Understanding Maternal Cognitive Changes: Associations between Hormones and Memory

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Maternal cognitive changes are anecdotally described but have eluded empirical validation. The impact of maternal hormones on cognition is not clear. We prospectively investigated pregnancy and postpartum cognitive and hormone changes in healthy, primigravid women (n = 28). A focused battery of neuropsychological instruments was administered and compared to salivary concentrations of progesterone, DHEAS, testosterone, estrone, estradiol, and estriol collected concurrently. Subtle deficits in late pregnancy attention and verbal and spatial memory, associated with elevated estrogens, were observed. Following parturition, all areas of cognitive performance improved except verbal memory. Postpartum improvements were associated with less dramatic changes in pregnancy to postpartum estrogens and androgens. Maternal cognitive deficits exist and may be associated with hormones.

Background

Pregnancy related cognitive changes have been described anecdotally but have thus far eluded conclusive empirical validation (Brett & Baxendale, 2001). As many as 80% of pregnant/postpartum women report memory problems compared to 10-16% of non-pregnant women (Brindle, Brown, M., Brown, J., Griffith, & Turner, 1991; Jarrahi-Zadeh, Kane, Van De Castle, Lachenbruch, & Ewing, 1969; Parson & Redman, 1991; Poser, Kassirer, & Peyser, 1986; Sharp, Brindle, Brown, & Turner, 1993). Nevertheless, attempts to measure pregnancy or postpartum related cognitive deficits objectively show mixed results. Some investigators have found cognitive deficits in pregnant or postpartum women (Buckwalter et al., 1999; De Groot, Adam, & Hornstra, 2003; Brindle et al., 1991; Janes, Casey, Huntsdale, & Angus, 1999; Jarrahi-Zadeh et al., 1969; Keenen, Yaldo, Stress, Fuerst, & Ginsburg, 1998; Sharp et al), while others have not (Casey, Hunstdale, Angus, & Janes, 1999; Crawley, Dennison, & Carter, 2003; Morris, Toms, Easthope, & Biddulph, 1998; Swain, O'Hara, Starr, & Gorman, 1997; Vanston, 2005).

Despite the lack of consistent empirical evidence, perinatal women complain of difficulties with, and appear to test more poorly on, tasks associated with working memory (Henry & Rendell, 2007). Working memory, the ability to attend to, organize, and manipulate relevant information represents a fundamental step in learning (Lezak, 1995). Deficits in working memory result in diminished short-term memory span (Lezak), which has been observed in perinatal women (Rendell & Henry, 2008). Working memory deficits also contribute to mild impairment in general cognitive ability (Janowsky, Chavez, & Orwoll, 2000), which might not reach the level of clinical or experimental significance but are likely perceptible to the individual.

Cognitive tasks such as learning and memory are highly dependent upon adequate functioning of the hippocampi and the pre-frontal cortex (Amat et al., 2008; Andreasen et al., 1993; Akirav & Maroun, 2006; Lee & Kesner, 2003; Ranganath, Cohen, Dam, & D'Esposito, 2004). These regions of the brain are particularly sensitive to fluctuating concentrations of reproductive hormones (McEwen & Alves, 1999; Morrison, Brinton, Schmidt, & Gore, 2006; Sinopoli, Floresco, & Galea, 2006; Smith et al., 2006; Valle et al., 1997). Across pregnancy and parturition, progesterone, the estrogens (estrone, estradiol, and estriol) and androgens (dehydroepiandrosterone sulfate and testosterone) fluctuate dramatically (Carr, 2001). Maternal estrogens (estrone, estradiol, and estriol), for example, increase by 1000-fold (Carr) whereas progesterone increases by 200-fold (Darne, McGarrigle, & Lachelin, 1987). The estrogens and progesterone plummet to pre-pregnancy levels immediately following parturition (Carr).

Estradiol, progesterone, and the androgens are neuroactive (Berman et al., 1997; Baulieu, 1998; Farr, Banks, & Morley, 2000; McEwen & Alves, 1999; Gulinello & Smith, 2003). When administered individually, each is linked to dose- and region-dependent changes in rodent learning and memory (McEwen & Alves; Eddinger & Frye, 2007). In human research, generally assessing elderly populations,

estradiol and dehydroepiandrosterone sulfate (DHEAS) tend to improve memory (Davis et al., 2008; Gleason, Carlsoson, Johnson, Atwood, & Asthana, 2005; Morrison et al., 2006; Valle, Mayo, & Le Moal, 2001), although by different mechanisms whereas progesterone impairs memory (Arafat et al., 1988; Birzniece et al., 2006). The findings for testosterone are mixed (Cherrier et al., 2001; Eddinger & Frye, 2007; Gray et al., 2005; Janowksy, Chaves, & Orwoll, 2000; Su et al., 1993) and estrone and estriol have not been investigated. Similar research regarding the relationship of maternal hormones and cognitive changes is severely lacking, with few published studies examining both variables (Buckwalter et al., 1999; Jarrahi-Zadeh et al., 1969; Keenen et al., 1998; Swain, O'Hara, Starr, & Gorman, 1997; Vanston, 2005).

