediate the neurocognitive changes anecdotally reported by pregnant and postpartum women? There is evidence to suggest that it does both because of its own conformational changes and

because of the influence these changes exert on other systems, particularly the glutaminergic and dopaminergic systems.

From the BDZ animal research, we know that physiological tolerance to the drug involves stages of GABAergic receptor change, which upon withdrawal profoundly influences cortical and hippocampal NMDA and α -amino-3-hydroxy-5-methyl-4-isoazole propionic acid (AMPA) density (Izzo, et al. 2000). Tolerance to BDZ involves the gradual change in GABAA receptor conformation and binding preferences, beginning with the uncoupling of subunits associated with sedation and followed by the loss of anticonvulsant and anxiolytic subunits (Izzo, et al. 2000). Concurrently, glutaminergic transmission is enhanced and AMPA receptor density is increased (Izzo, et al. 2000). Upon withdrawal, researchers believe that behavioral⁶ signs of dependence emerge as the changes in GABAergic function mediates changes in glutaminergic transmission, increasing glutamate levels in the frontal cortex, occipital cortex and hippocampus (Izzo, 2000). Interestingly, the behavioral changes do not emerge in full until 96 hours after withdrawal from the drug. Researchers speculate that while the changes in GABAergic function mediate tolerance to the drug, the changes in glutaminergic function elicit the signs of dependence.

In a human study measuring BDZ receptor density using single photon emission tomography in nine subjects over the course of a 24-day per/oral administration of 2mg/day alprazolom, researchers found sedation and deficits in delayed recall were present at 16% receptor occupation (Fujita, et al. 1998). From days 3-10 of administration, receptor occupancy dropped to 10%, as did reports of sedation and

⁶ The behavioral changes are measured as decreased percentage of open-arm entries in the elevated plus maze which is presumed to indicate withdrawal induced anxiety (Izzo, 2000).

deficits in delayed recall. Receptor occupancy normalized at day 17, as did the sedative effects of the drug. However, the deficits in delayed recall did not resolve until day 24 (Fujita, et al. 1998). This is interesting because it suggests that even after physiological tolerance occurs (as measured by receptor occupancy), it still takes several days for memory deficits to resolve. It also suggests that GABAA receptor density may not be the ideal method for measuring drug tolerance/dependence, especially when one considers the research discussed above, linking GABAA subunit composition to receptor binding properties.

Nonetheless this research does offer some insight into the time course of BDZ dependence and tolerance, which should to some degree be similar to that of progesterone. However, unlike the research models put forth thus far where a single dose is administered at constant intervals over a relatively short period of time, pregnancy hormones rise sharply and continuously throughout the term making the degree of physiological change likely to be associated with this hormone more akin to those of a chronic drug user and the withdrawal period just as severe. Thus, it is surprising that so little data exist linking hormone changes to mental and emotional well-being, particularly in pregnancy where the change of circulating hormone levels is so radical.

DHEA and DHEAS

DHEA and its sulfated ester DHEAS have garnered considerable attention in recent years for their role in a variety of psychological and physiological functions, including mood, memory, immune function and blood-sugar regulation. DHEA is synthesized in the adrenals and is a parent precursor for the estradiol, estrone and testosterone synthesized in peripheral tissues. DHEA is also considered a neurosteroid,

thought to be synthesized in the CNS; but as of yet no receptors have been identified (Compagnone and Mellon, 1998). Though not a lot is known about DHEA, researchers have found some striking connections between emotional well-being, particularly in women, and declining DHEA levels in the elderly (Berr, LaFont, Deburie, Dartigues and Baulieu, 1996; Wolkowitz, et al. 1997;). DHEA replacement therapy not only returned DHEAS and androgen levels to normal but also improved mood and fatigue in patients with Addison's disease (Hunt, et al. 2000). Buckwalter et al. (1999), found DHEA to be consistently correlated with better mood during pregnancy and to better visuospatial performance and with fewer perseverative errors.

DHEAS, the sulfated ester of DHEA, is the most abundant steroid hormone in human circulation (Hammer, et al. 2005). During fetal development, the fetal adrenal produces vast amounts of DHEAS which is readily converted to DHEA and then to other hormones such as testosterone and estradiol. Upon delivery, DHEAS production slows and continues to decline until puberty where again adolescent adrenals produce large quantities of this hormone. DHEAS levels peak between the ages of 20-30 and then decline to as low as 70-80% of those levels by age 70 (Rainey, Carr, Sasano, Suzuki, and Mason 2002).

As a sulfate, DHEAS was considered until recently, to be the inactive storage reservoir for what was thought to be the biologically active DHEA. Recent research suggested that DHEAS is active in its own right. DHEAS is a GABAA antagonist (Jacobs, Edelman, Coleman and Herzog 1999; Roberts, 1999). DHEAS is also capable of locally inducing tyrosine hydroxylase in the adrenal medulla and has been shown to potentiate norepinephrine release in rat hippocampal cells via NMDA evoked potentials

(Charalampopoulos, et al. 2005). DHEAS mediated events are thought to occur via membrane receptors rather than nuclear receptors because of the rapidity with which activity occurs (Charalampopoulos, et al. 2005). Given the potential antagonism by DHEAS on the GABAA receptor, combined with the conformational changes of the receptor after chronic progesterone exposure, it is possible that together these hormones mediate many of the negative mood symptoms associated with postpartum depression.

Testosterone

Testosterone excess causes a number of recognizable physiological disorders such as hirsutism, alopecia and acne and together with other androgens often marks pathological adrenal hyperactivity (Carminas and Lobo, (2001). Anabolic steroid use upregulates testosterone levels in both men and women with concurrent physiological and psychological symptoms. Typical behavioral changes linked to anabolic steroid use and hyper-elevated testosterone levels include depression and insomnia, psychosis, paranoia, mania, delirium and suicidal or homicidal ideation or behavior (Trenton and Currier, 2005). Recent research suggests that anabolic steroid use dimorphically downregulates GABAA activity in the female, but not the male, rat medial preoptic nucleus. Researchers found that chronically elevated testosterone reduces mRNA production of the adrenergic $\alpha 1$ and $\alpha 2$ receptor subunits (Penatti, Porter, Jones and Henderson 2005). Other research suggests the testosterone increased myometrial relaxation more potently than progesterone in both pregnant and non-pregnant human uterine tissue (Persquia, Navarrate, Jasso-Kamel and Montano 2005). Finally, Buckwalter et al. (1999) found that elevated postpartal testosterone levels corresponded with several domains of negative mood while Hohlagschanddtner, Husslein, Klier and

Ulm (2001) showed strong negative correlations between testosterone and postpartal negative mood.

Summary

As is presented in the following section, much of the research on pregnancy, mood and cognition is potentially hampered by an incomplete understanding of hormone synthesis, metabolism and the regions of the brain most affected by the reproductive hormones. Without a strong theoretical foundation guiding the choice of instrument, detecting change is much more difficult. Hence the measures chosen not only vary widely from study to study, which is a problem in and of itself, but they may not be capable of detecting what are likely to be subtle changes in behavior elicited from a specific pattern of neuromodulation. Furthermore, most projects do not measure hormones at all and those that do use plasma or serum to measure bound, inactive hormone which is arguably not as sensitive a measure as the unbound biologically active component of the hormone. Listed below is a fairly exhaustive review of studies exploring the relationship between hormones and mood and hormones and cognition in pregnancy and postpartum. Also included is research from the premenstrual syndrome (PMS) and the depression paradigms.

Hormones and Mood

Prior to adolescence the rates of depression in boys and girls is fairly similar with boys showing a slightly higher rate (Angold and Wortham 1993). However, after about age 15, the rate of depression in girls and women is nearly two times that of boys and men (Angold and Wortham 1993; Spinelli, 1998). Moreover, the increase in

susceptibility to depression correlates with the hormonal and physical changes associated with puberty (Angold and Wortham 1993). The onset of puberty for girls also shows an increased risk for cyclic psychosis that seems to correspond with late luteal phase drops in progesterone (Amblas, 1993; Stein, Hanukoglu, Blank and Eleizer 1993); the cyclic psychosis remits during the menstrual and follicular phases.

Childbirth is another particularly vulnerable time for women. The immediate postpartum period is marked by considerable mood lability for at least 80% of all women (Spinelli, 1998). Up to 15% of women suffer a bout of full clinical depression following parturition and for 40% of those women the depression can last upwards of a year (Panay, Sands, Studd, 1998). One to two percent of pregnancies result in maternal hospitalization as a result of postpartum psychosis (Spinelli, 1998). Statistics show that during the postpartum period, women are some 20 times more likely to develop psychosis than at any other time. With the increased risk of psychosis, the risk of suicide increases 70-fold during the first year postpartum (Sharma, 2003). Furthermore, 72% of all cases of postpartum psychosis occur within the first 10 days after delivery (Klompener and van Hulst 1991). Given the exponential increase and precipitous decrease of hormones during pregnancy and after delivery, one would assume a strong correlation between hormones and mood existed, but it does not. To date, there has been no clear and consistent link shown between pregnancy hormones and postpartum mood lability. The lack of evidence is likely due to a number of factors, but what stands out most, is the lack of theory driven testing. Questions such as “which areas of the brain are most likely affected by each hormone?” and “what are the consequent behaviors?” are rarely asked. Even questions about when to measure the hormones are not asked. For example, in the

premenstrual syndrome research where hormones levels have not been consistently correlated with mood disruptions, even though measures of affect and mood show significant symptom exacerbation premenstrually (Redei and Freeman 1994), hormones are typically measured at the peak of either the follicular or luteal phases and again at menstruation; this presumably is to show the largest change from one phase to the next. However, one group of researchers measured throughout the cycle and found that women with PMS showed significantly higher levels of progesterone in the late follicular phase (when estrogen levels are typically very high and progesterone is generally low) and early luteal phase than did controls, preceding symptoms a full 5-7 days (Redei and Freeman, 1994). It is possible that there is a similar pattern waiting to be discovered in pregnancy research.

Following parturition, women experience significant changes in hormone levels and statistics show that up to 80% of all women experience mood lability (Spinelli, 1998), but research has thus far failed to connect the change in hormone levels to the change moods. According to a recent meta-analysis and subsequent literature reviews, only two studies in 30 plus years showed a significant association between hormones and mood and supported the hypothesis that hormone changes underlie mood changes (Granger and Underwood, 2001; Harris et al. 1994, Nott, et al. 1976). Other studies suggest the possibility of a link, but because of differences in methodology and direction as well as small sample sizes, most fail to reach significance (Granger and Underwood, 2001). The two studies reaching significance are reviewed below as are the few others reporting trend between hormones and mood.

In 1976, Nott and associates measured ovarian hormones in 27 primiparous and multiparous women via blood 3 times at weekly intervals from 2-6 weeks before delivery, the day of delivery, on alternate days for the first week after delivery and every 3rd -5th day for 5-10 weeks thereafter. They compared hormonal measures with several measures of mood over a period of several weeks. The results indicated that higher pre-delivery estrogen was correlated with increased irritability ($r = .36, p < .05$) and lower post-delivery estrogen was correlated with increased reports of sleep disturbance ($r = .43, p < .05$). The magnitude of change from pre-delivery progesterone to post-delivery progesterone correlated with depression at 10 days postpartum ($r = .35, p < .05$) but was negatively correlated with postnatal sleep disturbances ($r = .49, p < .05$). It would have been interesting to see the pattern of pre- and post-delivery hormones in relation to the various measures of mood, but these data were not provided.

The Cardiff study, by Harris et al. (1994) is by far the most ambitious study to date taking a total of 9654 salivary assays of cortisol and progesterone from 120 women over a period from two weeks before delivery up to four weeks after delivery. Harris and colleagues (1994) showed a significant relationship in the magnitude of change between antenatal and postnatal progesterone and depression scores as measured with a number of scales: the Edinburgh Postnatal Depression Scale and the Stein Scale for Maternity Blues and the Beck Depression Inventory. They were unable to find any relationship between cortisol and mood. Although this was a very good study, they measured only depression and not the other aspects of mood, mental state or cognitive functioning that could be presumably affected by the rise and fall of progesterone. Recall from the BDZ research that irritability and anxiety are the most prevalent symptoms appearing during

withdrawal. If we look at the constellation of symptoms associated with postpartum mood changes, we see that anxiety and irritability may underlie many of the symptoms (see Table 2) particularly in the more severe cases. By focusing on depression, most studies potentially limit their results.

Other studies, including 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 α_2 -adrenoreceptor binding capacity, which was in turn correlated with measures of postpartum mood lability. Kuevi, et al. (1983) reported a trend towards higher FSH and lower estrogen and progesterone levels in women with the blues, particularly those women who showed a consistent state of 'blues' versus women who experienced brief periods of mood lability. Finally, 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, either of which could indicate endocrine involvement. Notice that each of these studies implicates hormone involvement in postpartum mood lability at least indirectly; this is important because each research group utilized entirely different measures and, in fact, had different definitions of postpartum mood disturbances.

Hormones and Cognition

If there is a relationship, however tenuous at this point, between hormones and mood, might hormones mediate cognitive function? Some research suggests that they do. Phillips and Sherwin (1992) report variations in memory function across the menstrual cycle, with visual memory significantly impaired during the menstrual phase as compared to the luteal phase, and paired-associate learning correlated with high estradiol during the luteal phase. Interestingly, testosterone was negatively correlated with paragraph recall. Hampson (1990) found that articulatory and fine motor skills improved during the late follicular phase, while spatial tasks faltered compared to the scores during menstrual phase.

Thompson, et al. (2000) found that estrogen fluctuation mediates various measures of cognitive function for women with and without psychosis. When estrogen levels were at their highest (during the second peak in the luteal phase), women with psychosis performed significantly worse than controls on Purdue pegboard. Both groups showed significantly better scores on spatial tests when both estrogen and progesterone were low (menstruation) compared to when the hormones were high and performance on Trails A was better when estrogen was low. These results suggest that estrogen adversely affects spatial skills. Interestingly, the women with psychosis not only had much higher incidence of endocrine problems, obviously some associated with the neuroleptics but also reported histories of menstrual dysfunction prior to their first episodes. Moreover, these women showed abnormally elevated progesterone levels during the follicular phase compared to controls, followed by lower than normal progesterone in the luteal phase (Thompson, et al. 2000). This follows the pattern of mood disturbance reported by Harris,

et al. (1994) linking magnitude of change in progesterone to increase in mood disturbance. It also suggests some common link between higher than normal levels of progesterone in the follicular phase and PMS as reported by Redei and Freedman (1995).

Some studies have suggested changes in cognitive function both during and after pregnancy. Jarrahi-Zadeh et al. (1969) measured multiple 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. Scoring for both tasks reflected only total time required to complete the task and did not include errors. The results showed a significant difference between pregnant and non-pregnant controls and between postpartum and non-pregnant controls in Porteus Maze completion times. The authors reported increased subjective complaints with concentration at both time points and suggested that the combined test results and subjective data indicated that pregnant and postpartum women showed difficulties in concentration and planning. Difficulties in concentration and planning would be consistent with elevated progesterone and estrogen, as would motor slowing. Another possible explanation would be that spatial skills appear to falter with high levels of both hormones but improved when levels wane, as was suggested by Hampson (1990).

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. These findings are particularly interesting given recent research in the dissociation between explicit and implicit memory systems. Explicit memory, the conscious recall of information, appears to involve both frontal and temporal activation, particularly the cingulate gyrus and hippocampal formation; implicit memory or unconscious recall of information involves activation of the particular sensory area called into action during the task (Fleishman, Vaidya, Lange and Gabrieli 1997). For example, retrieval of procedural memory involves activation of the basal ganglia and the cerebellum, while visually presented implicit recall tasks involve activation of the medial dorsal occipital/temporal regions (visual association areas-Brodmann's areas (BA) 17, 18, 19) (Samuelsson, Bogges and Karlsson 2000). Most of the neurocognitive tests for implicit memory are visual in nature and hence should activate BA 17, 18, 19. Individuals with lesions to the BA 17, 18, 19, show severe deficits in implicit memory as tested by visual priming tasks, but not in auditory or procedural tasks (Samuelsson, et al. 2000). Normal participants performing the visual priming tasks while being measured by fMRI, however, show diminished activation in those areas as compared to when performing explicit memory tasks perhaps indicating that the region is part of a more extensive loop that may be regulated by other regions, particularly the frontal cortex (Buckner, et al. 1995). Another interesting finding in the Buckner et al. (1995) study was that explicit and implicit recall tasks showed left and right PFC activation, right hippocampal activation and no left temporal activation. Recall from the BDZ research discussed previously (Izzo, et al. 2000) that tolerance to BDZ is measured by withdrawal characteristics and one of the more prominent characteristics was an increased transmission of glutamate and concurrent increased AMPA receptor density in the several

regions of the brain including the prefrontal cortex (PFC), hippocampus and the occipital lobe. It is possible that glutamate changes in the occipital region modulated by progesterone mediate the implicit memory deficit observed in pregnant women either directly via glutamate/AMPA or indirectly via changes to upstream neural pathways in the PFC. In either case, both Brindle, et al. and Sharp, et al. provide a clue to possible cognitive changes during pregnancy. Sharp, et al., Jarrehi-Zaddeh et al. and Brindle et al. 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. This indicates that the women were aware of the changes in memory.

