PERGAMON

Psychoneuroendocrinology 24 (1999) 69–84

PNEC

1998 Curt P. Richter Award

Pregnancy, the postpartum, and steroid hormones: effects on cognition and mood

J. Galen Buckwalter [a,*], Frank Z. Stanczyk [b], Carol A. McCleary [c], Brendon W. Bluestein [d], Deborah K. Buckwalter [d], Katherine P. Rankin [d], Lilly Chang [b], T. Murphy Goodwin [b]

[a] *Andrus Gerontology Center, University of Southern California, University Park, MC-0191, Los Angeles, CA 90089, USA*

[b] *Department of Obstetrics/Gynecology, University of Southern California, University Park, MC-0191, Los Angeles, CA 90089, USA*

[c] *Department of Neurology, University of Southern California, University Park, MC-0191, Los Angeles, CA 90089, USA*

[d] *Graduate School of Psychology at Fuller Theological Seminary, 180 North Oakland Avenue, Pasadena, CA 91101, USA*

Received 11 March 1998; accepted 23 July 1998

Abstract

The effects of pregnancy on cognition and mood were examined using a repeated-measures design. Nineteen women, average age 33, were tested with a comprehensive neuropsychological battery during their last 2 months of pregnancy and again within 2 months of delivery. Blood samples were obtained from all subjects and assayed for a variety of steroid hormones implicated in cognitive and mood functioning. Most participants also completed several self-report measures of mood. In comparison with performance after delivery, women showed significantly more impairment in aspects of verbal memory during pregnancy and also tended to report more negative mood states. Memory deficits were not explained by mood disturbances. No hormone assayed consistently related to cognitive performance during pregnancy. During pregnancy, higher levels of progesterone (P) were associated with greater mood disturbances and higher levels of dehydroepiandrosterone (DHEA) with better

* Corresponding author. Tel.: +1-213-7407777; fax: +1-213-7408241; e-mail: buckwalt@mizar.usc.edu.

PII: S0306-4530(98)00044-4

mood. After delivery, testosterone (T) was strongly and consistently associated with greater reported mood disturbances. Our results confirm a peripartal memory deficit, which cannot be explained by the dramatic rise in circulating steroid hormones, or by mood status during pregnancy. Steroidal hormones, namely P, DHEA and T, appear to play a role in mood disturbances during, and after, pregnancy. Studies beginning earlier in pregnancy and continuing for an extended period of time after delivery are needed to confirm and expand these observations.

Keywords: Pregnancy; Postpartum; Cognition; Mood; Steroid hormones

1. Introduction

Cognitive and mood changes during pregnancy and in the postpartum period are frequently self-reported and have been documented empirically. Mood, as it relates to pregnancy, has been addressed primarily in relation to postnatal depression. However, available estimates of negative affective symptomatology during pregnancy suggest a sizable proportion of women are affected (Nott et al., 1976; O'Hara et al., 1984; O'Hara, 1986). Mood changes in the postnatal period include mild forms of dysphoria, typically referred to as the blues (Harris, 1980; Pritchard and Harris, 1996), and anxiety and tearfulness (Kennerly and Gath, 1986). Mild to moderate depression is $\approx 3\times$ higher in the month following delivery than in non-gestational controls (O'Hara et al., 1990).

While negative affective state has been investigated in relation to a number of sociodemographic variables, postnatal depressed mood has been related to the hormonal changes of the perinatal period. Nott et al. (1976) report a correlational trend for greater antenatal irritability with higher estrogen levels, as well as a greater likelihood for subjects with larger progesterone (P) declines to rate themselves as depressed postnatally. O'Hara (1986) also examined P and mood from the second trimester of pregnancy to the 9th postpartum week but failed to find a similar correlation. However, estrogen withdrawal was identified as a possible cause of postpartum blues. A prospective study of primiparous women, which assessed mood and concentrations of P and cortisol antenatally and in the month following parturition, found that women with maternity blues had significantly higher antenatal P concentrations and lower postnatal concentrations than women without blues (Harris et al., 1994). In contrast, Heidrich et al. (1994) reports no significant difference in estradiol (E_2) or P levels between women with and without postpartum blues.