Given the large changes in neuroactive hormones across pregnancy and parturition, it is likely that perinatal women experience some changes in cognitive ability. The purpose of this study was to assess maternal cognitive ability and to determine whether and in what manner perinatal hormone changes influenced cognitive performance. Six hormones (DHEAS, progesterone, testosterone, estrone, estradiol, and estriol) were selected for the present study because of their role in human pregnancy (progesterone, DHEAS, estrone, estradiol, and estriol; Carr, 2001) and/or evidence of influence on learning and memory (progesterone, DHEAS, testosterone, and estradiol) (Arafat et al., 1988; Birzniece et al., 2006; Buckwalter et al., 1999; Janowsky, Chavez, & Orwoll, 2000; Jarrahi-Zadeh et al., 1969; Valle, Mayo, & Le Moal, 2001). Based upon data from animal research (McEwen & Alves, 1999; Sinopoli, Floresco, & Galea, 2006), we propose that tasks associated with prefrontal and hippocampal functioning, such as attention, working memory, and executive function would be impacted by maternal hormones. In light of the data showing that both excessively high and low hormones contribute to learning impairment (Newton, Slota, Yuzpe, & Tummon, 1996; Sinopoli, Floresco, & Galea; Valle, Mayo, & LeMoal; Zurkovsky, Brown, Boyd, Fell, & Korol , 2007), we suggest that perinatal women may experience cognitive difficulties both during periods of excessively high hormones (late pregnancy) and during periods of excessively low hormones (early postpartum).

Methods

Enrollment

This study was approved by the University of Nevada, Las Vegas, Institutional Review Board. All women voluntarily provided written, informed consent prior to enrollment. Healthy, primigravid women were recruited from local childbirth education classes and enrolled in our study at 35-36 weeks of pregnancy. Exclusionary criteria included a history or evidence of psychiatric, neurological, or endocrine disease; history or evidence of alcohol or elicit drug use or abuse; and medication use. Upon enrollment, demographic information was collected, the Barona Index was calculated, and the North American Adult Reading Test (NAART) was administered. Intelligence scores were estimated using both the Barona Index and the NAART (Spreen & Strauss, 1998).

Testing

In order to capture the states of excessively high and low hormone concentrations and to detect the greatest change in hormonal state, testing occurred at approximately 37 weeks of pregnancy (T1) and within the first 10 days postpartum (T2). Since both excessively high and low hormone concentrations may impact cognitive performance, capturing statistically significant differences in cognitive performance between the two testing time points, and distinguishing between those deficits associated with high hormones versus those associated with low hormones, was expected to be difficult. Nevertheless, it was deemed important to test at these times in order to provide data regarding patterns of deficits associated with each hormonal state.

Steroid Hormone Procedures and Analysis

Procedures and Analyses: Non-stimulated, preprandial saliva specimens were collected via expectoration the morning of each testing session. For the postpartum testing session, participants were further instructed to avoid breastfeeding within 2 hours of the collection interval to prevent feeding-stimulated hormone release that might confound results. Specimens were shipped by 2-day courier to the analytical facility (AllVia Diagnostic Laboratory, Phoenix, AZ) where they were stored at -20 C° for <24 hours, then thawed and analyzed for progesterone, DHEAS, estrone, estradiol, and estriol concentrations by enzyme-linked immunosorbent assays. Testosterone was measured using luminescence immunoassay. The lower and upper bounds of quantification were as follows: Progesterone 10-3000 pg/mL; DHEAS 100-12,000 pg/mL; testosterone .3-760pg/mL; estrone .3 pg/mL-60 pg/mL; estradiol .1-100 pg/mL; estriol 1-4000 pg/mL. Intra- and inter-day coefficients of variation for each analyte did not exceed 10%, except for inter-day estrone (16.25%).

Cognitive Testing Instruments and Procedures

The battery of tests and order of test administration was as follows: the Symptom Checklist 90-Revised (SCL-90-R), the California Verbal Learning Test-II (CVLT-II) part one, Paced Auditory Serial Attention Test (PASAT), the CVLT-II-part two, the Rey Complex Figure Test (CFT) - copy, the Finger Tapping Test (FTT), the Purdue Pegboard, the Verbal Fluency Test, CFT-recall, and the Design Fluency Test. To compensate for practice effects at T2, alternate test forms were administered for the CVLT-II, and the Rey CFT. Breaks were given as requested and when needed to allow for down-time between tests. Testing took approximately 1 hour and 30 minutes.

The SCL-90-R is a 90-item self-report inventory that measures nine clusters of psychiatric symptoms. Results for the SCL-90-R are reported elsewhere (see Marrs, Ferraro, Cross, & Rogers, 2009). Briefly, pregnancy and postpartum psychiatric symptoms were present in approximately 40-50% of the women, respectively, and were associated with hormone concentrations. For the present study, the SCL-90-R global severity index (GSI) was used as a marker of psychiatric distress.