Eidelman, 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 immediately after delivery have more to do with memory function than anything else.

Recently de Groot, Adam and Hornstra (2003) reported deficits in selective attention at 36 weeks that had resolved by 32 weeks postpartum. Researchers used what a spatial finger precuing task wherein subjects were given cues regarding the spatial location of an upcoming target stimulus. Researchers believe that this task measures selective attention, which they define as the ability to identify, discriminate and select a

target. It also measures motor speed. The precuing task, like other priming tasks, should improve performance over baseline measures. However, pregnant women performed significantly worse than did controls and showed little to no priming effect. Although de Groot, et al. suggest that this task measures selective attention, its similarity to standard measures of implicit memory is overwhelming. As such, one could suggest that the deficit measured by these researchers involves the procedural implicit memory system and the activation or inactivation of basal ganglia and cerebellar regions. It is also possible that during pregnancy the sedative effects of progesterone slow motor responsiveness and thereby prevent women from improving on this particular task.

Dysregulation in these areas would be expected given the pattern of GABA and NMDA/glutamate activation mediated by progesterone. Recall from Bixio, et al. (1997) that the sedation-inducing metabolites of progesterone (allopregnanolone and 5 α -DHP) are heavily concentrated in the cerebellum and substantia nigra as well as in other regions. Recall also that these metabolites modulate NMDA receptor density, glutamate and DA transmission in the basal ganglia (Cabrera, et al. 2002; Cabrera and Navarro 1996; McEwen, 1998). Given the exponential increase in progesterone during pregnancy one would expect deficits in these areas, and would also expect them to dissipate by 32 weeks postpartum.

Finally, Crawley, Dennison and Carter (2003) found no differences between pregnant and non-pregnant controls in a variety of cognitive modalities tested during the second and third trimesters as well as at six weeks and one year postpartum. They did find that a significant portion of the women tested reported a higher incidence of perceived memory deficit during the third trimester.

Thus far none of the studies discussed herein collected hormone data. To date there are only a few studies that have collected hormone data at all and even fewer that have correlated those data with cognition. More research appears to have been done in the PMS paradigm than in the pregnancy/postpartum paradigm. In the pregnancy postpartum arena, an extended search on PsychInfo and Medline revealed only one study in the last 30 years that measured perinatal hormones, cognition and mood, Buckwalter et al. (1999).

Buckwalter and associates (1999) measured cognitive function, mood and hormone levels in 19 primiparous women at approximately 36 weeks of pregnancy and 2-4 weeks after delivery. Unlike all previous studies, they utilized a full standard battery of neuropsychiatric assessment tools that included a range of neurocognitive and psychiatric measures. They also took two blood samples and used RIA to measure estradiol, testosterone, progesterone and DHEA. Researchers asked three questions: 1) were there changes in cognition during pregnancy? 2) were there changes in mood during pregnancy? and 3) were hormones associated with cognition or mood during and after pregnancy? They found that indeed there were changes in both mood and cognition during pregnancy and that these changes persisted at least through four weeks postpartum.

Regarding changes in cognition during pregnancy, Buckwalter, et al. found that pregnant women performed significantly worse on several aspects of the California Verbal Learning Test (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; they also showed significantly lower learning slopes ranking

only in the 32nd percentile. Authors of the CVLT suggest that low scores on trial 1 occur often in individuals who are depressed and/or anxious but resolve by trial five and show normal learning across the five trials. Buckwalter et al. (1999) showed that indeed pregnant women were impaired on trial 1, but they were also impaired on trial five as well as on trials 1-5 combined and showed a diminished learning curve compared to norms. Dellis et al. (2000) suggest that impairment in trial 1, barring depression or anxiety related performance (which may be a factor in pregnant/postpartum women), indicates poor auditory attention span. Since different neurological deficits show discrete patterns of reduced learning across the trials, a reduction in the learning curve could indicate a number of neurological impairments; but since Buckwalter et al. did not list the scores from trials 2-4 it is impossible to interpret these results. According to Buckwalter, et al. 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. Dellis et al. suggest that impaired performance across all tasks indicates problems with retention and that an elevated number of intrusions indicate problems with either confabulation or disinhibition, the sum total of which appears to indicate some sort of left frontal and temporal dysfunction (Dellis, et al. 2000).

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, but failed to reach statistical significance (46th, 47th, 16th percentiles

respectively). These results suggest a fairly diffuse pattern of left hemisphere impairment that the researchers were unable to elucidate. This pattern of left hemisphere impairment may be significant or it may indicate that right hemisphere activity has yet to be consistently measured. What these results do not show is a glaring deficit in any one cognitive domain, which is perhaps why so many researchers fail to attribute the cognitive changes associated with pregnancy to pregnancy related hormones.

Buckwalter, et al. (1999) also measured affective changes associated with pregnancy and postpartum. Of the 19 women in the study, 15 completed the Symptom Checklist-90 (SCL-90), which measures clusters of symptoms relating to common psychiatric profiles including somatization, obsessive-compulsive behavior, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism and the Profile of Mood States (POMS), which measures five clusters of symptoms, depression, anxiety, confusion, fatigue and vigor. Unfortunately they found no consistent association between hormones and cognition, or hormones and mood or mood and cognition. But they did find some interesting trends, particularly with DHEA and cortisol. During pregnancy DHEA was associated with higher scores on the Judgment of Line task ($r = .65$, $p = .006$) and cortisol was significantly correlated with fewer perseverative errors⁷ on the CVLT ($r = -.57$, $p = .01$). Neither estradiol nor progesterone was correlated with any cognitive measure. After pregnancy, both DHEA and cortisol were associated with better performance on a number of measures.

⁷ Perseverative errors is a misnomer in CLVT nomenclature. Perseveration typically refers to failure to shift set. In the CVLT perseverative errors refer to the number of repeated words in the list. In the CVLT-II, test designers have reclassified perseverative errors to repetition errors (Delis, Kramer, Kaplan, Ober, 2000).

DHEA was correlated with better mood during pregnancy but showed a more inconsistent pattern after delivery. During pregnancy, DHEA was correlated with lower scores on the Beck Depression Inventory as well as on several of the dimensions of the SCL-90 and POMS. Testosterone was associated with negative mood symptoms after delivery but not during pregnancy. The change of hormone levels from pregnancy to postpartum also showed correlations to mood. The change in estradiol was significantly correlated to a decrease in phobic anxiety, confusion, fatigue scores on the SCL-90 and POMS measures.

The DHEA findings are interesting, particularly when one considers that DHEA levels are inversely related to progesterone levels so that when progesterone is high DHEA is low (Compagnone and Mellon, 1998). According to Buckwalter et al. (1999) DHEA was associated with better mood during pregnancy, since they did not mention whether or not progesterone was especially low in those women who reported better mood states, we can speculate that it was in as far as increased progesterone was associated with negative mood during pregnancy. Moreover, since progesterone levels are greatly diminished after pregnancy, one might speculate that DHEA levels should be increased to maintain hormonal equilibrium. Researchers reported that diminished DHEA levels postpartum correlated with depressed mood, which is consistent with the physiological relationship between the two hormones. If both hormones were diminished postpartum, as these data appear to suggest, then the feedback loop between the two could be impaired and may suggest a physiological marker linked to postpartum psychopathology.

These results are important because they confirm that steroid hormones are linked to changes in both mood and cognition. But like almost all other studies on this topic, they do not appear to show a clear pattern of behavior associated with pregnancy related hormones. Some hormones are correlated with some mood changes but not consistently, and no hormones were correlated with the cognitive deficits. This is where understanding the synthesis and metabolism as well as the neurotransmitter systems modulated by these hormones comes into play. For example, the relationship between DHEA and progesterone as well as between testosterone and estradiol are often overlooked, but are exactly the relationships that may yield the most important factors predisposing some women to postpartum mental illness.

Recall from the earlier discussion, that each of the hormones modulates each of the neurotransmitter systems to some degree or another. Also recall that individually estrogen is generally considered excitatory while progesterone is considered highly sedative; together, however, they work synergistically. Progesterone potentiates the actions of estrogen (particularly in the area of synaptogenesis) and estrogen primes receptors for progesterone (progesterone alone will not initiate synaptogenesis). Recall also that 1) progesterone is the precursor for many of the other hormones 2) progesterone produces very active metabolites and 3) progesterone is inversely related to DHEA levels and probably, though this is not reported related to estrogen, testosterone and other downstream hormones. Since the presence or absence of progesterone modulates effects of the other hormones on individual neurotransmitter systems, perhaps what needs to be measured is the relationship among progesterone, estrogen, testosterone and behavior.

Recall also from Bixo, et al. (1997) and the several animal studies cited earlier (Cabrera, et al. 2002; Fink, et al. 1998; Keefe, 2002; McEwen, et al. 2001; McEwen, et al. 1997) that progesterone is heavily concentrated in the several regions of the brain including the amygdala, cerebellum, frontal cortex, cingulate gyrus, substantia nigra, hippocampus, the thalamus and hypothalamus. Given its relative dispersion, one would expect a fairly diffuse pattern of change that affects not only mood state, but a variety of cognitive behavioral functions in a somewhat more pervasive than gross manner. From all of the studies thus far, this is exactly what we have: a relatively pervasive diminution of left hemisphere function. It is likely that right hemisphere function is also affected but as of yet this has not been tested.

To fully measure the pattern of changes associated with perinatal hormones several factors need to be addressed. First, the neuropsychiatric measures should focus on the modalities most affected by progesterone, but also include measures not hereto indicated (right hemisphere) to rule in/out potential impairment in other regions. Secondly, the relationship between progesterone and the other ovarian hormones should be assessed in association with performance on behavioral measures. Thirdly, a topic thus far not addressed is the possibility that the relationship between hormones and behavior is non-linear thereby preventing linear statistics from delineating the pattern of significance.

Summary

Given the data presented throughout this document it is clear that pregnancy hormones modulate virtually every neurotransmitter system within the central nervous system. What should be particularly clear is the role that progesterone plays in neuromodulation. Progesterone is a precursor to many steroid hormones, effectively

modulates numerous neurotransmitter systems on its own, and attenuates the actions of other hormones; likewise other hormones, particularly estrogen, play a vital role in progesterone's efficacy.

However complex the relationship is between the various hormones, each is to some degree or another dependent upon progesterone. Given this, it seems logical to base the predictions about the effects of steroid hormones on behavior on progesterone's pattern of distribution and inherent properties. Thus, the sedative properties of progesterone should produce changes in concentration, attention, motor and/or cognitive slowing. Its anxiolytic properties should reduce anxiety during pregnancy but increase anxiety toward term and after delivery during the withdrawal phase. Its affinity to GABAA receptors in the hippocampus should affect learning and memory (McEwen, 1998), especially where processing speed is involved, while its presence in the raphe nucleus might alter arousal and excitability (Klink, et al. 2002; Oades, 1978). The increase in circulating DA during pregnancy, particularly in the nucleus accumbens, should increase motivational or pleasure seeking activities as an addictive drug might, but the precipitous decline in DA after delivery should cause a bevy of withdrawal type symptoms, including increased anxiety. Since one of the major projection pathways from the nucleus accumbens is to the frontal cortex, the decline in both GABA and DA should have adverse effects on planning, organization and executive function as well as affect regulation particularly with regard to social judgment and motivation via their connections with the amygdala and other limbic structures.

To the extent that the exhibited behaviors differ from what is expected, based upon the primacy of progesterone, one can surmise possible dysregulation at other

junctions within the pathway. For example, if ratio of progesterone to estrone/estradiol is disturbed it is possible that behaviors exhibited by the subject would be more consistent with elevated estrone/estradiol than with diminished progesterone; since neither the appropriate ratios of one hormone to the next nor the associated behaviors therewith have been identified, this is only speculation.

Hypotheses and Predictions

Given the complexity of steroid endocrinology and the lack of research in this area, the current predictions and hypothesis are necessarily broad. This is a preliminary study that is driven by the physiology of a system that is not entirely understood. With this in mind, it is predicted that during pregnancy the subjects will experience general cognitive decline in each of the areas tested as compared to age- and education-matched norms. At time two, ten days after delivery, the deficits will remain but may have improved slightly. The magnitude of change in progesterone from antenatal to postnatal will correlate with measures of mood; however, what the pattern will be is as of yet unclear.

CHAPTER 3

METHODS

Participants

Inclusionary Criteria

Participants were healthy, primigravid women, ages 21-40 without histories of drug/alcohol abuse or neurological disorder. It was originally intended to exclude women taking medication. After discovering the high number of women taking a wide variety of medications during pregnancy, this criterion was modified to exclude only psychotropic medications and/or those medications that might interfere with either hormone levels or performance on psychological tests. All medications were reviewed before the participant was admitted into the study. This study was approved by the University of Nevada, Las Vegas Office for the Protection of Human Subjects prior to initiation (Appendix A).

Recruitment

Participants were recruited primarily from presentations given at area childbirth education classes. Other recruitment means were employed such as press releases, distribution of flyers to area physicians and around campus, booths at baby fairs and seminars on postpartum depression, but fully 98% of all participants were recruited from presentations given at childbirth classes. Presentations outlined the study's purpose, design and exclusionary/inclusionary criteria. Following each presentation, those interested were asked to sign-up for a follow-up call where questions were answered and

enrollment appointments made. Presentations were given at multiple hospitals on a weekly basis for approximately 10 months. Childbirth education classes ranged in size from two or three to 20 participants and approximately a quarter of women per class were qualified and/or interested in the study.

Over the course of 10 months, approximately 75 women expressed initial interest in the study. Of the 75 who expressed interest, 38 were enrolled in the study. The thirty-seven women who expressed interest and subsequently did not enroll were either disqualified for health or medication issues, multiparity, or upon follow-up lost interest. An unknown but seemingly high number of women expressed verbal interest in the study but self-excluded because of psychotropic medications.

Descriptives and Demographics

Of the thirty-eight women enrolled in the study, 32 were tested at time one (T1) and 28 of the 32 were tested at time two (T2). Six women who enrolled into the study gave birth prior to the first testing session. Two of those six were in labor on the day of the first testing session. Four women tested at T1 failed to complete the T2 postpartum testing. Of those women who failed to complete postpartum testing, one woman missed her second appointment, one chose not to complete the study due to postpartum stress, one participant had a medical emergency related to childbirth, and the remaining participant failed to return calls for postpartum scheduling. Of the 32 who entered the study, T1 hormone data was lost by FedEx for one participant. Five of the women admitted into the study were taking medications. Two were taking allergy medications, two were taking antacid type medications and one was prescribed a blood thinner during the last weeks of pregnancy.

All of the 28 women who completed the study gave birth to healthy babies. Out of the 32 women who entered the study, 16 had girls and 16 had boys. Twenty-four of the women gave birth vaginally and eight had cesareans. Labor was induced in nine of the women who delivered vaginally. Of the cesareans none were scheduled in advance and all became necessary either because of a medical emergency or because labor had stalled. The average length of gestation was 275 days with a range of 260-289 days.

All of the women who enrolled in this study were employed full-time in a range of positions through the majority of their pregnancies. As a whole the women were highly educated. They averaged 15.73 years of education with a range of 12-19 years. Full scale IQ as estimated using the Barona Index and confirmed by the National Adult Reading Test (NART) was 111.98, with a range from 101 to 115. The group was predominately Caucasian, (n =29), one African American woman was tested at T1, but subsequently dropped out. Two Hispanic women entered the study and were tested at T1, but only one completed the study.

Enrollment and Testing

Participants expressing interest in the study were contacted by phone and enrollment appointments were set. Enrollment appointments took place in the participants' home or office. At the enrollment, participants were given and signed the informed consent (appendix B). Demographic information was collected (Appendix C) and inclusionary evaluations were made. Upon qualification for the study, the NART was administered, instructions for specimen collection were given (Appendix D) and T1 appointments were set. Participants were enrolled from 32 weeks of pregnancy until 36 weeks of pregnancy.

The first testing session took place at 37 weeks of pregnancy +/- 2 days. The second testing session took place within the first 10 days postpartum for all but three participants, who were tested on day 11 or 12. The average postpartum testing session occurred on day eight with the earliest occurring on day four. Both pre and postpartum testing sessions were at the participant's home.