Estrogen levels may be associated with changes in mood in non-pregnant women. The use of ERT is associated with less depression in the post-menopause (Sherwin and Gelfand, 1985; Ditkoff et al., 1991). Hormonal fluctuations across the menstrual cycle have been inconsistently associated with changes in mood (Halbreich et al., 1986; Phillips and Sherwin, 1992b; Redei and Freeman, 1995; Fink et al., 1996).

Fewer studies have analyzed cognitive changes during and after pregnancy. Sharp et al. (1993) found deficits in the recall of word lists in both primigravid and multigravid pregnant women when compared with non-pregnant women. This

deficit was greater for incidental recall than when the women were explicitly instructed to remember items. A similar pattern was found for pregnant women in all trimesters of pregnancy. Eidelman et al. (1993) found that women in the 3rd month of a high risk pregnancy performed worse than nonpregnant controls on the ability to recall a short passage of prose, but not on a visual memory task. In a separate group of women with normal pregnancies, deficits in both passage recall and visual memory were reported during the 1st postpartum day but not during days two and three. Silber et al. (1990), testing women in the 36th week of pregnancy, within 3 days after delivery, and at 3, 6 and 12 months postpartum, found no differences between pregnant women and controls during pregnancy, at the immediate postpartum or at the 3 month testing. However, the women who had been pregnant showed significant increases in performance on word list learning and reaction time at the 6 and 12 month testings, when compared with the controls. The authors interpret this as indicative of a peripartal cognitive impairment. In a longitudinal study, Keenan et al. (1997), find explicit memory deficits, using paragraph recall, only in the third trimester, when pregnant women are compared with controls. Subjective reports of cognitive dysfunction during pregnancy have been noted. Poser et al. (1986) found symptoms such as forgetfulness, disorientation, confusion, and reading difficulties to be common among pregnant professional women. Subjective memory complaints during pregnancy have also been associated with impairments in implicit memory (Brindle et al., 1991). None of the studies on cognitive functioning have simultaneously evaluated mood, which is essential to determine if cognitive changes are reflective of changes in mood.

The mechanism for any cognitive changes associated with pregnancy remains to be determined. Silber et al. (1990) found no consistent associations between cognitive changes and changes in oxytocin levels. In studies not involving pregnancy, there is compelling support for an effect of steroid hormones on both cognitive and mood functioning. Among women, fluctuations in circulating estrogens, from either endogenous or exogenous sources, are associated with specific cognitive profiles. This has been most widely reported for administration of estrogen replacement to women after either surgical (Sherwin, 1988; Phillips and Sherwin, 1992a) or natural menopause (Kampen and Sherwin, 1994; Robinson et al., 1994). Studies also suggest that the estrogen deficiency that results with the use of gonadotropin-releasing-hormone (GnRH) agonists is associated with decreased memory (Kortepeter et al., 1992; Newton et al., 1996), an effect that is reversed by add-back estrogen therapy (Sherwin and Tulandi, 1996). Endogenous fluctuations in estrogen associated with the menstrual cycle have also been associated with cognitive changes such that specific cognitive skills are elevated at times during the cycle when estrogen levels are high (Hampson and Kimura, 1988; Hampson, 1990).

Other hormones have been associated with cognitive and mood status including P (Freeman et al., 1993; Baker et al., 1995), testosterone (T) (Janowsky et al., 1994; Sands and Studd, 1995), dehydroepiandrosterone (DHEA) (Morales et al., 1994; Wolkowitz et al., 1997), and cortisol (Carroll et al., 1981; Lupien et al., 1994). These hormones also change dramatically during pregnancy and with parturition.

In an effort to better understand both the cognitive and mood effects of pregnancy and the postpartum, we evaluated a group of women during the last

month of pregnancy and again within 2–6 weeks after delivery. These times were chosen to allow for a determination of the effects of late pregnancy, when hormones are elevated, in comparison with performance in the postpartum, after the initial trauma of labor has subsided, while steroid hormones are still greatly reduced. We utilized a comprehensive battery of neuropsychological tests that have widely used norms available. Tests of mood are included to allow for evaluation of mood during and after pregnancy and to be able to determine if any cognitive changes are independent of mood. A range of steroid hormones, known to have effects on cognition and mood, were evaluated in an attempt to elucidate the mechanism underlying any effects of pregnancy and the postpartum on cognition or mood.