The CVLT-II (Delis et al., 2000) measures immediate recall (trials 1-5), recall after a distracter list (Recall B) and with a break, short and long-term recall, both free and cued. These recall measures are arguably linked to left hippocampal functioning. Cognitive tasks associated with frontal functioning included 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 do not belong to the original list, a marker of disinhibition) (Delis, Kramer, Kaplan, & Ober, 2000). Comparing distracter list scores (Recall B) to trial 1 scores yields a measure of proactive interference, the ability to filter previously learned information from new information (Egeland et al., 2005).

The PASAT assesses cognitive aspects of verbal working memory (Jenkins et al., 1998; Schweitzer, Hanford, & Medoff, 2006; Sweet, Rao, Primeau, Mayer, & Cohen , 2004) and information processing including sustained attention and vigilance along with the ability to hold, retain, and manipulate information (Lezak, 1995; Spreen & Strauss, 1998). The PASAT consists of a taped presentation of randomly presented numbers. In each trial, the participant adds 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 difficult presentation rates (2.4, 2.0, 1.6, and 1.2 numbers per second by trial). Successful manipulation of verbal information within the short-term memory buffer is measured. Neuroimaging studies document that the greatest PASAT-associated activation is in the left frontal hemisphere (Awh et al., 1996; Braver et al., 1997; Sweet at al.).

The Rey CFT measures components of visual memory including visuo-spatial constructional ability (copy task; Meyers & Meyers, 1995; Shin at al., 2006) and amount of information retained over time (recall); tasks linked to right hippocampal functioning. In addition, the complexity of the figure necessitates active frontal involvement allowing for the qualitative assessment of neurocognitive processes such as attention, planning, and organization (Choi et al., 2004; Gooding & Braun, 2004; Lezak, 1995; Shin et al.; Spreen & Strauss, 1998; Zappala & Trexler, 1992). During administration, participants copy a complex figure and after a delay and without prior warning, reproduce it again from memory. The total CFT score is 36, with 18 aspects of the drawing rated 0-2 points according to accuracy and placement.

To assess lateralized frontal and hippocampal functioning further, the verbal and design fluency tests were administered. The phonetic portion of the verbal fluency test requires participants to generate words beginning with different letters (F, A, S) within 60 seconds. It is followed by a semantic category task in which participants generate names of animals, within 60 seconds. The generative nature of these tests and the ability to retrieve words from long-term storage and appropriately categorize responses, while systematically filtering irrelevant information, requires long-term memory and left hippocampal involvement as well as executive and frontal cortex functioning (Abwander, Swan, Bowerman, & Connolly, 2001; Raskin & Rearick, 1996)

Similarly, two conditions of the visual design fluency task, free and fixed, measure aspects of right frontal and hippocampal functioning (Spreen & Strauss, 1998). In the free condition, participants draw as many novel figures as possible within 5 minutes. In the fixed condition, individuals must draw multiple novel figures containing only four lines, within 4 minutes.

The Purdue Pegboard assesses fine motor dexterity and motor processing speed as well as right-left dominance (Spreen & Strauss, 1998). Participants 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 30 seconds and is scored by the number of pegs placed during each time period.

The finger tapping test measures fine motor speed and right-left dominance. Participants 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 & Strauss, 1998).

Data Analysis

Percentile rank and normative data comparisons for the cognitive measures were calculated using age and gender-matched normative data provided by the test designers (CVLT-II, PASAT, Purdue Pegboard, FTT) or where available, age, gender and education-matched data (CFT, Verbal and Design Fluency Tests; Spreen & Strauss, 1998). Qualitative tests (CFT and Design Fluency) were scored independently by two individuals with disputes resolved by a third party following published guidelines (Meyers & Meyers, 1995; Spreen & Strauss).

Paired *t*-tests were performed to calculate the differences between T1 and T2 scores. Bivariate Pearson product-moment correlations were calculated to assess the potential associations between steroid hormone concentrations and cognitive measures. The large number of correlations calculated, along with the relatively small sample size in this study, precluded the use of Bonferonni adjustments to the *p*-values reported for the tests. Thus, the correlations presented in this study need to be qualified as to their definitiveness. The statistical software package SPSS 15.0 (SPSS Inc., Chicago, IL) was used for all data analyses.

Results

Demographics

Demographic data are listed in Table 1. Twenty-eight, predominantly right-handed, Caucasian, highly-educated women completed testing both during pregnancy and following parturition. Participants demonstrated above average intelligence as estimated by both the Barona Index and the NAART.