Specimen collection was tightly controlled. The morning of each testing session, participants were instructed to spit into a vial upon arising, at 9 AM, before eating drinking or brushing teeth. At the postpartum testing session they were also instructed to not spit within two hours of breastfeeding. At T1 the mean saliva collection time was 8:46 AM, the median and mode were 9:00 AM. At T2, the mean saliva collection time was 8:26 AM, the median was 8:46 AM and the mode was 9:00 AM. All salivary samples were picked up at the testing session and mailed via FedEx to AllVia Diagnostic Lab in Phoenix, AZ for analysis.

The order of testing was also controlled and was as follows for each testing session: the Symptom Checklist 90-revised (SCL-90R), 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 as requested and when needed to allot for down-time between tests. Testing at T1 took approximately one hour and fifteen minutes. Testing at T2 sometimes took two hours or more in part because of interruptions and the participant's interest in discussing the birth. To compensate for practice effects at T2, alternate test forms were administered for the CVLT-II, and the Rey CFT.

Neurocognitive and Neuropsychiatric Measures

Intelligence

Intelligence was estimated using two measures the Barona Index and the North American Adult Reading Index (NART). The Barona Index provided a quick and reliable estimate of general intelligence using basic demographic and educational information (Spreeen and Strauss, 1991). The NART also provided a quick and reliable estimate of intelligence by using a reading test of 50 irregularly spelled words to assess premorbid intellectual ability. The NART is considered very reliable and highly correlated with other measures of general intellectual ability (Spreeen and Straus, 1998).

Mood

Mood will be measured using the SCL-90R. The SCL-90R is a 90 item, self-administered measure with nine clusters of symptoms relating to common psychiatric profiles and a global severity scale to measure average severity of symptoms (Derogatis, 1994). The symptom clusters measured included somatization, obsessive-compulsive behavior, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism.

Cognitive Functioning

Neurocognitive functioning was assessed using multiple tools including 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; Spreeen and Straus, 1991). Results are evaluated based upon total recall,

total errors, short and long delay recall, cued-recall and recall with intrusions (Lezak, 1995; Spreen and Straus, 1991). Buckwalter et al. (1999) found significant impairment in pregnant women both antenatally and postnatally. 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) areas potentially affected by steroid hormone changes.

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 is 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 and Straus, 1991). The PASAT is believed to be especially sensitive to subtle changes in attentional abilities. Pregnant women receiving magnesium sulfate to slow early labor performed significantly more poorly on the PASAT than when not receiving magnesium sulfate (Ghia, et al. 2000). Recall from the Buckwalter et al. (1999) study that pregnant women scored well below norms in all five trials of the CVLT. Authors of the CVLT-II suggest that such low scores may be attributed to poor auditory attention span (Dellis, et al. 2000).

The CFT measured visual spatial and constructional ability as well as visual memory, planning, organizational and problem solving (Lezak, 1995; Spreen and Straus, 1991). Subjects 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 and Straus, 1991). Cummings and Trimble (1995) suggest that this measure is particularly adept at identifying frontal cortex dysfunction.

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 are 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 and Trimble, 1995). Both tasks are particularly difficult for individuals with dorsal lateral prefrontal cortex (DLPFC) injuries; the DLPFC is one pathway that should be affected especially hard by progesterone withdrawal both because of its effects on GABA and on NMDA-mediated DA release.

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 and Straus, 1991).

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 and Straus, 1991).

Factors Determining Assessment Timing and Instrument Choice

To capture the largest change in hormones, it was decided in the present study to test each subject at approximately 37 weeks and within the first ten days postpartum. Studies show that hormones continue to rise until immediately before delivery when they then begin to decline slowly and decrementally in preparation for delivery (Harris, et al. 1993). After the fetoplacental unit is delivered, the woman's circulating level of hormones decreases rapidly to a level below that of her normal menstrual cycle (Challis and Lye, 1998; Harris, et al. 1993). The decreased level of circulating ovarian hormones is maintained for as long as the woman breastfeeds; it is not until breastfeeding ceases that FSH increases sufficiently to stimulate follicle growth which in turn stimulates estradiol and the subsequent LH and progesterone surges required for menstruation (Griffin and Ojeda 2000; Kaplan, et al. 2003). Researchers have chosen to assess hormone levels and either cognitive or affective factors at a variety of time points postpartum, arguing that since hormone levels do not return to normal until breastfeeding stops, it doesn't matter when one tests. This is problematic for two reasons. First, although hormones may remain unusually low for several months postpartum, neural and behavioral adaptation is likely to occur over time thereby diminishing the outcome measures. Secondly, studies in postpartum psychosis indicate that over 70% of all incidents occur within the first ten days postpartum (Klompenhouwer and van Hulst 1991). It seems that that if there were a change in affective regulation and even cognition, it would occur sooner rather than later. Given these two facts, it was decided to test both at 37 weeks and within the first ten days postpartum. However, because both excessively low hormones and excessively high hormones are likely to adversely affect mood and

cognition, measuring at these times makes capturing differences in behavior between the two time points statistically difficult. Additionally, even with the most targeted and sensitive instruments, it is not likely that one would be able to distinguish between those deficits associated with high hormones versus those associated with low hormones. Nonetheless, testing at these time points provided important data regarding the patterns of deficit associated with a particular hormonal state that will guide future studies and potential test designs.

Testing within the first ten days postpartum presented some logistical difficulties, including mothers who were hesitant to leave their newborns to participate in the research, particularly since the testing took an extended period of time. To compensate for this possibility, all tests chosen were portable and could be performed at the participant's home. In addition, each test was chosen not only because it measured the functioning of a particular brain region, but also because each could be performed relatively quickly.

Data Analysis

Data analysis looked at two groups of questions. The first group asked: 1) are there changes in mood during pregnancy compared to norms? 2) Are there changes in mood after pregnancy related to norms? 3) Do these changes correlate with any of the hormones measured? 4) Are there changes in mood from T1 to T2? 5) Do mood changes correlate with any of the cognitive measures? The second group asked: 1) are there changes in cognitive functioning during pregnancy compared to norms? 2) Are there changes in cognitive function after pregnancy compared to norms? 3) Are there changes

in cognitive functioning from pregnancy (T1) to postpartum (T2)? 4) Do these changes correlate with any of the hormones measured?

Since there was no control group for this study, z-scores from both the mood and cognitive measures were calculated and compared to z-scores from available age and education matched norms to give percentile rank.

To compute the relationship between hormones and individual tests, multiple correlation matrices were used to correlate each hormone at T1 with each neurocognitive test and symptom cluster from the SCL-90 at T1. Likewise each hormone was correlated with each neurocognitive and mood test at T2. Changes in hormone levels from T1 to T2 were correlated with changes in cognition and mood from T1-T2. Additionally, pregnancy hormones were correlated with postpartum mood to determine if there are early biological markers of postpartum negative mood.

It is acknowledged that the sheer number of analyses being performed increased the type 1 error rate and the limited number of participants decreased the power. However, this was a preliminary study for which there was little precedent. It was, therefore, important to assess a number of areas in order to delineate all possible patterns.

CHAPTER 4

RESULTS

Results

Statistics

This was a comprehensive study designed to measure the full spectrum of cognitive and affective correlates associated with a broad range of reproductive hormones during late pregnancy and early postpartum. This necessitated measuring not only a thoroughly representative number of cognitive and affective variables but also a full complement of reproductive hormones. Measuring multiple hormones is inordinately expensive and, thus, limited the number of participants in the present research. The large number of cognitive, affective and hormone variables coupled with the small participant pool diminished both the sensitivity and reliability of the statistical analyses performed and compromised interpretation of the data obtained.

To compensate for reduced statistical power and increased error, researchers typically employ statistical corrections such as the Bonferonni method, or they increase the reportable alpha level. Insofar as this was an exploratory project meant to guide the direction of future research, it was decided not to do either of those procedures; instead all statistically significant relationships were reported with the caveat that statistical power was limited and the possibility of over-reporting significance existed in the present research, as does the possibility of reporting artifactual versus real relationships.

Nonetheless, the data reported in this study provide a critically important step in understanding the relationship amongst hormones, cognition and mood.

This study utilized both between and within factors for analysis. Comparisons were made between collected data and published normative data when available, as well as between the participants themselves. Given the large data set and number of analyses run, the results section was organized first into three broad sections that include the main variables within the study, hormones, mood and cognition. Within each section, descriptive statistics were given followed by t-tests comparing collected data to published data and/or z-scores and percentile scaled scores. This was followed by correlations between the individual variables as well as analyses and correlations of change scores.

Part One: Hormones

Methods

Unlike other studies that typically have measured only one or two hormones, this study measured five hormones important to pregnancy. Hormones were measured from saliva using the ELISA method. Un-stimulated, morning salivary samples were collected according to the protocols outlined previously from each woman at each test time.

Salivary samples were shipped via FedEx to AllVia Diagnostic laboratory in Phoenix, AZ where they were frozen immediately at -20 degrees Celsius and processed within 24 hours. The inter-assay coefficient of variation for each hormone was as follows: progesterone 2.9%, DHEAS, 3.7%, estrone, 16.25%, estradiol, 3.4%, estriol, 3.6% and testosterone, 4.9%. Descriptive data for each hormone obtained during pregnancy and postpartum are given in Table 3.

Assessing the face validity of these results was particularly difficult insofar as there are very few published studies with salivary hormone levels in pregnant and postpartum women. This was compounded by the fact that hormone data in general are marked by huge inter-individual variation (Griffen and Ojeda, 2000). The data in Table 3 are consistent with that finding. Of the published reports, salivary data are available only for progesterone, estradiol and estriol during pregnancy. There are no published data for salivary estrone, testosterone or DHEAS at either time point; nor are there published data for postpartum progesterone, estradiol or estradiol within the first two weeks postpartum. There are however, unpublished clinically recognized reference ranges for non-pregnant women in general, supplied by AllVia Lab.

Making comparisons between hormone values observed in this study and the scant published data was hindered further by limitations in the design and methodology employed by various investigators. First, most studies do not control for the time of day of sample collection and many hormones have diurnal rhythms. Test time in this study was very tightly controlled and all samples were collected in the morning at approximately 9:00 AM. Secondly, most investigators do not control for food intake even though food intake confounds salivary hormone analysis. All samples in this study were collected after an overnight fast and eating, drinking or even brushing one's teeth were prohibited prior to salivary collection. Thirdly, some protocols involve the collection of stimulated samples where participants suck on lemon crystals or chew gum; this also impairs analysis by increasing salivary flow rates and ultimately hormone values. In this study, all samples were collected un-stimulated. Finally, most of the published reports utilized radioimmunoassay which, although similar to the enzyme linked immunoassay used in this study, produces somewhat different hormone values. Each of these factors made comparisons between these data and published reports especially difficult.

Nonetheless, comparisons were made for those hormones where published data are available. Pregnancy progesterone values for this study were not statistically different than those collected by Harris, et al. (1994) ($p < .848$). Harris et al. (1994) reported mean progesterone levels of 1132 pg/ml⁸, data from this study show mean progesterone levels at 1112.43 pg/ml. Pregnancy estriol values observed in this study were statistically lower from the mean salivary values published in the literature ($p < .000$), (Darne, McGarrigle

⁸ The hormone data reported by Harris et al. (1994) was reported in bi-weekly increments (36, 38 weeks) in SI units. Data was converted from SI (pmol/l) to conventional units (pg/ml) by dividing reported value by the progesterone conversion factor of 3.18. To estimate the 37 week values, the sum of mean values from 36 and 38 weeks was divided by two.

and Lachelin, 1987; Fisher-Rasmussen, Gabrielsen and Wisberg; 1981; Kos-Kudla, et al. 1999; Haeckel, Walker and Colic 1989; Lachelin and McGarrigle 1984). Moreover the mean observed values in this study were below the range of published estriol values. The range of published estriol levels at 37-38 weeks of pregnancy was 922 pg/ml to 1557 pg/ml. In this study, the mean estriol level at 37 weeks of pregnancy was 501.96 pg/ml. The aforementioned issues in methodology likely account for differences between published values and the observed values from this study.

There are no published values for progesterone at or near 10 days postpartum; nor are there published values for postpartum estradiol or estriol. Furthermore, there are no published data for salivary DHEAS, estrone or testosterone for either pregnant or postpartal women. There are unpublished reference ranges for each of these salivary hormones for non-pregnant women. Listed in Table 4 are unpublished salivary reference ranges provided by AllVia Diagnostic Lab followed by the observed values for each hormone for both pregnant and postpartum women. Since hormone values fluctuate throughout a woman's menstrual cycle, reference ranges are given for both the follicular (high estrogen) and luteal (high progesterone) phases of the cycle.

Obtained postpartum mean hormone values fell within lab reference ranges for non-pregnant women. Notice that mean pregnancy values are substantially above the non-pregnant ranges. Notice also that, as illustrated by Table 5, with the exception of DHEAS, postpartum values decreased markedly from pregnancy and fell within the low range of the non-pregnant values. This is consistent with the widely recognized assumption that reproductive hormones increase exponentially during pregnancy and decrease precipitously within the first three to four days postpartum, continuing to fall for

up to 30 days after delivery (Harris et al. 1998). Hormone data collected in this study affirmed that assumption, for the most part.

As illustrated in Table 5, progesterone levels decreased postpartum in each of the 27 subjects. The mean change was 1095.58pg/ml or 93%. Estrone levels decreased in all but one participant an average of 34.33 pg/ml or 91%. In the one individual whose estrone increased, it did so only nominally (+.1pg/ml). Estradiol decreased in all but three participants; the mean decrease was 9.96 pg/ml or 65%. Estriol, which is all but nonexistent in non-pregnant women, decreased in all participants with an average change of 98% or 452.84 pg/ml.

Testosterone increased in five participants but decreased in 21 participants. The average change in testosterone from pregnancy to postpartum was 17.92pg/ml or 49%. It should be noted, however, that the magnitude of change in testosterone was varied with some women showing little to no change between pregnancy and postpartum and others exhibiting huge differences.

Finally, unlike other studies showing serum DHEAS levels decreasing postpartum (Milewich, et al. 1978; O'Leary, Boyne, Flett, Beilby, James, 1991; Tagawa, et al. 2004; Ylikorkala, Stenman, Halmesmaki, 1988), participants in the current study exhibited a net increase of 34% or 402.03 pg/ml for salivary DHEAS. Furthermore, DHEAS increased in 21 of the participants and decreased in only six participants (see Table 5).

The postpartal increase in DHEAS is noteworthy not only because it contradicts currently held hypotheses, i.e. that DHEAS levels decrease postpartum (Milewich, et al. 1978; O'Leary, et al. 1991; Tagawa, et al. 2004; Ylikorkala, et al. 1988), but also because

DHEAS along with testosterone and estradiol form what may be a dominant metabolic pathway linked to postpartum mood lability. Indeed, as will be discussed subsequently, the relationship between these hormones and negative mood was statistically significant and does suggest a hormonal predictor of postpartum mood dysfunction.

Summary

Data from this section of the study are consistent with the currently held view that progesterone, estriol and estrone levels are high toward the end of pregnancy and fall immediately after parturition, but question that assumption for estradiol and testosterone at least on an individual basis. With each of these hormones, there were postpartal increases in a few participants and minimal decreases in others, suggesting the possibility that the great decline following parturition is not necessarily accurate for all women, even though mean data show large postpartal declines for these hormones. Larger studies are needed to determine whether or not these postpartal increases occur more frequently than has been traditionally reported.

For DHEAS, data from this study definitely contradicts the currently held presumption that this hormone decreases to pre-pregnancy levels postpartum (Milewich, et al. 1978; O'Leary, et al. 1991; Tagawa, et al. 2004; Ylikorkala, et al. 1988). Data from this study clearly show, postpartal DHEAS levels increasing substantially in the majority of participants.

Part Two: Mood

As reviewed previously, postpartum mood lability is often presumed in the literature to be a consequence of childbirth that is attributed to the drop in hormones that occurs in the days following parturition (Buckwalter, et al. 2001; Harris et al. 1994; Meakin, et al. 1995; Nott, et al. 1976; Russell, et al. 2001; Sundstrom, et al. 2003; Weick, 1989). Anecdotal and case report research suggests that postpartum mood lability and dysfunction begins during pregnancy and could, if systematically measured, be identified antenatally. Most characterizations of postpartum mood are focused on depressive symptoms and, thereby, have failed to acknowledge other possible concomitant mood and/or somatic symptoms. Given the knowledge of hormonal actions on brain circuits reviewed previously and the subsequent behavioral changes known to be associated with those actions, it seems possible that both pregnancy and postpartum are marked by specific but different constellations of mood changes. It seems feasible that these changes are characterized to some extent by active anxiety type symptoms in addition to those of the depressive type.

In order to fully understand perinatal mood, the present study measured the full spectrum of mood changes likely associated with pregnancy and postpartum. This was accomplished using the standardized clinical assessment scale, SCL-90R. Results from the SCL-90R were analyzed separately for pregnancy and postpartum and were compared to the normative data of other female non-psychiatric patients as provided by the authors of the SCL-90R (Derogatis, 1994). To determine what extent hormonal factors modulate affective functioning, each of the nine mood domains and the global severity index were compared to each of the hormones at each test time. Finally, in an attempt to identify

antenatal predictors of postpartal mood dysfunction, hormone levels during pregnancy were correlated with postpartum mood.