2. Methods

2.1. Subjects

Participants were recruited through private practice offices of Los Angeles area gynecologists and through birthing classes conducted at a major Los Angeles hospital. All subjects were primary English-speakers and had uncomplicated pregnancies. Twenty-five subjects were enrolled into the study and 19 completed the neuropsychological tests on both occasions and are included in current analyses. The average age of the subjects was 33.1 years ($\pm$ 4.7) and average education was 16.0 years ($\pm$ 1.3). Testing during pregnancy (T_1) was completed on average 19.8 days prior to delivery and again 26.5 days after delivery (T_2). All subjects had singleton pregnancies, 13 delivered girls, six boys. None had delivery by Cesarean section. All but one were breast-feeding their infants at the time of the second testing.

2.2. Procedures

The protocol was reviewed and approved by the Institutional Review Board at the University of Southern California. Subjects were initially screened via a telephone interview to verify that they met inclusionary criteria and were tested in their residence by one of three trained neuropsychological examiners. Prior to their neuropsychological testing, the subjects completed the tests of mood and a questionnaire on reproductive history and clinical changes associated with the pregnancy. Fifteen subjects completed the mood tests on both occasions (18 at T_1 and 16 at T_2) and analyses of change in mood are limited to these subjects.

The neuropsychological battery included the following: general level of intelligence was assessed by the Test of Nonverbal Intelligence (TONI). Episodic verbal memory was evaluated with the California Verbal Learning Test (CVLT), which presents a list of 16 words (from four semantic categories) over five trials and then assesses short- and long-term delayed memory. Standardized indices of learning effectiveness, strategy, and types of errors were calculated. Semantic memory was assessed with the Boston Naming Test. Verbal attention and mental control were

assessed with the Digit Span Forward and Backward test from the Wechsler Adult Intelligence Scale-Revised. Auditory comprehension was tested with the modified Token Test from the Boston Diagnostic Aphasia Examination. Executive control processes were evaluated with the Trail-Making Tests A and B and the Stroop Color and Word Test. The Judgment of Line Orientation (JLO) was used to evaluate visuoperceptual skills. Standardized alternate forms were used for the CVLT, the JLO and the TONI to preclude practice effects. With the 60 item BNT, we created two separate 30-item tests (using odd and even numbers) and used these to again minimize any practice effect. Order of form administration was counterbalanced to preclude any systematic effect of form bias. These tests are all commonly used in clinical neuropsychology and as such have widely used normative information available (Table 2).

Mood was evaluated with the Beck Depression Inventory (BDI), Profile of Mood States (POMS) and the Symptom Check List-90 (SCL). The Beck Depression Inventory (BDI) is a 21-item scale evaluating aspects of depressive symtpomotology (e.g. sense of failure, mood, appetite, indecisiveness). The POMS assesses mood on six dimensions: tension–anxiety, depression–dejection, anger–hostility, vigor–activity, fatigue–inertia, and confusion–bewilderment. The SCL develops nine subscales relating to various psychiatric profiles: somaticization, obsessive–compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. A total index of symptomatology can also be created from the SCL.

A certified phlebotomist obtained a 10 ml tiger top vacutainer prior to the neuropsychological testing. The blood was transported on ice to the Andrus Gerontology Center at the University of Southern California (USC) where it was centrifuged and the serum removed and frozen at -75°C for later transportation to the Reproductive Endocrine Research laboratory at USC.

Hormone levels were determined for E_2 (Stanczyk et al., 1988), P (Scott et al., 1978), T (Goebelsmann et al., 1974), DHEA (Dorgan et al., 1994) and cortisol (Cassidenti et al., 1990) in serum using radioimmunoassay (RIA) methods as described in the accompanying references. Prior to RIA, T, DHEA and E_2 were extracted with diethyl ether and then subjected to Celite column partition chromotography. Cortisol and P were extracted with hexane:ethyl acetate and *n*-hexane respectively. Intra- and inter-assay coefficients of variation for the five RIA's ranged between 5 and 10% and between 10 and 15% respectively. The assay sensitivity of each assay, after correction for dilutions and procedural losses, was 10 pg/ml.