Table 1. Demographics

Variable	Category	Statistic
Sample Size		28
Sample size by ethnicity	Caucasian	27
	Hispanic	1
Sample size by handedness	Right	26
	Left	2
Mean (SD) for demographic variables	Age	29.79 (4.2)
	Education (total years)	16.07 (4.20)
	NAART	38.61 (5.08)
	EVIQ-Barona*	114.12 (3.6)
	EVIQ-NAART†	119.31 (5.68)
	EPIQ-Barona	110.6 (2.51)
	EPIQ-NAART	113.84 (4.02)
	EFSIQ-Barona	112.7 (4.34)
	EFSIQ-NAART	118.76 (5.48)

* †Calculation procedures outlined in Spreen and Strauss, 1998.

Cognitive Performance and Psychiatric Distress

The SCL-90-R GSI score was not significantly associated with any cognitive measure at either test time.

Left Hippocampal and Frontal Functioning

CVLT-II: Compared to non-education or IQ-matched normative data, participants in this study demonstrated slightly below average verbal learning skills. As is illustrated in Table 2, performance across the CVLT-II ranged from the 45-50th percentile during pregnancy and remained relatively stable following parturition with few significant changes.

Table 2. CVLT- II Performance.

	Pregnancy				Postpartum				Difference	T1-T2
	Mean	SD	CVLT-II*	CVLT**	Mean	SD	CVLT-II	CVLT	t_{obs}	Sig.
Trial 1	7.32	1.66	45	21	6.86	1.92	45	16	1.35	ns
Trial 5	12.75	1.92	45	na	13.04	1.62	45	na	0.63	ns
Trial 1-5	53.43	7.56	48	6	54.43	6.87	49	8	0.576	ns
List B	6.11	2.15	45	3	5.61	1.66	45	1	0.94	ns
Short Delay Free	11.39	2.09	45	2	11.61	2.6	50	3	0.61	ns
Short Delay Cued	12.61	2.5	45	na	12.57	2.25	45	na	1.12	ns
Long Delay Free	12.61	2.13	50	16	12.14	2.48	50	8	0.851	ns
Long Delay Cued	13.29	2.16	50	na	12.75	2.55	50	na	0.978	ns
Semantic Clustering Trials 1-5	1.56	2.1	48	na	2.72	2.32	77	na	0.17	0.023
Semantic Clustering SD	3.03	2.61	52	na	4.13	2.8	55	na	0.07	0.038
Semantic Clustering LD	4	2.85	51	na	4.74	2.73	50	na	0.47	ns
Total Intrusions	2	3.36	50	34	2.68	4.22	61	45	0.66	ns
Repetitions	7.29	4.38	55	63	4.39	3.53	46	34	3.01	0.005
Learning Curve	1.3	0.56	45	na	1.49	0.62	50	na	0.1	ns

n=28

* Percentile score based on age, gender-matched normative references (Delis et al. 2000).

** Percentile score based on age, gender and IQ-matched normative references (Spreen & Straus 1998).

Women in the present study were highly educated and demonstrated an above average estimated full-scale IQ of 114-118 (Barona and NAART, respectively). Published CVLT-II normative data is neither IQ nor education adjusted. Only 20% of the normative sample (n = 1,087) tested by Delis et al. (2000) included persons with 16 or more years of education, and no IQ data are given. With the less educated reference group used in establishing CVLT-II norms, determining accurate performance levels for more highly educated populations is problematic. The level of impairment may be significantly underestimated (Delis et al.; Strauss, Sherman, & Spreen, 2006). The CVLT is stratified for age and IQ. Test authors suggest the raw

scores from the two tests are equivalent (Delis et al.). By way of reference, scores from the present study were compared to CVLT IQ-adjusted normative ranges (Spreen & Strauss, 1998) and to scores published in Buckwalter et al. (1999), the only reference on perinatal CVLT performance. When compared to the gender, age, and IQ-matched normative data for the CVLT (Spreen & Strauss), ranked scores for this group of women ranged from the low single-digits to 20th percentile across recall measures. Raw scores from the present study trended lower than those observed by Buckwalter et al.

Verbal Fluency: As indicated in Table 3, participants performed below average on both the phonetic (FAS) portion and semantic (animal) portions of the verbal fluency test during pregnancy (40th and 34th percentiles, respectively). Postpartum performance improved non-significantly for both tasks (55th and 67th percentiles, respectively), perhaps due to the reduced novelty of the task. Moderate practice effects for both indices were observed.

Table 3. Neurocognitive performance.