Mood to Normative Data Comparisons

The SCL-90R manual (Derogatis, 1994) provides normative T-scores to which all mood data comparisons in this study were made. Each of the mood 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 6 are mean T-scores for each of the symptom domains measured by the SCL-90R during pregnancy and postpartum.

Looking at the scaled T-scores, one notices that as a group, pregnant and postpartum women score closely to or slightly above the mean in each of the mood domains and that, as a group, negative mood appears to improve slightly postpartum in most of the domains. For example hostility, paranoia, somatization, obsessive compulsiveness, interpersonal insensitivity and depression all improve postpartum. Only, anxiety, phobia and psychoticism worsen postpartum.

The general assumptions regarding perinatal negative mood are that mood deteriorates postpartum and that depressive symptoms predominate, hence the popular nomenclature postpartum depression. The obtained data presented in Table 6 challenge both assumptions. Not only do mean depression scores improve postpartum (although not significantly $p < .403$), but as Table 6 illustrates, the range of mood symptoms is broad during pregnancy and postpartum. This may be seen more clearly by dividing the women into groups based upon the direction of the mood change from pregnancy to postpartum. As Tables 7 and 8 illustrate, there are three distinct groups of women, those whose moods

improve postpartum, those whose mood symptoms were stable across time and domain and those whose moods worsen. Thus, the data obtained in this study show that as often as not mood changes either remained stable or improved postpartum. Caution is suggested however, since only 10-15% of women experience postpartum depression with approximately 1-3 out of 1000 exhibiting severe psychotic symptoms. In a sample of 28, it is likely that only three women would be expected to exhibit significant negative symptoms and it is unlikely that any of the participants would experience the severity of symptoms associated with postpartum psychosis. This was in fact the case. Of the 28 who completed the sample, two participants experienced severe postpartum mood dysfunction and one participant who failed to complete the study did so because of expressed postpartum mood difficulties.

Dividing the women into groups based upon direction of symptoms change brings to bear several factors that were not necessarily visible in the total group analyses. First, mood scores for those women whose moods remained stable from pregnancy to postpartum (Table 8) hovered around or below mean scores compared to the SCL-90R female non-patient normative sample, except for depression scores which were at their worst almost one standard deviation above mean normative scores for all three groups. For the stable group, the mean depression score was 59.5. For the improved group, the pregnancy depression score was 61.21 while the postpartum score was 54.79. For the group that worsened postpartum, pregnancy depression was measured at 58.5 and increased to 64.83 postpartum. This suggests that depressive symptoms are likely a component of the perinatal experience as argued by most investigators and that depression does worsen postpartum for some but by no means all women.

Secondly, also from Table 8, it is apparent that the mood scores of women whose symptoms were stable across test times fell close to or below the lowest mean scores of both of the other two groups. It is possible that in these women hormone changes either were not associated with mood changes at all or the hormone levels in these women were not extreme enough to illicit noticeable behavioral changes. Since the inter-individual range of hormones was broad, either of these explanations is possible.

Thirdly, phobic anxiety is clearly present both during pregnancy and after delivery. Of the women who improved from pregnancy to postpartum, improvement was minimal with scores still more than one standard deviation above the mean at 63.67. Of the women who worsened postpartum, their postpartum phobic anxiety scores were similar to the improved groups' pregnancy values at 62.37.

Finally, the overall severity of distress as measured by the global severity index (GSI) was similarly elevated at approximately one standard deviation above the mean during pregnancy for both the improved and worsened groups. For those women whose symptoms improved, scores returned to a level identical to the stable group. For those women whose distress increased postpartum, their pregnancy GSI scores were similar to the improved groups' scores (58.5 and 59.33 respectively) but increased to 63.38 postpartum.

Correlations between Hormones and Mood

Given the observed and substantial changes in hormone levels from pregnancy to postpartum, it is reasonable to suspect that those hormone changes underlie perinatal mood. Accordingly, many researchers have sought to correlate reproductive hormones with perinatal mood dysfunction. Most have focused on progesterone and estradiol and

their relationship with postpartum depression. As has been discussed previously, this study looked at five hormones and multiple mood domains both during pregnancy and postpartum in an attempt to not only to characterize perinatal mood and hormone changes but to potentially also identify early markers of postpartum mood dysfunction. Toward that end, data analyses in this section begin with an overview of all of the correlations for both time points for all participants. Subsequently, participant data were divided into the three groups identified previously and as illustrated in Tables 7 and 8 and were correlated with hormone levels.

Pregnancy Global Correlations

Considering the entire group of participants, pregnancy testosterone (n=31) and DHEAS (n=32) levels were significantly and negatively associated with an array of mood symptoms during pregnancy. Testosterone was negatively correlated with phobia ($r=-.384$, $p<.05$), psychoticism ($r=-.410$, $p<.05$), somatization ($r=-.445$, $p<.05$), and overall severity of distress ($r=-.351$, $p<.05$). What was particularly interesting with testosterone was the direction of the relationship. Even though testosterone levels increase substantially during pregnancy as most of the other hormones did, it was lower not higher levels of testosterone that were significantly associated with an increase in negative mood.

DHEAS was also linked to negative mood such that as DHEAS levels increased so too did negative mood symptoms. During pregnancy, DHEAS was significantly and positively correlated with paranoia ($r=.366$, $p<.05$) and psychoticism ($r=.376$, $p<.05$). No other hormone was associated with negative mood during pregnancy.

Postpartum Global Correlations

After delivery (n=26) testosterone was no longer associated with negative mood in any capacity but DHEAS (n=27) was strongly and positively correlated with several mood domains including anxiety ($r=.461$, $p<.05$), phobia ($r=.472$, $p<.05$), paranoia ($r=.441$, $p<.05$), psychoticism ($r=.541$, $p<.01$), somatization ($r=.508$, $p<.01$) and global severity of distress ($r=.387$, $p<.05$). Estradiol (n=27) was significantly associated with paranoia ($r=.482$, $p<.01$) and interpersonal sensitivity ($r=.437$, $p<.01$).

Summary

The results above indicate that diminished pregnancy testosterone levels and elevated postpartum DHEAS as well as estradiol levels play a major role in perinatal negative mood. These results challenge the assumption the progesterone modulates perinatal negative mood.

Pregnancy by Group Analyses

In addition to the correlations between hormones and mood for the entire participant group, women were separated into three groups based upon the direction of symptom change from pregnancy to postpartum.

For the group who exhibited more distress during pregnancy than postpartum, progesterone was negatively correlated and DHEAS was positively correlated with phobia ($r=-.59$, $p<.05$; $r=.99$, $p<.02$, respectively). This is particularly noteworthy considering that the total group analyses showed no connections between progesterone and any of the mood domains. Moreover, progesterone and DHEAS showed an inverse relationships (data not shown) suggesting perhaps that diminished progesterone was mediating the rise in DHEAS levels and possibly the subsequent connections to negative

mood for this group. Consistent with the other findings, testosterone in this group was negatively correlated with a host of mood symptoms including paranoia ($r = -.6$, $p < .04$), somatization ($r = -.63$, $p < .005$), obsessive compulsive behavior ($r = -.56$, $p < .02$), depression, ($r = -.58$, $p < .03$) and the GSI ($r = -.76$, $p < .004$).

The group whose mood symptoms were stable across test times also showed an array of correlations between hormones and mood domains. For this group, DHEAS and estrone were significantly correlated with anxiety ($r = .87$, $p < .02$; $r = .8$, $p < .05$); testosterone was correlated with interpersonal sensitivity at $r = .99$, $p < .01$, but there were only three participants in this particular group.

The final group whose symptoms worsened postpartum, showed a statistically significant relationship between DHEAS and paranoia ($r = .96$, $p < .03$) during pregnancy. Unlike the other groups this group showed no correlations between testosterone and mood during pregnancy nor did they show any relationships to progesterone.

Postpartum by Group Analyses

In the group where symptoms improved from pregnancy to postpartum, a number of negative symptoms were still present and still strongly associated with hormones after delivery. Postpartum progesterone appeared to play a significant role in mood symptoms for this group. Progesterone was strongly and significantly associated with anxiety ($r = .75$, $p < .02$), hostility ($r = .53$, $p < .04$), and depression ($r = .6$, $p < .03$). Notice that the direction of the relationship between progesterone and mood has changed. Elevated progesterone is now associated with negative mood. Since progesterone levels fell so low postpartum, elevated progesterone is difficult to determine in absolute terms, but the directional change in the relationship may signal an altered route of hormone synthesis

relative to pregnancy. This is supported by the fact that DHEAS and estrone are no longer associated with any of the mood domains postpartum and the relationship between testosterone and mood is now much more limited. Whereas during pregnancy testosterone was negatively correlated with a number of mood domains, it is now only correlated to hostility ($r = -.73$, $p < .001$). Estriol was associated with increased somatization ($r = .52$, $p < .02$).

For the stable group, DHEAS was strongly associated with phobia ($r = .64$, $p < .007$) and paranoia ($r = .73$, $p < .003$). Increased estradiol was significantly associated with psychoticism ($r = .63$, $p < .02$). No other hormone was associated with a mood domain postpartum from this group.

In the group whose symptoms worsen postpartum increased paranoia and psychoticism was observed in relation to DHEAS ($r = .99$, $p < .007$; $r = .78$, $p < .01$). Estrone was again associated with anxiety ($r = .89$, $p < .001$) and with depression ($r = .56$, $p < .05$). Estriol was associated with obsessive compulsive behaviors ($r = .67$, $r = .04$) and testosterone was associated with anxiety ($r = .64$, $p < .02$). Notice that with this group progesterone was not involved in any of the negative symptoms and testosterone was positively associated with anxiety, but not any of the other mood domains as was the case with the group whose symptoms improved postpartum.

Summary

Although definitive interpretation of these results is limited by the post hoc nature of these assignments, the group analyses preliminarily suggests that there are three distinct subsets of perinatal mood each differentially mediated by a distinct hormonal

pattern. Further proactive studies with larger samples are needed to confirm and fully explore these patterns.

Possible Hormonal Predictors of Postpartum Negative Mood

Global Correlations

One of the goals of this research was to look for pregnancy biomarkers of postpartum mood dysfunction. To do this, pregnancy hormone levels for the entire group of participants, were correlated with postpartum mood. Consistent with the previously discussed findings, diminished testosterone during pregnancy was associated with negative mood postpartum. Testosterone ($n=26$) was negatively correlated with almost every mood domain including anxiety ($r=-.469$, $p<.05$), hostility ($r=-.609$, $p<.001$), psychoticism, ($r=-.411$, $p<.05$), somatization, ($r=-.497$, $p<.05$), obsessive compulsive behavior ($r=-.589$, $p<.01$), interpersonal sensitivity ($r=-.642$, $p<.001$), depression ($r=-.471$, $p<.05$) and overall distress ($r=-.628$, $p<.001$). Diminished pregnancy ($n=27$) estradiol was also correlated to increased postpartum depression scores ($r=-.422$, $p<.05$).

Group Analyses

Analyses by group indicated that the group whose symptoms improved postpartum was clearly affected postpartum by diminished pregnancy levels of testosterone whereas the group whose symptoms worsened postpartum was not. In the former group, diminished pregnancy testosterone was correlated with increased anxiety ($r=-.67$, $p<.05$), hostility, ($r=-.74$, $p<.001$), psychoticism, ($r=-.88$, $p<.02$), somatization, ($r=-.7$, $p<.001$), obsessive compulsive disorder ($r=-.7$, $p<.02$), interpersonal sensitivity ($r<-.58$, $p<.009$), depression ($r=-.69$, $p<.009$) and the severity of mood disruption as measured by the global severity index ($r=-.84$, $p<.0001$).

The group whose symptoms worsened postpartum showed an altogether different pattern of hormone to mood correlations, perhaps due to the smaller sample size in this group for each of the mood domains ($n = 4-12$). Testosterone was not associated with any mood domain. Elevated DHEAS levels were noticeably but not significantly associated with paranoia and obsessive compulsive behavior. Estrone was associated with paranoia ($r=.96, p<.04$) and estriol was negatively associated with depression ($r=-.66, p<.02$).

Although these data appear contradictory, they are not because each group exhibited distinctly different hormone values during pregnancy. For example mean testosterone levels for the group whose anxiety symptoms improved postpartum was much higher than the group whose symptoms worsened postpartum at 41.7 pg/ml during pregnancy and 19.8 pg/ml postpartum compared to 29.29 pg/ml and 14 pg/ml respectively. For those women whose anxiety levels remained stable, pregnancy and postpartum testosterone levels were measured at 47.55 pg/ml and 29.7 pg/ml, respectively. Additionally, the range of testosterone levels within each group was huge so it is possible that those women who were at the lower end of the range in each group were those who suffered the most distress. Thus when the groups are combined, lower testosterone is correlated very strongly with postpartum negative mood.

Correlations between Changes in Hormone Levels to Postpartum Mood

A leading theory in the field of postpartum mood research stipulates that postpartum mood is related to the extreme and rapid changes in postpartum hormone levels following parturition. Indeed with such significant hormonal changes one would expect significant behavioral and physiological correlates. Most researchers thus far have focused on changes in progesterone and estradiol levels and have only shown weak

relationships at best. This study was much more successful, in part, because the definition of negative mood was not limited to depressive type symptoms and, in part, because this study measured multiple hormones. Thus, not only were there strong significant associations between estradiol and several postpartum mood domains, but consistent with the earlier findings outlined above, testosterone and DHEAS were again significantly associated with negative mood.

The magnitude of change in DHEAS, testosterone and estradiol levels from pregnancy to postpartum were significantly associated with multiple mood indices. Change from pregnancy to postpartum DHEAS levels was associated with increased anxiety ($r=.461$, $p<.05$) and somatization ($r=.460$, $p<.05$). The change in estradiol levels was associated with increased anxiety ($r=.476$, $p<.05$), hostility ($r=.464$, $p<.05$), phobia ($r=.465$, $p<.05$), obsessive compulsive behavior ($r=.417$, $p<.05$), interpersonal sensitivity ($r=.557$, $p<.01$), depression ($r=.418$, $p<.05$), and the overall severity of distress ($r=.530$, $p<.01$). The change in testosterone levels was associated with anxiety ($r=.395$, $p<.05$), hostility ($r=.436$, $p<.05$), somatization ($r=.488$, $p<.05$), obsessive compulsive behavior ($r=.482$, $p<.05$), interpersonal sensitivity ($r=.422$, $p<.05$) and the overall severity of distress ($r=.522$, $p<.01$). No other hormone was associated to any mood domain.

Previous analyses from this study indicated that lower pregnancy estradiol was significantly associated with elevated postpartum depression while increased postpartal estradiol was associated with increased paranoia and interpersonal sensitivity. Here the change in estradiol levels is significantly correlated with depression and with many other mood indices. Additionally, diminished testosterone was previously shown to be correlated with negative mood. Here, the change in testosterone is positively correlated

with negative mood meaning that the larger the change in pregnancy to postpartum testosterone levels the greater the severity of negative mood scores.

These results are likely a result of two factors. First, in the group analysis, it was evident that hormones followed distinct patterns of distribution based upon the direction of mood change. When negative symptoms arose either in pregnancy or postpartum, certain hormone patterns were distinguishable when compared to participants with little or no negative symptoms. Thus change in direction of the correlation between estradiol or testosterone and negative mood does not necessarily represent an absolute change in the direction of the relationship. It is more likely indicative of a relative change in the overall balance of hormones of which both hormones are markers.

Secondly, given the change in relative values of hormones and the fact that each of these hormones has potent neuromodulatory effects it is likely that there is a specific dose-response curve relative both to the absolute amount of circulating hormone and its ratio to other hormones. Since both estradiol and testosterone are excitatory neuromodulators capable of exerting action throughout the central nervous system, it is possible that behaviors seen in this study relative to these hormones follow a pattern similar to other psychostimulants that of an inverted u-shaped curve. In such a curve, diminished circulating levels are associated with negative behavioral effects such as depression and hyper-elevated levels are associated with an increase in anxiety, paranoia and psychoticism and the optimal dose, whatever that may be, improves attention and mood.

Finally, although this is perhaps the clearest indicator of estradiol's role in postpartum mood, it is possible that the connections seen between estradiol's change

scores and negative mood are linked more to DHEAS and testosterone insofar as estradiol's synthesis is intimately tied to both testosterone and DHEAS levels.