One subject had levels greater than three standard deviations above the mean for T at T_1 and T_2 and for P at T_2. This subject was excluded from all analyses involving hormone levels. Mean hormone values for the remaining subjects are reported in Table 1.

2.3. Data analytic strategy

Data analyses targeted three primary questions: (1) were there changes in cognition associated with pregnancy; (2) were there changes in mood associated

with pregnancy; and (3) were hormone levels associated with cognition and mood during and after pregnancy. Repeated measures ANOVA's were used to test scores from the two testing occasions for significant change. Separate analyses were used, for each test of cognition and mood, to address questions 1 and 2. If changes in cognition were observed, post hoc analyses were planned to determine if these changes were associated with mood. Three correlation matrices were developed to address question 3. Hormone levels from time 1 (T_1) were correlated with all cognitive and mood tests at T_1, levels from time 2 (T_2) were correlated with tests from T_2, and changes in hormone levels from T_1 to T_2 were correlated with changes in test scores from T_1 to T_2. We used two-tailed significance tests throughout. We report all significant ($p \leq .05$) and near significant ($p \leq .1$) tests to allow for a comprehensive review of the patterns of associations that may exist in these data (note to readers who wish to know the criteria for multiple comparisons, using the Bonferoni procedure, $p < .005$ would be needed for significance on the neuropsychological tests, 0.004 for indices of the CVLT, 0.008 for the POMS and 0.005 for the SCL). Given the use of multiple significance tests, we interpret as relevant only those instances where there are multiple findings among the analyses conducted to address each question. By limiting interpretation to times when there are multiple significant findings we provide some protection against type I errors as well as maintain our limited statistical power.

3. Results

3.1. Pregnancy and cognition

Descriptive and statistical information for all cognitive tests is provided in Table 2. Subjects showed no change in general intelligence level during and after

Table 1
Steroid hormones levels during pregnancy (T_1) and after delivery (T_2)

Hormone	Time	Mean	S.D.	Minimum	Maximum
Cortisol (ng/ml)	T_1	30.55	9.95	18.70	51.30
Cortisol (ng/ml)	T_2	12.21	5.58	5.50	23.50
DHEA (ng/ml)	T_1	4.46	1.72	0.85	6.97
DHEA (ng/ml)	T_2	2.48	1.03	1.06	4.55
Estradiol (ng/ml)	T_1	25.07	8.23	13.80	42.00
Estradiol (ng/ml)	T_2	0.024	0.012	0.013	0.066
Progesterone (ng/ml)	T_1	174.11	33.62	128.00	267.00
Progesterone (ng/ml)	T_2	0.501	0.878	0.030	3.480
Testosterone (ng/dl)	T_1	57.52	23.06	20.70	105.50
Testosterone (ng/dl)	T_2	24.58	10.84	4.10	48.90

Table 2
Neuropsychological tests during pregnancy (T_1) and after delivery (T_2)