	Pregnancy			Postpartum			Difference T1-T2	
	Mean	SD	Percentile	Mean	SD	Percentile	t_{obs}	Sig.
Phonetic	42.61	8.38	40	46.14	11.87	55	1.844	ns
Semantic	19.82	5.22	34	21.43	5.34	45	1.519	ns
CFT Copy	33.95	2.38	55	34.29	1.84	66	0.933	ns
CFT Recall	18.39	8	32	24.25	6.75	66	4.254	.000
Design Free	16.36	5.97	55	20.25	7.52	79	2.72	.037
Design Fixed	16.5	5.27	34	20.86	6.51	63	3.765	.001
PASAT 2.4	40.54	12.7	25	46.21	10.9	45	4.209	.000
PASAT 2.0	37.64	12.75	37	42.29	12.11	50	4.008	.000
PASAT 1.6	32.32	13.56	39	35.89	12.15	50	2.772	.010
PASAT 1.2	21.93	10.43	30	26.39	10.79	45	3.808	.001
FFT (D)	45.63	5.42	61	47.34	5.08	70	2.39	.039
FTT (ND)	47.46	4.99	90	42.8	3.76	66	5.311	.024
Purdue (D)	15.04	1.5	12	15.61	1.77	19	1.951	.000
Purdue (ND)	14.68	1.6	16	14.67	1.59	18	2.197	ns

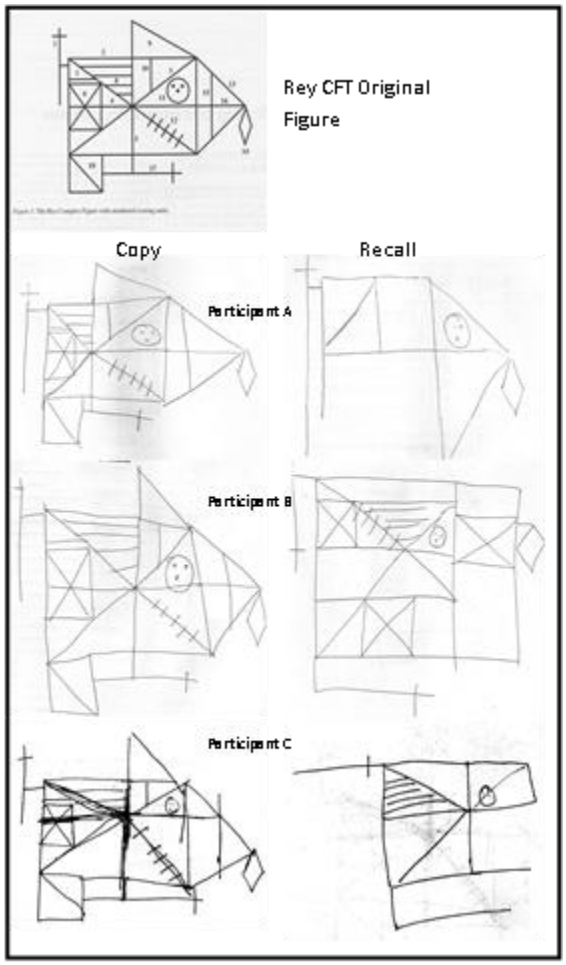
n=28

Right Hippocampal and Frontal Functioning

The Rey CFT: Spatial memory performance was mixed (Table 3). CFT copy scores during pregnancy were average whereas recall scores were below average (55th and 32nd percentiles), respectively. Both copy and recall scores improved from pregnancy to postpartum although only recall scores were significantly improved ($p < .001$).

Qualitative review of both copy and long delay figures suggests a copy strategy characterized by a lack of organization. Figure 1 includes the original figure and copy and recall figure from select participants during pregnancy. Notice that each participant failed to recognize the basic components of the original figure during the initial copy phase. They did not identify the rectangle (2) and forward triangle (13) as the base of the drawing, and instead focused more on the individual details within the rectangle. They also missed the contiguity of the horizontal (4), vertical (5), and diagonal (3) lines that cross at the center of the figure. The failure to recognize the contiguity of the lines is evident in the recall phase where each participant remembered only portions of these lines and entire sections of the figure are missing. Similar problems were noted postpartum.

Figure 1. Rey CFT original figure and representative participant copy and recall figures during pregnancy. All figures have been reduced and are not to scale.



Design Fluency

Design Fluency: In the free condition of the design fluency test, participants performed just above average (55th percentile) but were well below average

in the fixed condition (34th percentile) during pregnancy. There was significant improvement on both tests from pregnancy to postpartum (79th and 63rd percentile, respectively; p = .037, p = .001, respectively).

Attention, Cognitive, and Motor Processing Speed

PASAT: Scores on the PASAT, the Purdue Pegboard and the FTT tests were consistently below average at both test times (Table 2). Percentile rankings during pregnancy ranged from the 25th to 39th percentile by trial. After delivery, rankings improved significantly from the 45th to 56th percentile by trial. Motor processing speed was above average at both test times, but the pattern of change from pregnancy to postpartum was in the opposite direction for the dominant and non-dominant hands. Motor speed improved from pregnancy to postpartum for the dominant hand (p = .024) whereas the non-dominant hand was slower postpartum than in pregnancy (p < .001).

Fine motor dexterity as measured by the Purdue Pegboard was well below normal at both time points. Dominant hand performance ranked in the 12th and 19th percentiles at pregnancy and postpartum respectively, while non-dominant performance was ranked at the 16th and 18th percentiles. Dominant hand performance improved significantly from pregnancy to postpartum (p < .001).