Summary

In sum, these data suggest that it is not the ovarian hormones progesterone and estradiol that modulate negative mood for most women, but rather the adrenal androgens testosterone and DHEAS. Moreover, these data reveal that there are patterns of hormone to mood relationships, that, although are not fully characterized at this point, are definitely present and merit further investigation. Moreover, contrary to current literature and nomenclature, "postpartum depression" is equally likely during pregnancy as it is postpartum and is characterized by a spectrum of changes in mood marked largely by anxiety type symptoms. Finally, these results clearly illustrate that hormones are related to perinatal negative mood. In particular, diminished pregnancy testosterone and elevated DHEAS suggest an altered adrenal steroidogenic pathway associated with perinatal mood disorders.

Part Three: Cognition

Part three of this study looked at the cognitive correlates of reproductive hormones during pregnancy and postpartum as well as the relationship between negative mood and cognition.

Ample anecdotal evidence suggests that pregnant women suffer from some degree of memory impairment. Indeed a common complaint of many pregnant women is the perceived decrement in memory. Many researchers have sought to measure this deficit, some more successfully than others (Brindle, et al 1991; Crawley, et al. 2003; deGroot, et al. 2003; Sharp et al. 1993), but only one other researcher to date has attempted to link memory to perinatal hormones (Buckwalter et al. 1999). Moreover, only one other investigator has measured other possible deficits in cognitive functioning associated with pregnancy (Buckwalter, et al. 1999)

The purpose of this study was to provide a comprehensive picture of perinatal affective and cognitive functioning and connect those findings to the hormonal milieu. Given the breadth of influence that steroid hormones have on neural functioning combined with the large changes in circulating hormone levels during pregnancy and postpartum, it is reasonable to assume that such changes would elicit recognizable cognitive changes. To test this hypothesis, a comprehensive but focused battery of neuropsychological tests was administered to each of the participants both during pregnancy and within the first 10 days postpartum.

The cognitive portion of the study addressed several questions. First, are there measurable cognitive changes during pregnancy and postpartum as compared to normative samples. Secondly, are there changes in cognitive function from pregnancy to

postpartum? Thirdly, are observed cognitive changes associated with hormonal changes at either time point? Fourthly, are cognitive changes associated with mood changes at either time point?

Test Selection

Rather than administer a broad, standard battery of neuropsychological instruments designed to measure gross dysfunction and, therefore, likely not capable of detecting what may be subtle changes in functioning, tests for this study were carefully chosen based upon two factors. First, the instrument had to be capable of detecting subtle changes in performance. This meant that it had to be sufficiently difficult so as not to create a ceiling effect. Secondly, the instrument had to measure cognitive function relative to a particular brain region. Based upon binding patterns of the hormones measured, two brain regions were identified as potentially susceptible to hormonal fluctuation. These areas included the frontal cortex, both prefrontal and motor areas, and the hippocampal region. Given the functional specialization of each hemisphere, it was important to test both left and right frontal cortex functioning as well as left and right hippocampal functioning. Accordingly, the tests administered in this study measured frontal and hippocampal functioning for both the right and left hemispheres.

Left Hippocampal and Frontal Functioning

Verbal memory is controlled in large part by the left hippocampus, with marked influence from the frontal cortex. The CVLT-II is a standardized, reliable and valid measure of several components of verbal memory arguably linked to left hippocampal functioning and frontal cortex functioning. The CVLT-II measures immediate recall (trial 1-5) and recall after a distracter list (Recall B) and with a break, short and long term

recall both unassisted (free) and cued. These recall measures are linked to hippocampal functioning.

Recall can be aided by frontal cortex functioning insofar as the participant is able to organize information and attend to the pertinent parts of the task. To determine the degree to which memory is helped or hindered by the frontal cortex, the CVLT-II assesses several domains associated with frontal functioning. These include semantic clustering, (categorical organization of words recalled); repetitions, (number of words repeated during trials, an indication of perseveration) and intrusions (number of words added to recall that don't belong, a marker of disinhibition). Finally, comparing distracter list scores (Recall B) to trial 1 scores yields a measure of proactive interference demonstrating the degree of difficulty participants have in separating previously learned information from new information and is argued to be a particularly telling indicator of executive dysfunction (Egeland, et al. 2005).

CVLT-II results from this study were compared to the standard age and gender matched normative data provided by the test designers (Dellis, Kramer, Kaplan and Ober 2000) as well as to age, gender and IQ matched normative data provided by Spreen and Strauss (1998). Comparisons to IQ adjusted normative data were based upon participants' estimated average full scale IQ determined by the Barona Index as presented earlier.

By way of preview, the results from this study revealed that both pregnant and postpartum women performed more poorly on several aspects of verbal memory when compared to normative samples. When compared to IQ matched normative samples, performance fell substantially below what would be expected. Interestingly, performance declined from pregnancy to postpartum, even though most women perceived themselves

as having improved. Detailed analysis of CVLT-II performance is presented next. The relevant CVLT-II data obtained in this study are shown in Table 9 with comparisons to age and gender matched normative data provided by test designers. Table 10 shows the same observed data compared to age, gender and IQ-matched samples provided by Spreen and Strauss (1998).

Pregnancy

During pregnancy, immediate recall varied from trial to trial, with a lower than normal learning curve of 1.35 words per trial that ranked only in the 39th percentile compared to age and gender matched normative data. Immediate recall in the first trial was poor with only an average of 7.29 words recalled and a 42nd percentile ranking. Total immediate recall across the five trials was somewhat better with the women scoring at the 57th percentile. Recall on the distracter list B was poor, with participants scoring only in the 32nd percentile, as was the short delay free recall with scores only in the 39th percentile.

Performance in long delay was somewhat better with a 43rd percentile ranking. Cued recall, both with short and long delays, was better at the 43rd and 46th percentiles respectively suggesting that verbal recognition is only nominally impaired compared to short and long term recall.

Performance on indices that measure frontal cortex functioning were somewhat better, but still very poor compared to normative scores. Semantic clustering, a measure of learning strategy was slightly above average compared to age, but not education matched normative data, with the women scoring in the 58th and 51st percentiles for the immediate and long delay trials respectively. While pregnant, participants exhibited an

abnormally elevated repetition score (67th percentile) and showed a slightly above average number of intrusions (56th percentile). The repetition score is indicative of increased perseveration, while the intrusion scale suggests recall disinhibition difficulties. Lower list B recall scores were obtained compared to trial 1, with 6.06 (list B) versus 7.29 (trial 1) words. The lower score on trial B indicates increased vulnerability to proactive interference or difficulty separating what has been learned previously from what needs to be learned in the new trial (Dellis, et al. 2000)

Postpartum

Performance on the CVLT-II was somewhat worse postpartum than during pregnancy with a few notable exceptions. The number of repetitions was significantly lower postpartum ($p=.007$), the learning curve improved, although not significantly, and semantic clustering for both short and long delays also improved, but again not significantly. Recall scores were either stable or fell and the number of intrusions increased although not significantly.

Comparison to IQ-Matched Normative Data

Given that the women in this study were relatively well educated, averaging almost 16 years of education, and exhibited a somewhat above average estimated full scale IQ (111) and verbal IQ (114), it was appropriate to compare their scores to age, gender and IQ matched normative scores. As seen in Table 10 comparisons to IQ-matched normative data as provided by Spreen and Strauss (1998) reveal clear and consistent performance deficits. Where non-IQ matched comparisons yielded slight to moderate deficits in verbal memory (Table 10), IQ-matched comparisons clearly illustrated severe decrements in verbal memory at both time points. For example

comparisons to the IQ-matched data yielded percentile rankings from as low as the 2nd percentile (immediate recall B) and the 7th percentile (immediate total recall) during pregnancy to below the 1st percentile (immediate recall list B) and the 8th percentile (immediate total recall) postpartum.

During test administration, many women failed to organize the words semantically, thus hindering recall performance. As a group, semantic clustering scores were about average compared to normative data, but the range of scores was broad during pregnancy and postpartum (-2 to 9) with some women showing absolutely no ability to cluster the words by category, while others did quite well. Likewise repetition and intrusion scores were broadly distributed with scores ranging from zero repetitions or intrusions to as many as 16 repetitions and 18 intrusions overall.

Semantic clustering was in turn highly correlated to recall scores. Higher semantic clustering led to higher recall across trial with correlation ranging from $r = .708$, $p < .001$ to $r = .817$, $p < .001$ in the long and immediate recall trials respectively. Conversely, elevated repetition scores were associated with poorer performance on recall tasks postpartum with correlations ranging from $r = -.493$, $p < .01$ to $r = -.577$, $p < .01$, but repetition was not associated with performance during pregnancy even though repetition scores were higher in pregnancy than postpartum (mean 7.65 vs. 4.46). The intrusion scores, although elevated, did not impair performance at either time point.

Changes in Verbal Memory from Pregnancy to Postpartum

Although there were few statistically significant changes in performance from T1 to T2 (Table 9), women performed more poorly at time T2. This is particularly interesting considering that most women perceived themselves as having had great improvements in

memory from pregnancy to postpartum. Despite decrements in memory, the learning curve improved from 1.35 to 1.48 words per trial and total repetitions diminished significantly from an average of 7.65 to 4.46 words ($p=.007$), perhaps accounting for the perception of improvement. The number of intrusions increased slightly postpartum, and semantic clustering deteriorated. Recall on trials 1 and B declined, and proactive interference also increased.

Summary

The results from the CVLT-II demonstrate that pregnant and postpartum women have strikingly poorer verbal recall (particularly when compared to IQ-matched normative samples), suffer from perseveration, have difficulties with disinhibition, and are susceptible to proactive interference. Moreover the degree of memory impairment is clearly associated with the ability to categorize information. Performance postpartum was generally worse than during pregnancy across all recall trials, but learning curve, semantic clustering and perseveration improved while disinhibition and proactive interference increased. From these results it is evident that pregnancy and postpartum have deleterious effects on memory and executive function, but whether these problems arise from hippocampal or frontal functioning is difficult to gauge.

Right Hippocampal and Frontal Cortex Functioning

Spatial Memory

Spatial memory resides in the right hippocampus with planning and organizational capacity influenced by the frontal cortex (Lezak, 1995; Cummings and Trimble, 1995). To determine the degree to which right hippocampal functioning was affected by pregnancy related hormone changes, the Rey Complex Figure Test (CFT)

was given. This task measures multiple components of spatial memory including visuoconstructional ability (copy task) and amount of information retained over time (recall). Because the figures are relatively complex, both the copy and recall components require a high level of organizational ability. Diminished organization is arguably linked to poor executive function and drastically reduces recall ability (Choi, et al. 2004; Gooding and Braun, 2004; Lezak, 1995; Shin et al. 2004; Spreen and Strauss 1998; Zappala and Trexler 1992).

The maximum score on the CFT is 36 points, with each aspect of the drawing given 0-2 points for accuracy and placement. The complex figure test was administered in both the copy and long term delay formats at both time points. To minimize practice effects, an alternate but comparable (Kuehn and Snow, 1992) complex figure test produced by L. Taylor in 1969 was utilized at T2. The CFT was scored independently by two individuals with disputes resolved by a third party. Tests were scored using the L. Taylor scoring method and normative comparisons were made using the L. Taylor scoring data as provided by Spreen and Strauss (1998).

During pregnancy, copy scores were just above the mean at the 56th percentile and delay scores were well below normal at the 29th percentile compared to age-matched normative data. The mean copy score during pregnancy was 33.98 out of 36 points and the mean delay score was 18.2. The postpartum scores were also very low, but the pattern reversed. At T2 the mean copy score was 30.8, placing it in the 4th percentile, while the mean delay score was 20.3 placing it in the 41st percentile. To put these scores in perspective, the mean pregnancy delay scores observed in this study were similar to or below scores that have been observed in patients with moderate closed head injuries

(M=22.5) (Bigler, Rosa, Schultz, Hall and Harris, 1989) obsessive compulsive disorder (M=18.19) (Roh, et al. 2005), schizotypy (Gooding and Braun, 2004), and schizophrenia (M=19.2) (Fenning, Mottes, Richter-Levin, Treves and Levkovitz, 2002)

As was the case with performance on the CVLT-II, organizational ability played large role in performance on the CFT. Qualitative review of both copy and long delay performance suggests that underlying the low scores was an impressive lack of organizational ability and that performance on these tests may have been related more to diminished executive function than to reduced memory capacity, although memory is certainly impaired in many cases. To illustrate this point, Figures 2-8 include copy and recall figures from a few of the women during pregnancy as well as the original figure used in this task.

Notice that each of these participants failed to recognize the basic components of the original figure during the copy phase. They did not identify the rectangle (2) and forward triangle (13) as the base of the drawing, instead focused more on the individual details within the rectangle. By doing so they were limited in their capacity to organize and remember the figure appropriately in the recall trial. They also missed the contiguity of the horizontal (4), vertical (5), and diagonal (3) lines that cross at the center of the figure. This impaired recall substantially insofar as each section of each line had to be recalled separately rather than as part of a whole pattern. The failure to recognize the contiguity of the lines is evident in the recall phase where each participant remembered only portions of these lines. Notice also that entire sections of the figure are missing from each of the three figures in the recall phases. Similar problems were noted postpartum but are not presented. Thus failure to correctly identify and organize the inherent pattern of

the figure impaired recall during pregnancy and may speak to some hormonal influence on the frontal cortex during pregnancy. Given that there were also deficits in memory it is also likely that hippocampal functioning was impaired. The results of the CVLT-II together with CFT illustrate that both right and left frontal and hippocampal systems are impaired perinatally.

Cognitive and Motor Processing

To determine what role pregnancy hormones might have on cognitive and motor processing and to rule out confounding deficits that might diminish memory performance, participants were given the PASAT, the Finger Tapping Test and the Purdue pegboard. The PASAT is a serial auditory processing task that measures attention, cognitive processing speed and working memory. The Finger Tapping Test and the Purdue Pegboard both measure motor speed and fine motor dexterity.

PASAT

The PASAT is a serial processing task in which participants are asked to add pairs of numbers that are read at ever increasing pace. There are four trials, with 60 numbers in each trial. Trial 1 is read at a pace of one number per 2.4 seconds, trials 2, 3, 4 increase to 2.0, 1.6 and 1.2 numbers per second respectively. The PASAT requires the participant to add the numbers serially, without adding subsequent numbers to the sum, while retaining the previous number in memory. As such, the PASAT measures cognitive processing speed, auditory attention span and working memory (Gronwall, 1977). The PASAT is a demanding task thought to be especially sensitive to mild and moderate brain damage (Brittain, et al. 1991; Lezak, 1995).

Published normative data for the PASAT differs somewhat between studies depending upon whether or not demographic variables such as gender, education, IQ and ethnicity are considered. Nonetheless, comparisons between the present data and normative data detailed in the PASAT manual (Stuss, Stethem, and Pelchat, 1988) indicate that during pregnancy women perform very poorly compared to age matched non-pregnant normative samples. Rankings for pregnant women on PASAT ranged from the 22nd to 37th percentile, by trial. After delivery, rankings improved ranging from the 46th to 52nd percentile, but given the possibility of practice effects it is difficult to determine the nature of the improvement. Stuss, et al. report significant practice effects if retesting occurs six days after the first test is given.

Since diminished cognitive processing speed and poor auditory attention are likely to hinder performance on memory tasks (Dellis, et al. 2000), one would expect PASAT scores to be highly correlated to CVLT-II scores. This was not the case. PASAT performance was correlated only with the CVLT-II semantic memory scores in the immediate recall condition during pregnancy ($r=.432$, $p<.015$) and was not correlated with long delay semantic memory at either test time. Conversely, PASAT scores were correlated with immediate recall scores postpartum ($r=.516$, $p<.005$) but not during pregnancy and showed no correlation to semantic memory. The limited and inconsistent correlations between the PASAT and the CVLT-II obtained herein suggest that although cognitive processing speed was obviously diminished, as was exhibited by the poor performance on the PASAT, it is not likely that cognitive processing speed was a factor on CVLT-II performance. Rather, the correlation between the PASAT and semantic

memory suggests an attentional deficit, particularly in immediate recall where attentional demands are greatest.

Anecdotally, two women performed exceptionally well on the PASAT, scoring near 100% on each trial. Three other women were unable to complete all of the trials, with one of the three unable to get past the first trial, even though her math abilities and education level suggested that she should have performed otherwise.

Finger Tapping Test and the Purdue Pegboard

The Finger Tapping Test (FTT) and the Purdue Pegboard were administered to assess motor processing speed and lateralization. Scores obtained for the FTT in the present study were compared to normative data provided by Spreen and Strauss (1998). The results showed motor slowing during pregnancy that improved significantly postpartum ($p=.017$) for the preferred hand and worsened non-significantly postpartum for the non-preferred hand. Performance for dominant and non-dominant hands during pregnancy yielded ranked scores in the 43rd and 45th percentiles respectively. Postpartum performance was ranked at the 44th and 38th percentiles respectively.