Test	Mean $T_1 \pm$ S.D.	Percentile T_1	Mean $T_2 \pm$ S.D.	Percentile T_2	Mean change $\pm$ S.D.	% Improvement T_1 to T_2	p[a]
Token Test[1]	42.4 ± 3.3	65	41.9 ± 3.5	60	0.5 ± 1.8	-1.0	ns*
Boston Naming Test (BNT)[1]	26.5 ± 3.4	16 #	27.1 ± 2.4	28 #	-0.6 ± 1.9	2.2	ns
Test of Nonverbal Intelligence (TONI)[2]	103.9 ± 12.7	57	106.6 ± 14.3	62	-1.5 ± 8.2	2.3	
Trail-Making Test A[1]	26.9 ± 9.8	21	22.6 ± 7.5	46	4.3 ± 8.4	16.0	$<.05$
Trail-Making Test B[1]	55.4 ± 15.3	46	48.1 ± 19.1	60	7.3 ± 17.3	13.2	0.09
Stroop Test Word Condition	106.9 ± 12.7	47	111.8 ± 18.4	55	-5.1 ± 13.8	4.6	0.1
Stroop Test Color Condition	78.0 ± 13.7	45	78.9 ± 13.4	48	-0.9 ± 9.4	1.1	ns
Judgement of Line Orientation[3]	26.4 ± 2.9	70	26.7 ± 3.7	75	-0.3 ± 2.0	1.1	ns
Digit span forward[4]	6.8 ± 1.5	53[b]	7.0 ± 1.5	60	-0.2 ± 1.1	2.9	
Digit Span Backward[4]	5.3 ± 1.4	53[b]	5.9 ± 1.4	60	-0.6 ± 1.6	11.3	0.1
California Verbal Learning Test (CVLT)[5] Trial 1	7.5 ± 1.5	6	7.6 ± 2.3	19	-0.1 ± 2.3	1.3	ns
CVLT Trial 5	12.7 ± 2.2	5	14.1 ± 1.9	19	-1.4 ± 1.6	11.0	0.002
CVLT Trials 1–5	56.0 ± 7.6	6	58.8 ± 9.7	20	-2.8 ± 10.1	5.0	
CVLT Learning Slope	1.2 ± 0.6	32	1.5 ± 0.4	63	-0.3 ± 2.6	25.0	<0.04
CVLT Recall Consistency	85.7 ± 7.8	54	90.6 ± 5.5	64	-4.9 ± 7.7	5.7	0.01
CVLT Short Delay Free recall	12.0 ± 2.3	17	12.8 ± 2.8	30	-0.8 ± 2.7	6.7	ns
CVLT Long Delay Free Recall	12.9 ± 2.7	17	13.2 ± 2.4	20	-0.3 ± 2.2	2.3	ns
CVLT Free Recall Intrusions	2.9 ± 3.4	79	1.3 ± 2.1	45	1.6 ± 2.9	55.0	<0.03
CVLT Short Delay Cued Recall	13.0 ± 2.3	21	12.8 ± 2.5	19	0.2 ± 0.6	1.5	ns
CVLT Long Delay Cued Recall	13.3 ± 2.4	16	13.4 ± 2.4	17	-0.1 ± 2.4	1.0	ns
CVLT Cued Recall Intrusions	4.0 ± 4.8	77	2.6 ± 4.5	30	1.4 ± 4.3	35.0	0.18

[a] p-value for repeated-measures ANOVA of differences from T_1 to T_2.

* ns: $p > .2$.

Thirty item scores doubled to obtain normative information.

[b] Norms available for combined scores of digit span forward and digit span backward only.

[1] Spreen et al. (1991).

[2] Brown et al. (1990).

[3] Benton et al. (1983).

[4] Wechsler (1981).

[5] Delis et al. (1987).

pregnancy, performing slightly above the mean at both testing occasions, on the TONI. On the CVLT, subjects performed significantly worse when pregnant on the number of items recalled after the fifth trial ($F = 13.23$, $p = .002$). Subjects also showed a significantly lower learning slope across the five learning trials when pregnant ($F = 5.13$, $p < .04$). During pregnancy, the women also provided significantly more incorrect responses during the recall conditions ($F = 5.90$, $p < .03$) and showed less consistency in recalling the same items across the learning trials ($F = 7.75$, $p = .01$).

Subjects also performed significantly worse on Trail-Making Test A when pregnant ($F = 4.55$, $p < .05$). In addition, there were statistical trends ($.1 \geq p > .05$) for performance to be worse during pregnancy on the Trail-Making Test B, Digit Span Backwards, and the Stroop Test (Word Condition).

3.2. Normative evaluation of results

Tests of cognition are widely used and normative information is published for clinical and non-clinical populations. Table 2 includes normative information for our sample based on groups of women of similar age and education. Performance during pregnancy is most notable for impairment, relative to normative groups, in numerous aspects of verbal memory. While there is improvement after delivery, performance in these areas including semantic memory (BNT), continues to be below age norms. Cognitive performance is not impacted in all areas, however. This is most apparent in that IQ performance is slightly above average at both testing times.