Hormones and Cognition

Mean hormone values at each test time are reported in full in Marrs et al. (2009). Briefly, however, the range of T1 hormone concentrations were as follows: progesterone 221.6-2050.3 pg/mL; DHEAS 1089.16-5774 pg/mL; testosterone 2.6-94.3 pg/mL; estrone 1.7-72.5 pg/mL; estradiol 6.5-39.6 pg/mL; estriol 199.6-1003.9 pg/mL. T1 progesterone, estrone, estradiol and estriol concentrations fell within the published ranges for late pregnancy measured by other investigators (Darne, McGarrigle, & Lachelin 1987; Fisher-Rasmussen, Gabrielson, & Wisborg, 1981; Lewis, Galvin, & Short, 1987; Harris, Lovett, Roberts, Read, & Riad-Fahmy,1993; Harris et al., 1994) although estriol concentrations observed in this study were lower than those observed elsewhere. No late pregnancy salivary hormone ranges have been published for testosterone or DHEAS.

T2 concentrations were as follows: progesterone 20.3-176.1 pg/mL; DHEAS 449.1-4609.9 pg/mL; testosterone .2- 78.1 pg/mL; estrone 1.2-12.7 pg/mL; estradiol .6-28.3 pg/mL; estriol 4.5- 22.4 pg/mL. Currently, there are no published reports of salivary hormones measured at or around 10 days postpartum. Unpublished laboratory reference ranges for salivary hormone values for non-pregnant, menstruating women are as follows: progesterone 10-250 pg/mL (follicular phase), 100-600 pg/mL (luteal phase); DHEAS, 200-2500 pg/mL; testosterone 3-49 pg/mL; estrone .5-4.5 pg/mL; estradiol 1-25 pg/mL (follicular), .5-25 pg/mL (luteal); estriol .5-16 pg/mL.

Associations between test performance and hormone concentrations were consistently negative during pregnancy with the three estrogens most strongly associated with poor performance. Higher estrone concentrations were associated with lower learning curve scores on the CVLT-II (r = -.428, p < .05) and lower total PASAT (r = -.377, p < .05). Estradiol was associated with poor CVLT-II total recall scores (r = -.389, p < .05), whereas estriol was correlated with lower CVLT-II trial 5 and total immediate recall scores (r = -.366, p < .05 and r = -.389, p < .05 respectively) as well as poor PASAT trial 1 scores (r = -.377, p < .05). Higher testosterone concentrations were linked to increased repetitions across CVLT-II trials (r = .362, p < .05). Elevated repetition scores indicate poorer performance.

Following parturition, even though concentrations of estradiol and estriol decreased by 94% and 98% respectively (Marrs et al., 2009), higher estradiol and estriol concentrations were positively associated with aspects of cognitive performance. Estradiol was associated with greater success in resisting proactive interference on recall trial B of the CVLT-II (r = .405, p < .05) whereas estriol was associated with better overall verbal learning (r = .421, p < .05). The directional shift in postpartum hormone to cognition correlations may suggest an inverted U-shaped function where both excessively high and excessively low estrogen concentrations impair performance. Interestingly, higher postpartum estriol and testosterone concentrations were negatively associated with lower left-handed Purdue Pegboard performance (r = -.532, p < .01; r = -.444, p < .05), respectively.

DHEAS concentrations were elevated at T1 (Marrs et al., 2009) and not significantly associated with any of the cognitive indices. Following parturition, DHEAS increased by an average of 34% (Marrs et al.) and was associated with poor spatial recall on the CFT (r = -.379, p < .05).

Progesterone concentrations fell by 93% from pregnancy to postpartum (Marrs et al., 2009). This change in progesterone concentrations was associated with a reduction in the number of repetitions on the CVLT-II (r = -.386, p < .05), but may have hindered generative ability related to performance on both

verbal and design fluency tasks (r = -.501, p < .01 and r = -.402, p < .05 respectively). Similarly, larger increases in DHEAS from pregnancy to postpartum were associated with poorer CVLT-II recall trial 5 (r = -.433, p < .05), total recall (r = -.492, p < .01), semantic clustering (r = -.479, p < .05), but also was associated with reduced repetition scores (r = -.624, p < .01). The change in estradiol values was associated with poor performance on the copy portion of the CFT (r = -.467, p < .05).

Discussion

Research from animal studies consistently indicates relationships between steroid hormones, learning, and memory (Farr, Banks, & Morley, 2000; McEwen & Alves, 1999; Sinopoli, Floresco, & Galea, 2006; Zurkovsky et al., 2007). Neuroactive steroids influence learning and memory via multiple mechanisms but are especially important in tasks regulated by the pre-frontal and hippocampal regions such as working memory, attention, and executive function (Maki & Resnick, 2000; McEwen & Alves). Across human pregnancy and parturition, when maternal hormone concentrations fluctuate significantly, associations between hormones and cognitive performance are not well-established. That cognitive changes occur at all during pregnancy is even less certain and often debated (Crawley, 2002; Swain et al., 1997). The purpose of this study was to determine if cognitive deficits were apparent in late pregnancy or following parturition and if they were associated with maternal hormones. We proposed that tasks associated with prefrontal and hippocampal functioning, such as attention, working memory, and executive functioning would be influenced by maternal hormones and that cognitive difficulties would be pronounced at both test times.