Results from the Purdue Pegboard were compared to normative data listed in the Purdue Pegboard Manual. Observed performance on Purdue Pegboard was well below normal at both time points. Right handed performance ranked in the 14th and 19th percentiles at pregnancy and postpartum respectively, while left-handed performance was ranked at the 9th and 17th percentiles. In each case, performance improved postpartum. Improvement was not significant for the right hand, but was significant for the left hand ($p=.03$).

Overall, motor performance improved somewhat from pregnancy to postpartum. Preferred hand performance on the FTT improved slightly postpartum while scores from the non-preferred hand worsened slightly. On the Purdue Pegboard both hands improved slightly. Pegboard performance with both hands was not significantly different postpartum.

To assess lateralization, right-hand and left-hand scores were compared for each test at each time point. For each of the tests at each test time, right-handed scores were significantly better than left-handed scores. In the FTT right-handed performance was significantly better than left-handed performance both during pregnancy ($p < .000$) and at postpartum ($p < .000$). For the Purdue Pegboard this was also the case. During pregnancy right-handed performance was significantly better than left-handed performance ($p = .001$) as it was postpartum ($p = .012$). This was true for the three left handed participants as well. Given that all but three of the participants were right-handed these results are consistent with expectations and likely do not confirm or disconfirm that hormones preferentially affect one hemisphere or the other.

Left and Right Frontal Cortex Functioning

Verbal Fluency and Design Fluency

To further analyze the effects of pregnancy hormones on cognitive processing, particularly executive and hemispheric specialization, participants were given the verbal and design fluency tasks. Both tasks are thought to measure hemispheric frontal lobe function with the verbal fluency task assessing left frontal lobe functioning and the design fluency task measuring right frontal lobe functioning. These tasks are thought to

be particularly sensitive to dorsal lateral prefrontal cortex deficits (Cummings and Trimble, 1995) an area arguably susceptible to hormone influence.

The verbal fluency tests requires participants to generate words beginning with different letters (F, A, S) within 60 seconds. This portion of the task is referred to as phonemic categorization. It is followed by a semantic category task in which participants are required to generate animal types, again within 60 seconds. Researchers argue that the verbal fluency task measures both long term memory and frontal cortex functioning insofar as it requires participants to organize and categorize responses while systematically filtering irrelevant information (Abwander, Swan, Bowerman and Connolly 2001). Some researchers argue that it also taps long term memory insofar as participants are asked to retrieve words from long term storage (Raskin and Rearick, 1996). Finally, non-impaired participants are expected to produce more words on the semantic rather than the phonemic task because the added structure of the semantic task improves retrieval (Raskin, Sliwinski and Borod 1992; Troyer, Moscovich, Winocur, Alexander and Stuss, 1998).

Participants in this study performed below average on the phonemic portion of the verbal fluency test during pregnancy when compared to age and education matched normative data provided by Spreen and Strauss (1998), with a mean of 44 words generated and a ranking in the 40th percentile. Participants scored above average in the semantic portion, with mean score of 20 words which ranked in the 58th percentile during pregnancy. Postpartum performance improved non-significantly for both phonemic and semantic tasks, with mean scores of 46 and 21 words respectively and corresponding improvements in rank to the 46th and 67th percentiles for phonemic and semantic fluency

tasks. At both test times the pattern of results for the scaled scores followed the expected pattern of performance for non-impaired individuals (i.e. better semantic versus phonemic scores) but the absolute scores did not this pattern.

In the free condition of the design fluency test, participants performed just above average at 54th percentile but were well below average in the fixed condition with only a 33rd percentile ranking during pregnancy. The decrement in fixed condition performance was interesting because most participants expressed liking this task better than the free condition and because with the deficits in organizational ability exhibited by these participants, one would have expected performance here to be better. There was significant improvement on both tests postpartum ($p=.011$, $p=.001$, respectively) with corresponding percentile rank improvements to the 77th and 63rd.

Summary

Results from these tests indicate that pregnant and postpartum women exhibit mild to moderate impairment across all cognitive domains assessed by this battery. The pattern of deficit appears diffuse, contributing equally to impaired performance on tasks assessing both hemispheres. Performance on the CVLT-II when compared to age, gender and IQ-matched normative deficits showed moderate to severe impairment across recall trials bolstered only by semantic clustering abilities. Performance on the CFT indicated poor spatial recall that was marked by poor visuoperceptual and constructional organization. Results from the PASAT demonstrated mild to moderate declines in attention and cognitive processing speed while performance on tests of motor processing were only slightly impaired. Both generative tasks illustrated mild impairment during pregnancy when compared to normative data that improved somewhat postpartum.

Cognition and Hormones

To determine if hormones were associated with the observed cognitive deficits seen both during pregnancy and postpartum, cognitive indices were correlated with each hormone at each time point. Since researchers posit that it is the magnitude of hormone change from pregnancy to postpartum that modulates many of the behavioral changes postpartum (Buckwalter et al. 1999; Harris et al. 1994), the difference between pregnancy and postpartum hormones was correlated with postpartum cognitive function as well. As was the case with the hormone to mood relationships, the observed hormone to cognition relationships were complex and in some cases difficult to interpret without considering the biosynthetic pathways involved in hormonal regulation as well as the presumed neuromodulatory actions of each hormone. As will be seen, cognitive performance improved or deteriorated consistent with both the neuromodulatory actions of the hormones measured and according to the relative relationship among these hormones, but were not consistently correlated with any hormone.

The three estrogens were negatively associated with a number of cognitive indices during pregnancy but positively associated with other indices postpartum. Increased estrone during pregnancy was associated with a smaller CVLT-II learning curve ($r = -.428$, $p < .05$) and a lower total score on the PASAT ($r = -.377$, $p < .05$). Estradiol was negatively associated with immediate total recall ($r = -.389$, $p < .05$) and estriol was negatively associated with trial 5 and immediate total recall of the CVLT-II ($r = -.366$, $p < .05$; $r = -.385$, $p < .05$) as well as trial 1 of the PASAT ($r = -.379$, $p < .05$). In each of these cases increased circulating levels of the hormone were associated with poor cognitive performance.

Postpartum, estrone was not associated with any cognitive domain but estradiol was associated positively with trial B of the CVLT-II ($r=.405$, $p<.05$) and negatively with trial 2 of the PASAT ($r=-.410$, $p<.05$). Postpartum estriol was again associated with learning curve but this time the relationship was positive ($r=.421$, $p<.05$). Interestingly, postpartum estriol levels were very strongly and negatively correlated with performance on the left-handed portion of the Purdue Pegboard ($r=-.532$, $p<.01$) as were postpartum testosterone levels ($r=-.444$, $p<.05$). Testosterone was also correlated with the number of repetitions on the CVLT-II during pregnancy but not postpartum. DHEAS was associated only with performance on the recall portion of the CFT ($r=-.379$, $p<.05$) and only postpartum; it was not correlated with any other cognitive domain either during pregnancy or postpartum.

The change in circulating hormone levels from pregnancy to postpartum showed an altogether different pattern of association to postpartum cognitive performance and was more consistent with expectations based upon other findings in this study. Similar to findings in the mood section, the large changes in DHEAS levels were associated with poor performance on tests of verbal memory. In particular, the change in DHEAS levels was negatively correlated with immediate recall trial 5, total immediate recall ($r=-.433$, $p<.05$; $r=-.492$, $p=.01$), semantic clustering ($r=-.479$, $p<.05$), and number of repetitions ($r=-.624$, $p<.001$). Interestingly, changes in progesterone levels showed a negative correlation to the number of repetitions as well ($r=-.386$, $p<.05$). The change in progesterone was also associated with performance on both aspects of the design fluency task ($r=-.501$, $p<.01$; $r=-.402$, $p<.05$).

Summary

Given the large number of statistical analyses performed, it is possible that these associations are artifactual and at the very least they are difficult to interpret. It is also possible that these associations are consistent with the neuromodulatory effects of the hormones at varying dosages and relative to their relationship with the other hormones measured. Recall that estrogens are excitatory neuromodulators and should improve and focus cognitive ability when elevated and impair cognitive ability when diminished but only to a certain degree. Similar to other psychostimulants such as amphetamines, where lower doses improve and higher doses hinder performance, the hyper-elevated circulating levels of estrogen during pregnancy impaired performance, as did the extremely low levels of estrogens postpartum. Thus, postpartum cognitive performance improved to the degree that the circulating estrogens rose above the abnormally low postpartum levels. Likewise, pregnancy performance was impaired to the degree that estrogen levels rose above already abnormally high circulating levels.

The relationship between DHEAS and cognition is a lot less clear but is also likely attributable to an inverted u-shaped dose-response curve. Like the estrogens, DHEAS can be considered an excitatory neuromodulator. Indeed some studies with the elderly have found that DHEAS supplements improve a variety of cognitive functions (Berr, et al. 1996) perhaps as a result of conversion to DHEA. Since DHEAS levels decline substantially with age (Rainey, Carr, Sasano, Suzuki and Mason 2002), the improvement in cognitive performance reported in these studies is likely relative to the degree that DHEAS returns to “normal” circulating levels. In this study, DHEAS levels were elevated during pregnancy and increased to supra-elevated levels postpartum, thus

the relationship to postpartum performance was tied to the magnitude of change from pregnancy to postpartum levels and not to absolute levels.

Overall, the hormone to cognition results from this study were expected based upon their neuromodulatory roles within the central nervous system. However, the results offer limited interpretive validity both because of the small sample size and the large number of correlations. It is possible that, as was the case with the mood factors, cognitive to hormone relationships differ by the direction of change from pregnancy to postpartum. That is, it is possible that there were three distinct groups of women, those whose performance was better during pregnancy, those whose performance was better postpartum, and those who were consistent across testing times. But given the large number of cognitive variables and the small sample size, isolating real versus artifactual relationships among the three groups would be particularly difficult.

Cognition and Mood

Each mood domain in the SCL-90R was correlated to each cognitive domain to determine if negative mood symptoms influenced cognitive performance. The results shown in Table 12 counter the currently held notion that negative mood always hinders cognitive performance. Except for the few negative correlations shown in Table 12, the relationship between negative mood and cognitive performance was positive. That is, as negative mood increased, cognitive performance also increased. This was true at both time points. Increased depression was consistently and significantly correlated with better recall call scores during pregnancy,, but no relationships were found postpartum. Psychoticism, phobia and paranoia also were significantly and positively correlated with several CVLT-II scales and were highly correlated to the fixed condition of the design

fluency task. Only performance on trial two of the PASAT and the learning curve of the CVLT-II were negatively correlated with mood scores. Thus increases in phobic anxiety decreased processing speed on the PASAT ($r=-.365$, $p<.05$), and increased psychoticism was detrimental to the number of new words learned per trial ($r=-.361$, $p<.05$) on the CVLT-II.

Summary

These data indicate that negative mood does not always hinder performance on cognitive tasks. Indeed most mood domains showed no relationship to cognitive performance and many of the relationships between mood and cognition were positive.

CHAPTER 5

DISCUSSION

The purpose of this research was to characterize the cognitive and affective changes associated with perinatal hormones. Previous research had hereto presented only a partial picture of perinatal behavioral changes and had been unsuccessful in the attempt to associate those changes with perinatal hormones. This was due largely to the lack of sensitivity and specificity of the testing methods. The present study was able to overcome those issues by using more sensitive hormonal assays and a comprehensive but focused battery of neuropsychological instruments. Thus, data collected in this study challenge many of the empirical generalizations regarding perinatal hormones, mood and cognition.

Hormones and Mood

Previous research, with the exception of Buckwalter et al. (1999), focused almost entirely on depressed mood as the sole marker of the postpartum experience and had variously sought to link depressed mood to either progesterone or estradiol (Kuevi et al. 1983; Harris et al. 1994; O'Hara, et al. 1991; Metz et al. 1983; Nott, et al. 1976). Buckwalter et al. (1999) was the first and only study until now to address the possibility that postpartum and indeed pregnancy was likely marked by a range of mood and cognitive changes. The results of Buckwalter et al. (1999), although important, were mixed in part because hormones were assayed via serum, which measures bound rather

than active hormone, and in part because the battery of tests given was not nearly as focused as was necessary to measure what were in some cases subtle changes in behavior.

For the present study salivary hormone assays were used. Salivary hormone analysis affords a more sensitive approach than serum insofar as the active, unbound component of the hormone is present and measured in saliva. By increasing the sensitivity of hormone analyses, this study was able to confirm and challenge a number of findings both with regard to peripartal hormones in general and in as much as they relate to mood and cognition.

The general presumption about pregnancy hormones is that they increase exponentially until parturition where after they decrease rapidly. In the case of progesterone and estriol this was in fact the case for all of the participants of this study. It was not the case, however, for the other hormones. For five of the participants in this study, testosterone levels increased postpartum and for many others the change was not as substantial as would be expected. Additionally, estradiol levels increased in three of the participants and estrone levels increased in one participant.

Most striking were the changes in DHEAS. Previous literature measuring DHEAS levels in serum showed that DHEAS levels increased in the first and second trimesters and decreased in the third, particularly as parturition approached and fell to pre-pregnancy levels after delivery (O'Leary, et al. 1991; Milewich, et al. 1978; Tagawa, et al. 2004; Ylikorkala, et al. 1988). This pattern of change was not observed here. Salivary DHEAS levels were very high at 37 weeks of pregnancy and for 21 of the 27 women, DHEAS levels not only increased postpartum, but increased substantially. The

increase was especially large for those women who would experience adverse postpartum mood changes. Thus, by measuring the unbound, bioactive component of these hormones, data from this study challenge the currently held assumption that all perinatal hormones decrease postpartum for all women.

The relationship between perinatal hormones and mood was until now only tenuously linked. Again by increasing the sensitivity of the hormonal assays, expanding the number of hormones and type of mood domains measured, this study not only identified putative hormonal correlates of perinatal negative mood but disputes the current nomenclature and diagnostic interpretation associated thereafter. Indeed what has hereto been called postpartum depression is not necessarily either.

Results from this study clearly demonstrate that both pregnancy and postpartum elicit negative mood changes for almost equal numbers of women. Moreover, although depression is part of the perinatal experience, it is by no means the sole determinant of distress. Indeed SCL-90R scores from this study were consistently elevated across domains at each test time. This was particularly evident in the post hoc group analyses where each of the two groups exhibiting distress scored approximately one standard deviation above the mean on most every mood domain measured. These results thus question 1) the notion that “postpartum depression” is limited to depressive symptoms and 2) that distress occurs solely in the postpartum period.

Moreover, results from the present study identify an unmistakable pattern of hormonal correlates linked to perinatal negative mood. As discussed previously, research in this area has been limited by definition and focus. Most research hereto performed attempted and failed to link postpartum depression to the ovarian hormones progesterone

and estradiol. Given the enormous changes in these hormones from pregnancy to postpartum, the relationship between progesterone, estradiol, and mood suggested a reasonable line of inquiry. Indeed, many of the testing instruments selected for this study were selected based upon the presumed actions of progesterone on the GABA_A receptor in specific regions of the central nervous system.

Based upon animal research and receptor binding patterns it was thought that progesterone via its actions on the GABA_A receptor would mediate most perinatal cognitive and affective changes. Progesterone and many of its metabolites are potent positive allosteric modulators of the GABA_A chloride channels, increasing GABA influx on the postsynaptic cell. By this mechanism, progesterone is an effective sedative-hypnotic. Given the exponential and chronic increase in progesterone levels throughout pregnancy followed by the precipitous decline after parturition, it seemed likely that progesterone would mediate many of the affective changes associated with pregnancy and postpartum. This was the case, but only for a particular group of women.

Overall, progesterone was not correlated with any of the mood domains either during pregnancy or postpartum, but the post hoc analyses of groups showed strong correlations between progesterone, anxiety, hostility, and depression postpartum for the group whose symptoms were worse during pregnancy; the direction of the relationship however, was contrary to accepted research: it was positive, indicating that increased progesterone was associated with increased negative mood.

These results are perplexing and may be artifactual given the large number of statistical analyses performed, or they may signal some as of yet undetermined alteration in steroid synthesis relative to pregnancy. With such a small sample it is difficult to

determine which of these two possibilities is true. In either case, what was clear from these data was that although progesterone may indirectly underlie postpartum mood, it is by no means the main culprit of distress. Rather, it appears from data gathered in the present study that adrenal androgens may underlie much if not all of perinatal negative mood, with consequent changes in each of the other hormones linked directly or indirectly to some fundamental change in adrenal steroidogenesis.

The most important findings of the present study were the relationships between the adrenal androgens DHEAS and testosterone and nearly every negative mood symptom measured by the SCL-90R, both during pregnancy and postpartum. In this study, diminished pregnancy testosterone levels were clearly, consistently and strongly associated with elevations in postpartal anxiety, hostility, psychoticism, somatization, obsessive compulsive behavior, interpersonal sensitivity, depression and global severity of distress. Concurrently, increases in postpartal DHEAS levels were strongly and significantly correlated with anxiety, phobia, paranoia, psychoticism, somatization and global severity of distress. Together, these findings present a picture of perinatal mood disturbance marked by increased negative mood that are identifiable biologically by diminished pregnancy testosterone and elevated postpartal DHEAS levels.