3.3. Pregnancy and mood

Information on the mood tests is included in Table 3. For the 15 subjects included in the analysis of mood, subjects reported greater mood disturbances during pregnancy on the SCL Obsessive–Compulsive scale ($F = 5.04$, $p = .04$). There were statistical trends ($.1 \geq p > .05$) for scores to be higher during pregnancy for the SCL Total and POMS Tension.

3.4. Post hoc analyses

Given the presence of both cognitive and mood disturbances during pregnancy, we explored the possibility that cognitive deficits associated with pregnancy resulted from changes in mood. We conducted analyses of covariance (ANCOVA) for each cognitive test where there had been a significant difference between pregnant and non-pregnant conditions, covarying the change score on the SCL total. Those subjects who had missing data on the SCL were assigned the mean value for all other subjects. No change in level of significance was observed on any cognitive test where there had been a significant uncontrolled difference.

Table 3
Mood tests during pregnancy (T_1) and after delivery (T_2)

Test	Mean $T_1 \pm$ S.D.	Mean $T_2 \pm$ S.D.	Mean Change $\pm$ S.D.	Improvement T_1 to T_2 (%)	p^{Δ}
Beck Depression Inventory	10.2 ± 5.4	8.5 ± 3.4	1.7 ± 6.3	16.7	ns*
Profile of Mood States (POMS) Tension	11.2 ± 6.7	7.9 ± 5.6	3.3 ± 6.9	29.5	.07
POMS Depression	9.5 ± 10.1	6.1 ± 6.6	3.4 ± 9.9	35.8	.19
POMS Anxiety	9.8 ± 8.5	6.9 ± 5.3	2.9 ± 7.3	29.6	.12
POMS Confusion	7.5 ± 3.9	7.4 ± 3.4	0.1 ± 3.2	1.3	ns
POMS Fatigue	13.2 ± 5.7	12.4 ± 4.9	0.8 ± 6.4	6.0	ns
POMS Vigor	11.7 ± 5.5	11.8 ± 7.1	-0.1 ± 6.3	1.0	ns
Symptom Checklist-90 (SCL) Total	50.0 ± 35.8	33.3 ± 18.7	16.7 ± 30.4	33.4	.08
SCL Somaticization	57.7 ± 5.6	50.4 ± 14.8	7.3 ± 17.6	12.7	.15
SCL Obsessive–Compulsive	59.1 ± 12.0	50.3 ± 16.7	8.8 ± 17.6	14.9	.04
SCL Interpersonal Sensitivity	54.1 ± 10.9	48.4 ± 15.0	5.7 ± 20.1	10.5	ns
SCL Depression	57.8 ± 8.5	51.2 ± 14.7	6.6 ± 18.6	11.4	.12
SCL Anxiety	51.0 ± 10.4	45.3 ± 14.8	5.7 ± 13.6	11.2	.2
SCL Hostility	52.8 ± 10.3	51.7 ± 16.5	1.1 ± 17.2	2.1	ns
SCL Phobic Anxiety	46.1 ± 10.0	43.6 ± 14.2	2.5 ± 12.4	5.4	ns
SCL Paranoid Ideation	45.5 ± 13.4	41.4 ± 15.0	4.1 ± 13.6	9.0	ns
SCL Psychoticism	51.1 ± 10.3	43.3 ± 14.1	9.8 ± 16.3	19.2	.14

$^{\Delta}$ p-value for repeated-measures ANOVA of difference from T_1 to T_2.
* ns: $p > .2$.

3.5. Hormones and cognition

During pregnancy, there were no hormones that showed consistent associations with cognition. DHEA correlated with better performance on the JLO ($r = .65$, $p = .006$), with similar trends ($.1 \geq p > .05$) on Digit Span Backward and Short-Delay Free Recall from the CVLT. T correlated with worse performance on the TONI ($r = -.58$, $p < .02$). Cortisol was significantly associated with fewer perseverative responses on the CVLT ($r = -.57$, $p = .01$). Serum levels of E_2 and P did not significantly correlate with any cognitive test during pregnancy.