The women in the present study were predominantly highly educated professionals and demonstrated above average pre-morbid (pre-pregnancy) IQs as estimated by the Barona Index and the NAART. Despite these positive characteristics, the women exhibited mild impairment across multiple cognitive domains and performed especially poorly on measures that taxed working memory. Specifically, pregnant women had difficulty sustaining focus (PASAT) and were unable to manipulate and effectively organize incoming information (CFT). This potentially contributed to poor performance on measures of both short- and long-term memory such as the CVLT-II, CFT recall, and the verbal and design fluency tests. Following parturition, scores on spatial memory and attention tasks improved while scores on verbal learning and memory tasks remained low.

These findings are consistent with a recent meta-analysis demonstrating a pattern of perinatal working memory impairment (Henry & Rendell, 2007), most often observed as verbal learning deficits (Eidelman, Hoffman, & Kaitz, 1993; De Groot, Vuurman, Hornstra, & Jolles, 2006; Keenan et al., 1998). Specifically, investigators have noted deficits in attention and planning (Jarrahi-Zadeh et al., 1969; De Groot, Adam, & Hornstra, 2003), prospective memory (De Groot, et al., 2006; Rendell & Henry, 2008) and implicit memory (Brindle et al., 1991). Few studies have examined spatial memory deficits in perinatal populations (Silber, Almkvist, Larsson, & Uvnas-Moberg, 1990) and thus, these results provide preliminary evidence of spatial memory deficits in pregnant women.

Working memory is notably sensitive to hormone fluctuations (McEwen & Alves, 1999; Morrison et al., 2006; Sinopoli, Floresco, & Galea, 2006; Smith et al., 2006). In the present study, poor performance was related to both exceptionally high and low hormone concentrations. With the exception of DHEAS, whose trend was reversed, cognitive difficulties were associated with the higher hormones of pregnancy, the lower hormone concentrations that followed parturition and the large changes in hormone concentration from pregnancy to postpartum.

Specifically, increased estrogen (estrone, estradiol, and estriol) concentrations were associated with reduced verbal memory and diminished attention and processing during pregnancy. After delivery when concentrations of these hormones had fallen significantly, the associations were positive. For DHEAS, no associations were found during pregnancy, but following parturition when the concentration of this hormone increased significantly, associations were observed between DHEAS, the change in DHEAS concentration, and both reduced verbal and spatial memory performance. These data suggest the possibility that both unusually high and low hormone concentrations may be deleterious to cognitive performance.

In addition to the concentration-dependent changes in cognitive performance associated with the estrogens and DHEAS, our findings revealed some hemispheric asymmetries between the types of functions potentially influenced by maternal hormones. During pregnancy when many maternal hormones reached supra-physiological concentrations, mild to moderate impairments across all cognitive domains measured were noted. Following parturition and the dramatic decline in most maternal hormones, only verbal memory deficits remained and once again revealed the involvement of the estrogens. Spatial memory

performance improved following parturition and to the extent that some women still had difficulties, postpartum increases in DHEAS appeared to be involved.

Postpartum improvement in spatial memory suggests that right hemispheric functions may be more sensitive to higher hormone concentrations, compared to verbal memory, which was affected by both very high and low hormone concentrations. Supporting evidence for this hypothesis is equivocal (Hampson, 1990; Kampen & Sherwin, 1994; Leblanc, Janowsky, Chan, & Nelson, 2001; Phillips & Sherwin, 1992; Sinopoli, Floresco, & Galea, 2006; Thal et al., 2009; Zurkovsky et al., 2007) and may depend as much upon the dose and concentration of individual hormones as the type of task utilized to measure visuo-spatial memory (Golby et al., 2001; Sinopoli, Floresco, & Galea; Zurkovsky et al.).

Some researchers postulate that higher hormone concentrations engender more global cognitive influence while lower hormone values tend to increase functional cerebral asymmetries (Bayer & Hausmann, 2009). This hypothesis, if applied to the unique hormonal environment of pregnancy and postpartum, would predict more symmetrical performance between right and left hemisphere regulated tasks during pregnancy when hormone concentrations are elevated than following parturition when maternal hormone concentrations generally plummet (Bayer & Hausmann; Comptom, Costello, & Diepold, 2004; Hausmann & Gunturkun, 2000). The pattern of deficits and hormonal associations observed in this study provides some support for this hypothesis.