Given the numerous animal and molecular studies that indicate direct action by progesterone on the GABA_A receptors, were the suppositions proposed by this and other researchers incorrect? No, but they were incomplete on several levels.

Recall that the metabolism of steroid hormones is tissue specific. In non-pregnant, normally cycling women, metabolism of steroid hormones via the ovaries and adrenals follows the pattern illustrated in Figure 1, wherein progesterone is converted in the

ovaries into several other steroid hormones including testosterone, estradiol, and estrone. The predominant estrogen in non-pregnant women is estradiol synthesized in the ovary. During pregnancy and at menopause ovarian production of these hormones all but ceases, but circulating levels at least in the case of pregnant women remain high (Carr, 2001; Walsh and Schiff, 2001). In both instances, adrenal synthesis predominates (Walsh and Schiff, 2001). In the case of pregnant women, both the fetal and maternal adrenal glands produce increased levels of steroids, including those normally synthesized by the ovaries. The up-regulation of maternal adrenal steroid synthesis, coupled with the addition of fetal adrenal hormone synthesis, is presumably responsible for the elevated circulating steroid hormones and concomitant decrease following parturition (Carr, 2001). This makes sense given the quiescence of the ovaries throughout pregnancy and early postpartum.

With the perinatal shift of “ovarian” steroid hormone production, synthesis pathways and relative values of each hormone shift as well. Complicating factors even further is the fact that steroid hormone synthesis during pregnancy is a multi-compartmental process wherein the relative amount of steroid produced by each compartment is largely dependant upon variations in enzyme availability. Although a full explanation of fetal maternal and placental steroidogenesis is beyond the scope of this study a couple of points demand discussion.

First, at approximately 6-8 weeks of gestation the fetoplacental unit takes over steroidogenesis (Challis and Lye, 1998). Concurrently with that development, maternal adrenals begin producing large amounts of DHEA, which is then converted to DHEAS for storage. DHEAS is the most abundant steroid in human circulation (Hammer, et al. 2005; Siiteri, 2005; Walker et al. 2000) but is considered a reservoir for what is argued to

be the biologically active steroid DHEA, although data from this and other studies suggests DHEAS may indeed be active as well (Bonser, et al. 2000; Charalampopolous, et al. 2005), particularly in the central nervous system. Nonetheless, according to most models, activation of DHEAS requires that it be converted into DHEA via microsomal enzymes called steroid sulfatases (Hammer, et al. 2005). Once converted to DHEA, a variety of other hormones via multiple enzymes are then synthesized including testosterone, estrone and estradiol.

This is not the pattern of steroid biosynthesis during pregnancy when the fetoplacental unit takes over much of the steroid production. Fetal adrenals produce DHEA that is also converted into DHEAS, but where DHEAS was considered inactive in the downstream conversion of other hormones in the adult adrenal, in the fetal adrenal DHEAS is the parent hormone to many other steroid hormones both directly and indirectly. From DHEAS produced in the fetal adrenal, estriol is synthesized. Recall that estriol is considered the dominant estrogen of pregnancy. Fetal adrenal DHEAS is also converted into multiple androgens as well as into estrone and estradiol after it is transferred to the placenta. During pregnancy, approximately 90% of maternal estriol and 50% of estrone and estradiol are derived from fetal DHEAS (Challis and Lye, 1998). Estriol is synthesized from DHEAS via 16 α hydroxylation in the fetal liver while estradiol is aromatized from testosterone in the DHEA>androstenedione pathway. Also during this time, the placenta evolves as the major source of progesterone and by twelve weeks placental progesterone synthesis dominates (Challis and Lye, 1998).

The data from this study linking diminished pregnancy testosterone and elevated postpartal DHEAS to negative mood, together with shift from maternal ovarian to the

combined fetal and maternal adrenal steroid production during pregnancy, point to altered adrenal androgen synthesis in the etiology of perinatal mood dysfunction. The putative physiological mechanism is unknown, but is conceivably linked to dysregulation of one of the many enzymes actively involved in steroid synthesis.

The question remains, how does DHEAS modulate behavior? Recall that DHEAS is a potent allosteric GABA_A antagonist and reportedly blocks GABA_A receptors via a mechanism similar to that of picrotoxin, making DHEAS anxiogenic and pro-convulsant (Jacobs, Edelheit, Coleman and Herzog, 1999; Rogers, 1999). Elevated DHEAS would decrease postsynaptic GABA_A Cl⁻ influx and increase central nervous system excitability. The actions of DHEAS alone could account for the behavioral profile exhibited by the participants in this study; however, concurrent with the late term and postpartal rise in DHEAS levels, progesterone levels fell as well. While elevated progesterone is sedating and anxiolytic (Arafat, et al. 1988; Concas, et al. 1997; Johansen, et al. 2002; Selye, 1946), both chronic progesterone exposure and abrupt withdrawal are highly anxiogenic (Gulinello and Smith 2003; Foley, et al. 2003; Poromaa, et al. 2003). These two patterns are consistent with the behavioral findings of this study.

Even though direct evidence of DHEAS modulation of other downstream hormones is unavailable, there is indirect support. Research points to DHEAS facilitation of testosterone binding, especially albumin (Roberts, 1999). As most studies have utilized serum as the means to measure steroid hormones, the increased binding rather than absolute change in the level of hormone may or may not have been measurable. In the present study, the unbound portion of the hormone was measured, hence the associations

among DHEAS, testosterone, and negative mood. Whether there was a change in the absolute level of the hormone is difficult to determine, but these data clearly show decreases in unbound hormone testosterone.

Thus while the assertion that progesterone levels would mediate most of the perinatal mood changes directly was incorrect, the presumption that GABA modulation underlies many of the negative symptoms is still likely given that the pattern of correlations seen in this study and the direction of hormone change observed from pregnancy to postpartum. As GABA_A receptors become habituated to chronically elevated progesterone and receptor conformational changes ensue and as progesterone drops postpartum, GABA levels are likely also to decline. Concurrently, DHEAS levels are rising, in some cases several fold, blocking the few GABA_A receptors remaining and effectively increasing central nervous system excitation in the weeks leading to and following parturition. Moreover, pregnancy testosterone levels are possible early biological markers of the shift in adrenal steroidogenesis, but further research is needed to determine how the two are related.

Cognition

In addition to looking at perinatal mood changes, the present study measured a number of cognitive variables to determine if the anecdotally accepted perinatal decrements in memory existed, if other cognitive deficits were present and to what degree changes in hormones and/or changes in mood were responsible for perceived deficits. Unlike the mood data, the cognitive data collected herein was neither as clearly delineated nor as consistently tied to either hormonal or affective correlates. What was

evident however, was that during pregnancy and when compared to normative standards, participants in this study performed more poorly across multiple cognitive domains especially in tests of both verbal and spatial memory.

When compared to age, gender and IQ-matched normative data, performance on the CVLT-II was well below what was expected. Indeed, as a group these women scored below the 20th percentile on many variables suggesting significant verbal memory deficits. When these variables were compared either to the hormones or to the mood domains also measured in this study, however, no consistent pattern emerged. In fact during pregnancy, the most consistent relationship was between increased depression and better performance on a number of the CVLT-II trials.

Spatial memory as measured by the Rey CFT was similarly impaired for many of the participants as was evidenced by not only quantitative means, but also by qualitative review. Indeed, qualitative review illustrated striking impairment in organizational ability in both the copy and recall portions of the task. Scores of the CFT were similarly low when compared to other psychiatric populations (Ashton, Donders and Hoffman, 2005; Fennig, et al. 2002; Gooding and Braun, 2004; Zappala and Trexler, 1992) including those with moderate brain injury (Bigler, et al. 1989).

Although performance on this task fell well below population mean, hormones and mood were relatively independent of performance. Except for the small but significant negative relationship between CFT recall scores and psychoticism during pregnancy and between recall and postpartum DHEAS levels, no other hormones or mood factors were associated with CFT performance. Given the level of impairment exhibited in each of these tasks, it is possible that small sample size contributed to the

lack of association. It is also possible that hormones play an indirect and more subtle role in perinatal cognitive impairment than is currently able to be tested.

The level of impairment in both the CVLT-II and the CFT was characterized by a striking lack of organizational ability. This was particularly evident in the CFT where both copy and recall performance was impaired. Researchers speculate that there are at least two types of memory disorder: the amnesic type, marked by recall as well as recognition impairment, and the executive dysfunction type, marked by recall impairment only (Egeland et al. 2005; Penades, et al. 2005). Given that recognition was not an issue for these participants and recall scores were well below normal in the CVLT-II, as were in the CFT copy and recall tasks, it is conceivable that perinatal memory deficits resulted more from executive dysfunction than amnesic factors. This would suggest more frontal rather than temporal impairment, although it is impossible to rule-out either completely. If indeed perinatal cognitive is marred by executive dysfunction, concomitant mood changes would be characterized by either extreme mood lability and/or lack of motivation depending upon the region of frontal cortex most impaired (Lezak, 1995). Since mood lability is not measured by the SCL-90 (but is a common characteristic of perinatal mood), and lack of motivation is only measured as one factor within depression domain, the apparent lack of association between mood and cognition is understandable, except that depression was positively correlated with CVLT-II recall. Here again, these correlations may be artifactual and at the very least paradoxical for which no explanation is available. Despite the lack of interpretable correlation between memory and mood, results from this study demonstrate that perinatal mood and memory are impaired.

Other cognitive tests showed similar decrements in performance when compared to normative data, but no consistent relationship with any hormone or mood factor was revealed. Together these data suggest that 1) perinatal cognitive deficits do exist but from where they arise it is not clear, 2) cognitive deficits are relatively independent of hormones and mood and 3) cognitive performance is not necessarily and not uniformly impaired by negative mood.

Conclusion

The primary goal of this research was to elucidate the pattern of cognitive and affective behaviors associated with the elevated hormones of pregnancy and the diminished hormones following parturition and to that end, this study was very successful. Data from this investigation yielded the most complete picture of perinatal mood and cognition to date. Although statistical interpretation is marred somewhat by the large number of variables and the small sample size, without the comprehensive battery of tests many of the relationships described herein would not have been found. Accordingly, this study identified putative biological markers for perinatal mood dysfunction and in doing so challenged currently held hypotheses regarding the hormones and mood. Additional research is needed to fully articulate the role of adrenal androgens in perinatal mood.

EXHIBITS

Tables

Table 1: Progesterone Metabolites

Progesterone Metabolites	
Symbol	Steroid
P1	5 β -Pregnan-3 α ,20 α -diol
P3	5 β -Pregnan-3,20-dione (5 α -DHP)
P4*	5 α -Pregnan-3 α -ol-20-one
P6*	5 β -Pregnan-3 α -ol-20-one
P16	5 β -Pregnan-3 α -ol-11,20-dione
P17	5 β -Pregnan-3 α ,20 β -diol
(Arafat, et al. 1988)	

Table 2: Common Postpartum Mood Symptoms.

Baby Blues	Postpartum Depression	Postpartum Psychosis
Weeping	Weeping	Confusion/Disorientation
Irritability	Irritability/Anger	Agitation (motor and psychic)
Sleeplessness	Anxiety/Panic	Panic
Mood lability	Guilt/Alienation	Delusions
	Despondency	Mania
	Extreme mood lability	Severe mood lability
	Low sex drive/marital discord	Suicidal ideation
	Forgetfulness	Murderous thoughts
	Fatigue	

Table 3: Hormone Values during Pregnancy and Postpartum

<i>Hormone Values during Pregnancy and Postpartum</i>							
	pH	Progesterone pg/ml	DHEAS pg/ml	Estrone pg/ml	Estradiol pg/ml	Estriol pg/ml	Testosterone pg/ml
Pregnancy							
Mean	6.09	1112.43	1081.75	37.57	17.50	501.96	37.48
Median	6.10	1184.80	884.10	34.80	15.90	408.50	27.95
SD	0.35	555.61	135.5	13.60	9.11	241.20	29.86
Range	1.70	2050.70	5638.50	70.80	33.10	804.30	91.70
Minimum	5.20	221.60	1089.16	1.70	6.50	199.60	2.60
Maximum	6.90	2272.30	5774.00	72.50	39.60	1003.90	94.30
n	31	31	31	31	31	31	30*
Postpartum							
Mean	6.21	80.89	1462.40	3.07	6.08	11.84	19.17
Median	6.25	79.50	1104.35	2.65	3.20	11.20	15.55
SD	0.35	36.65	1062.17	2.19	6.52	4.96	18.04
Range	1.40	155.80	4160.80	11.50	27.70	17.90	77.90
Minimum	5.50	20.30	449.10	1.20	0.60	4.50	0.20
Maximum	6.90	176.10	4609.90	12.70	28.30	22.40	78.10
n	28	28	28	28	28	28	28

*One participant had undetectable testosterone levels.

All data collected at 37 weeks of pregnancy and within the first 10 days postpartum

Table 4: Hormone Reference Ranges

<i>Unpublished Salivary Hormone Reference Ranges for Non-Pregnant Women</i>						
	Reference Range		Pregnancy Observed		Postpartum Observed	
	pg/ml		pg/ml		pg/ml	
	Follicular	Luteal	Mean	Range	Mean	Range
Progesterone	10-250	100-600	1112.43	221.6-2272.3	80.9	20.3-176.1
DHEAS	200-2500	200-2500	1089.16	135.5-5774.00	1462.4	449.1-4609.9
Estrone	.5-4.5	.5-4.5	37.57	1.7-72.5	3.07	1.2-12.7
Estradiol	1-25	.5-25	17.5	6.5-39.6	6.08	.6-28.3
Estriol	.5-16	.5-16	501.96	199.6-1003.9	11.84	4.5-22.4
Testosterone	3-49	3-49	37.48	>.1-94.30	19.17	.2-78.1

Table 5: Hormone Change Scores

<i>Change in Salivary Hormone Levels from Pregnancy to Postpartum</i>						
	Progesterone pg/ml	DHEAS pg/ml	Estrone pg/ml	Estradiol pg/ml	Estriol pg/ ml	Testosterone pg/ml
Mean	-1095.59	402.03	-35.71	-9.96	-452.84	-18.93
Median	-1172.60	375.30	-33.60	-9.20	-361.10	-20.05
SD	556.84	957.68	13.28	10.16	218.9	34.75
Range	1998.90	5148.90	71.40	54.90	804.60	155.90
Minimum	-2195.00	-1237.80	-71.30	-19.30	-982.50	-80.40
Maximum	-196.10	3811.10	0.10	35.60	-177.90	75.50
Mean % Change	-93%	34%	-91%	-65%	-98%	-49%
n	27	27	27	27	27	26
By Participant Changes						
No. whose hormones increase	0	21	1	3	0	5
No. whose hormones decrease	27	6	26	24	27	21

Table 6: SCL-90R Scores

<i>Mean T-scores during Pregnancy and Postpartum for the SCL-90R</i>								
	Mean	SD	Min	Max	Mean	SD	Min	Max
	Pregnancy				Postpartum			
Anxiety	53.53	10.40	37.00	79.00	53.82	11.63	37.00	80.00
Hostility	56.25	6.89	42.00	74.00	52.89	7.52	42.00	64.00
Phobia	53.53	8.12	48.00	76.00	56.50	8.77	48.00	76.00
Paranoia	48.94	6.67	43.00	62.00	47.75	6.08	43.00	66.00
Psychoticism	52.13	6.98	47.00	71.00	54.64	8.19	47.00	71.00
Somatization	60.06	8.55	41.00	80.00	55.39	10.44	35.00	80.00
Obsessions & Compulsions	61.23	8.99	44.00	80.00	58.00	9.95	37.00	80.00
Interpersonal Sensitivity	55.13	7.18	39.00	69.00	52.54	8.77	39.00	67.00
Depression	60.44	5.86	51.00	71.00	59.43	8.91	38.00	74.00
Global Severity	58.78	7.23	46.00	76.00	56.32	9.64	33.00	76.00
	n= 32				n=28			

Table 7: SCL-90R by Direction of Change-Totals

Mood Changes from Pregnancy to Postpartum

	ANX	HOS	PHOB	PAR	PSY	SOM	OC	IS	DEP
Number Improved	9	14	3	11	6	20	17	19	14
Number Stable	7	5	17	12	13	2	2	3	2
Number Worsened	12	9	8	5	9	6	9	6	12

Table 8: SCL-90R by Direction of Change by Mood

<i>SCL-90R Scores by Direction of Change</i>										
	Improved				Stable		Worsened			
	Pregnancy		Postpartum		Both		Pregnancy		Postpartum	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Anxiety	58.11	10.34	47.77	9.09	47.14	9.26	54.42	10.28	62.25	8.83
Hostility	59.73	7.09	49.80	7.67	51.67	4.32	54.29	6.70	60.57	2.70
Phobia	66.67	3.51	63.67	5.13	52.47	8.54	52.13	5.77	62.37	4.69
Paranoia	54.64	4.80	47.82	4.47	44.92	3.70	48.00	8.27	54.40	6.95
Psychoticism	61.50	6.47	55.67	7.06	48.69	4.13	52.44	6.46	62.56	6.42
Somatization	61.05	7.45	53.00	7.95	53.00	16.97	56.50	10.63	64.17	13.17
Obsessions & Compulsions	62.76	8.80	55.71	9.95	53.50	4.95	58.22	9.95	63.33	9.21
Interpersonal Sensitivity	57.53	56.26	51.21	8.20	48.75	9.60	54.33	8.38	60.83	5.95
Depression	61.21	6.74	54.79	9.09	59.50	21.20	59.83	6.35	64.83	6.19
Global Severity	59.33	7.65	53.50	9.36	53.50	3.54	58.50	8.21	63.38	8.03

Table 9: Mean CVLT-II Scores

Mean CVLT-II Scores during Pregnancy & Postpartum Compared to Non IQ-Matched Normative Scores

	Pregnancy		z- score		Postpartum		z-score		Difference T1-T2	
	Mean	SD	Mean	Centile	Mean	SD	Mean	Centile	t _{obs}	Sig.
Immediate Recall Trial 1	7.29	1.63	-0.18	42.86	6.79	1.91	-1.05	30.85	1.86	0.074
Immediate Recall Trial 5	12.84	1.88	-0.45	32.64	12.93	1.59	-0.39	34.83	-0.15	0.88
Immediate Recall Total	53.48	7.64		57.00	53.96	6.56	-1.39	57.00	-0.41	0.96
Immediate Recall B	6.06	2.04	-2.04	31.72	5.61	1.66	-2.49	0.64	0.94	0.36
Short Delay Free	11.35	2.28	-1.46	39.72	11.61	2.47	-1.24	24.20	-0.07	0.94
Short Delay Cued	12.51	2.40	-0.16	43.64	12.53	2.28	-0.30	38.21	0.2	0.841
Long Delay Free	12.58	2.24	-1.02	47.00	11.96	2.44	-1.53	38.21	1.55	0.13
Long Delay Cued	13.23	2.20	-0.08	46.81	12.60	2.53	-0.43	25.46	1.54	0.14
Semantic Clustering IR	1.51	2.12	0.21	58.32	2.59	2.34	0.18	57.14	-1.78	0.09
Semantic Clustering LD	3.94	2.94	0.03	51.20	4.56	2.66	-0.05	48.01	-0.631	0.53
Total Intrusions ^a	2.13	3.45	-0.15	56.36	2.68	4.22	-0.03	59.10	-0.66	0.52
Repetitions ^a	7.65	4.41	0.46	66.64	4.46	3.71	-0.38	41.68	2.89	0.007
Learning Curve	1.35	0.55	-0.27	39.36	1.48	0.62	-0.05	46.01	-1.13	0.27

^a Positive intrusion and repetition scores indicate poorer performance. IR, immediate recall; LD, long delay.

Table 10: CVLT-II Scores compared to IQ-Matched Norms

*Mean CVLT-II Scores during Pregnancy & Postpartum
Compared to IQ-Matched Normative Scores*

	Pregnancy		z- score		Postpartum		z-score	
	Mean	SD	Mean	Centile	Mean	SD	Mean	Centile
Immediate Recall Trial 1	7.29	1.63	-0.18	21.48	6.79	1.91	-1.05	14.69
Immediate Recall Total	53.48	7.64	-1.47	7.08	53.96	6.56	-1.39	8.23
Immediate Recall B	6.06	2.04	-2.04	2.07	5.61	1.66	-2.49	0.64
Short Delay Free	11.35	2.28	-1.46	7.21	11.61	2.47	-1.24	10.75
Long Delay Free Semantic Clustering	12.58	2.24	-1.02	15.39	11.96	2.44	-1.53	6.30
Long Delay	3.94	2.94	0.03	51.20	4.56	2.66	-0.05	48.01
Total Intrusions	2.13	3.45	-0.15	44.04	2.68	4.22	-0.03	48.80

Table 11: Cognition and Mood

<i>Correlations between Cognition & Mood</i>											
	Pregnancy							Postpartum			
	ANX	PHOB	PAR	PSY	SOM	IS	DEP	PAR	PSY	IS	DEP
<i>Verbal Memory</i>											
Immediate											
Recall Total	-	-	-	-	-	-	*.359	-	-	-	-
Immediate											
Recall B	-	-	-	-	-	-		*.389	*.432	-	-
Short Delay	*.415	-	-	*.418	-	-	*.434	-	-	-	-
Learning Curve	-	-	*-.361		-	-	-	-	-	-	-
Semantic											
Clustering	-	-	-	-	-	-	*.420	-	-	-	-
<i>Attention & Processing</i>											
PASAT 2	-	*-.365	-	-	*-.362	-	-	-	-	-	-
<i>Spatial Memory</i>											
Copy	-	-	-	*-.368	-	-	-	-	-	-	-
<i>Motor Processing</i>											
Purdue Both	-	-	-	-	-	-	-	*.390	-	-	-
<i>Frontal Cortex</i>											
Design Fixed	-	*.405	** .477	-	-	*.434	*.435	-	*.399	*.444	*.505
*p<.05											
**p<.01											
***p<.001											

FIGURES

Figure 1

Steroid Biosynthesis

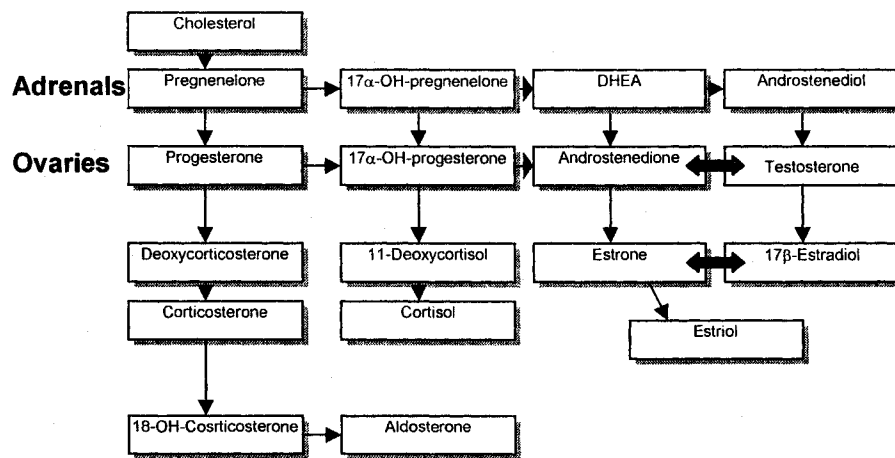


Figure 2

Rey Complex Figure-Original

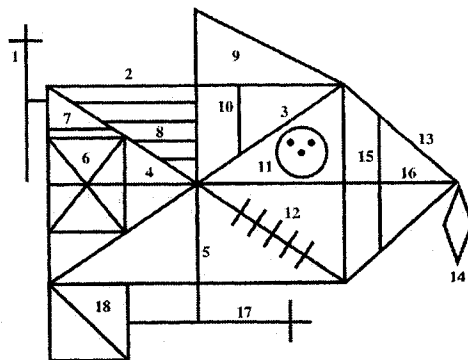
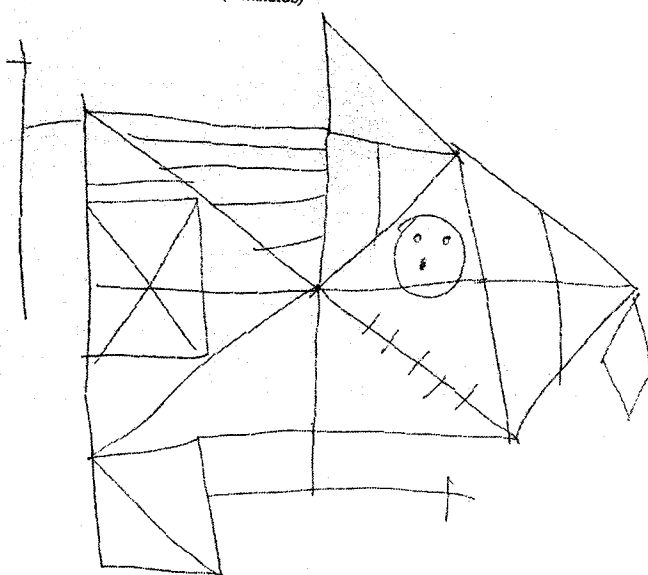


Figure 3

Participant A-Copy

Participant A is a high school math teacher, with 18 years of education⁹.



⁹ All figures reduced to 50% of original size.

Figure 4

Participant A-Recall

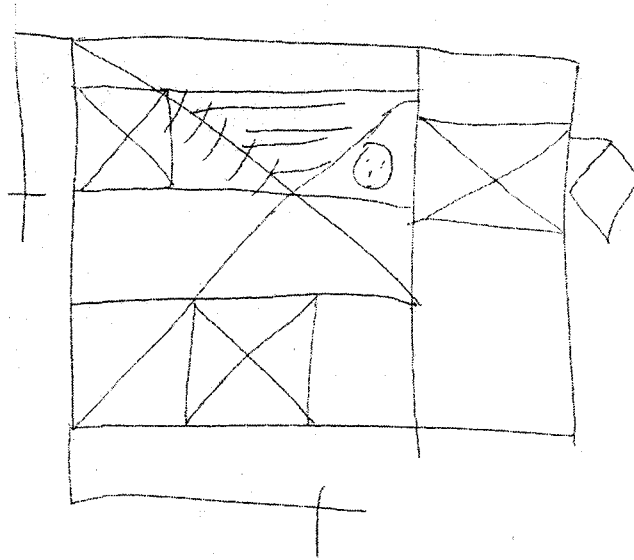


Figure 5

Participant B-Copy

Participant B is a lawyer with 19 years of education.

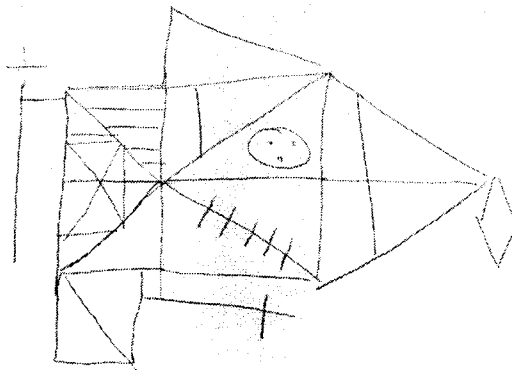


Figure 6

Participant B- Recall

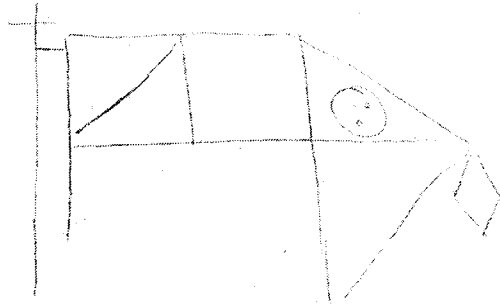


Figure 7

Participant C-Copy

Participant C was a clerical administrator with 14 years of education.

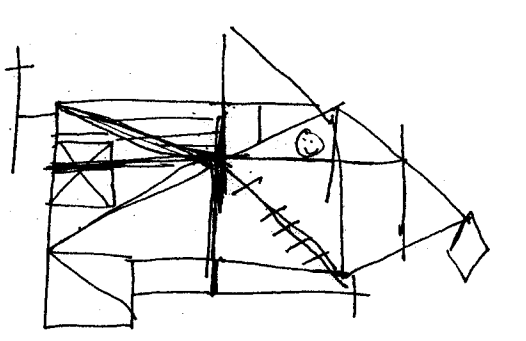
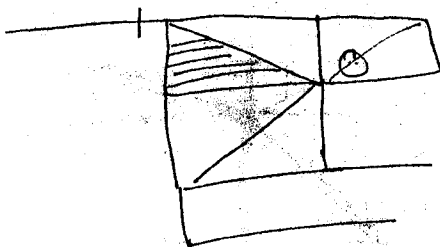


Figure 8

Participant C- Recall



APPENDIX A


OFFICE FOR THE PROTECTION OF HUMAN PARTICIPANTS APPROVAL



Social/Behavioral IRB - Full Board Review Approval Notice

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.

Office for the Protection of Research Subjects (OPRS)
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Website: <http://www.unlv.edu/Research/OPRS/>
Directions: Campus Map #63



**Social/Behavioral IRB – Full Board Review
Continuing Review Approved**

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

MAY 12 2005

MAY 12 2006

Continuing review of the protocol named above has been reviewed and approved.

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 OPRSHumanSubjects@ccmail.nevada.edu or call 895-2794.

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APPENDIX B

INFORMED CONSENT

UNIVERSITY OF NEVADA, LAS VEGAS
DEPARTMENT OF PSYCHOLOGY
INFORMED CONSENT FORM

1. **Introduction:** You are being asked to participate in a study being conducted by Chandler Marrs, MS, from the Psychology Department at the University of Nevada, Las Vegas. The study will look at the role of pregnancy hormones on cognition and mood.

Procedure: If you agree to participate in this study, you will be given a variety of tests that measure mood and cognitive abilities in learning, memory, attention and motor coordination. You will also be give hormone tests, which will require you to spit into a test vial. The saliva will then be analyzed to determine the levels of several hormones (progesterone, estrone, estradiol, estriol, testosterone, and DHEAS). Tests will be given first at 37 weeks of your pregnancy and then sometime within the first 10 days postpartum.

All of the mood and cognitive test are paper-and-pencil tests. Most are quite easy while others may seem more difficult. Some have time limits while others do not. Tests of learning and memory will ask you to learn and remember words or designs. Tests of attention will require you to add numbers in a sequence. Tests of planning will require you to copy complex figures. Each testing session will take approximately 1.5 hours to complete. You will be provided with rest breaks as needed. You will not receive individual feedback after the testing, but you will be given information on how to contact the researchers when the project is completed to receive the general results of the project.

2. **Benefits of Participation:** By participating in this study you will be adding to the understanding of the cognitive and mood changes associated with pregnancy and postpartum. This could lead to identifying early markers and treatment for postpartum mental illness.
3. **Risks of Participation:** There are minimal risks to you from participating in this study, apart from possible fatigue and/or boredom. You may experience some test anxiety, but the tests will not be administered in a stressful manner. You are encouraged to inform me of any discomfort or anxiety that may occur as a result of the testing procedures. I will try to answer any questions you have regarding the tests without invalidating the procedures.
4. **Cost /Compensation** There will be no financial cost to you to participate in this study. The study will take 1½ hours of your time. There is no compensation available for participation. The University of Nevada, Las Vegas may not provide

compensation or free medical care for an unanticipated injury sustained as a result of participating in this research study.

5. **Contact Information:** If you have any further questions about the study or if you experience any harmful effects as a result of participation in this study, you may contact me at 895-0547 or at mom.lab@ccmail.nevada.edu.

For questions regarding the rights of research subjects, any complaints or comments regarding the manner in which the study is being conducted you may contact **the UNLV Office for the Protection of Research Subjects at 895-2794.**

6. **Voluntary Participation:** Your participation in this study is strictly voluntary. You may refuse to participate in this study or any part of this study. You may withdraw at any time without prejudice to your relations with the university or any consequences. You are encouraged to ask questions about this study at any time during the study.
7. **Confidentiality:** All material gathered in this study will be kept private and confidential. No reference will be made in written or oral materials that could link you personally to this study at any time. All hormone samples will be coded using your first and last initial and month and year of birth. No identifying information will be given to the lab that is processing the samples. All paper records will be stored in a locked facility at UNLV for at least 3 years after completion of this study. After 3 years all records will be destroyed. All specimen samples will be disposed of completion of the analysis.

Participant Consent:

I have read or have had read to me all of the above information. I agree to participate in the study. I am at least 18 years of age. A copy of this form has been given to me.

Signature of participant

Date

Participant Name

Witness

APPENDIX C

ENROLLMENT QUESTIONNAIRE

UNLV
University of Nevada, Las Vegas
Maternal Health Lab
Intake Form

Study: Cognitive and Affective Correlates of Reproductive Hormones

Date:

Participant ID#:

(first & last initial & mo/yr of birth)

*Participant Information/ Barona Index**

Name

DOB

*Age

*Education

*Occupation

*Race

*White/Black/Other

*Pregnancy History/Exclusionary Criteria**

Delivery Due Date

Boy/Girl

*Twins Y/N

*Fertility treatment Y/N *Other children Y/N

*Head trauma Y/N

*Current alcohol or drug use Y/N

*Current medical condition requiring medical attention and/or medication Y/N

APPENDIX D

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.
4. Clean vial with paper towel
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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