Alternatively, practice effects and reduced novelty could be factors in the improved spatial memory performance. Even when using alternate forms of particular scales, research suggests that practice effects account for an approximately 10% improvement in test performance (Spreen & Strauss, 1998). In the case of the CFT, design fluency, and the PASAT, postpartum improvements exceeded 10%, and thus, may reflect actual improvement. Postpartum verbal recall scores did not improve. In fact, several measures of CVLT-II recall performance declined slightly despite significant improvements in semantic clustering ability from pregnancy to postpartum.

These results also demonstrate that estradiol and progesterone are not the only hormones that influence cognition in women, especially during pregnancy and postpartum. For example, progesterone was not associated with performance, while all three estrogens and DHEAS were. Even testosterone was associated with a few cognitive indices. This suggests that investigating a broader array of hormones in connection with maternal and other reproductive phase cognitive changes may be warranted.

The associations with DHEAS and the estrogens are especially interesting considering the altered metabolic pathway for these hormones during pregnancy. The fetal adrenals produce significant amounts of DHEAS from which, estrone, estradiol, and estriol derived. Approximately 50% of maternal circulating concentrations of estrone and estradiol and 90% of estriol are metabolized from fetal DHEAS (Carr, 2001). Estriol, in particular, plays a dominant role in fetal health and development (Carr). To our knowledge, neither estrone nor estriol has been examined in relation to cognitive performance in any population or species. Published data for maternal DHEAS and cognitive function is lacking with most research conducted using animals (Valle, Mayo, & Le Moal, 2001) and non-pregnant, older populations (Davis et al., 2008; Wolf & Kirschbaum, 1999). Data from this study indicate that a larger spectrum of steroid hormones may influence maternal cognitive performance.

This study was not without limitations. The sample was small in number, older, predominantly Caucasian, and well-educated, despite having recruited the women from diverse populations. Moreover, the observed changes in memory and attentional focus may have been affected by other variables not assessed by this study such as pregnancy- and childbirth-related disturbances in sleep or life style.

Comparisons to non-pregnant women presented a number of theoretical difficulties that were deemed beyond the scope of the present study. The hormonal environment of pregnancy and postpartum is significantly altered compared to other reproductive phases. Not only are progesterone and estradiol elevated during pregnancy, but estrone, estriol, and DHEAS are elevated and other hormones, not measured by this study, are altered as well. In comparison, steroid hormones fluctuate across the menstrual cycle significantly, but nevertheless by a magnitude far smaller than what is observed during pregnancy and following parturition. With the addition of oral contraceptives, which are commonly used by this age group, hormone patterns and concentrations are altered as well, though somewhat distinctly than those observed in naturally cycling women. Finally, even the smaller fluctuations in circulating steroids observed in normally cycling women, affect cognitive performance (Compton, Costello, & Diepold, 2004; Hampson, 1990; Hausmann & Gunturkun, 2000; Philips & Sherwin, 1992) in ways

that are not fully understood. For these reasons, selection of a control group was not feasible for this preliminary investigation.

In lieu of the control group, we utilized a within-subjects design and assessed deficits using normative standards that were established with large sample populations (n = 1,087), where any menstrual cycle related changes would have been subsumed by the mean data. Unfortunately, there are also problems associated with using published normative data. Namely, many of the instruments were neither education-, nor IQ-adjusted, which potentially led to an under-estimation of the level of cognitive decline for this highly educated study group. Future investigations, with a larger sample size and control groups that are age, education, and/or IQ matched and assessed by cycle phase, are needed to delineate fully the nature and severity of maternal cognitive difficulties.

Despite these limitations, however, results from this study provide a number of important insights regarding perinatal cognitive changes. First, cognitive performance declines subtly but globally during pregnancy and, except for verbal memory, appears to improve somewhat following parturition. The observed difficulties in cognitive performance appear to derive largely from problems with attention and working memory as has been suggested by other investigators (Henry & Rendell, 2007; Rendell & Henry, 2008).

Secondly, cognitive abilities were associated with changes in hormone concentration. Excessively high concentrations of hormones (late pregnancy estrogens and postpartum DHEAS), very low hormone concentrations (pregnancy testosterone and postpartum estradiol), and large, abrupt changes in hormone concentration negatively impacted cognitive performance. Although the manner in which individual hormones influenced specific aspects of cognitive performance was less clearly discernable, the estrogens yielded quantitatively more influence on cognitive performance than any of the other hormones tested. Estrone and estriol, in particular, were significantly correlated with a number of verbal memory indices. Whether the associations between estrone, estriol, and cognitive performance are unique to perinatal women, where these hormones assume a more dominant role than in non-pregnant women requires further investigation.

Finally, the pattern of observed correlations between hormones and cognition, points to a possible lateralization of influence. Excessively high hormones were globally deleterious to cognitive ability affecting both right and left hemisphere regulated tasks whereas only tasks regulated by the left hemisphere were impacted negatively by lower hormone concentrations.

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