After delivery, both DHEA and cortisol showed some associations with better cognitive performance. DHEA correlated with more rapid completion of Trails A ($r = -.52$, $p = .04$), better performance on the Stroop (Word Condition) ($r = .49$, $p < .05$) and CVLT Short-Delay Cued recall ($r = .48$, $p = .05$). Cortisol was significantly correlated with faster times on Trails A ($r = -.58$, $p < .02$) and with fewer perseverations on the CVLT ($r = -.54$, $p = .02$). Serum levels of E_2, T and P did not significantly correlate with any cognitive test after delivery.

Changes in hormone levels showed no pattern of associations with cognitive change.

3.6. Hormones and mood

DHEA showed a very consistent pattern of associations with better mood during pregnancy. DHEA correlated with lower scores on the BDI ($r = -.65$, $p = .005$), SCL Somaticization ($r = -.61$, $p = .01$), SCL Obsessive–Compulsive ($r = -.57$, $p = .02$), SCL Interpersonal Sensitivity ($r = -.73$, $p = .001$), SCL Depression ($r = -.50$, $p = .05$), SCL Anxiety ($r = -.54$, $p = .03$), SCL Paranoid Ideation ($r = -.55$, $p = .03$), SCL Psychoticism ($r = -.52$, $p < .04$) and the SCL Total Index ($r = -.65$, $p = .007$). DHEA levels were also negatively associated with scores from the POMS Tension ($r = -.51$, $p = .04$), Depression ($r = -.71$, $p = .002$), Anger ($r = -.62$, $p = .01$), and Confusion ($r = -.68$, $p = .004$) scales. *P* also showed several associations with mood, but with greater disturbances. *P* correlated positively with SCL Psychoticism ($r = .67$, $p = .005$) and with POMS Confusion ($r = .56$, $p < .03$). Trends ($.1 \geq p > .05$) of similar direction were found with the SCL Total, Phobic Anxiety, Depression and the POMS Depression and Fatigue scales. Cortisol correlated with higher scores on the SCL Phobic Anxiety ($r = .53$, $p = .03$) and T with lower scores on the SCL Psychoticism ($r = .50$, $p = .05$) scale. Levels of E_2 did not correlate with any measure of mood during pregnancy.

While levels of T did not correlate with mood during pregnancy, levels were consistently associated with worse mood after delivery. T correlated with greater reported symptomotology on the BDI ($r = .57$, $p = .02$), SCL Depression ($r = .74$, $p = .002$), SCL Hostility ($r = .76$, $p = .001$), and the SCL Total ($r = .68$, $p = .005$). T also correlated with POMS Tension ($r = .49$, $p = .05$), POMS Depression ($r = .49$, $p = .05$) and POMS Anger ($r = .70$, $p = .001$). T showed trends ($.1 \geq p > .05$) toward associations with higher scores on the SCL Interpersonal Sensitivity and Psychoticism subscales and the POMS Confusion and Fatigue scales. After delivery, DHEA

showed fewer associations with enhanced mood than during pregnancy. DHEA correlated with lower scores on the SCL Interpersonal Sensitivity ($r = -.55$, $p = .04$) and SCL Phobic Anxiety ($r = -.54$, $p < .05$). Neither E_2, P nor cortisol significantly correlated with any of the mood tests after delivery, although P did show trends ($.1 \geq p > .05$) with higher scores on SCL Somaticization and Interpersonal Sensitivity.

The changes in hormone levels from T_1 to T_2 were most clearly related to changes in mood for estrogen. Change in E_2 correlated positively with change on the SCL Phobic Anxiety ($r = -.54$, $p < .05$), the POMS Confusion ($r = .54$, $p = .04$) and POMS Fatigue ($r = .54$, $p = .04$). Thus, as E_2 decreased, reported mood disturbances did as well. E_2 correlated negatively with change in POMS Vigor ($r = -.60$, $p = .02$), meaning that as E_2 levels decreased vigor increased. The loss of DHEA that occurs after delivery did show associations with an increase in mood disturbances. A decrease in DHEA was related to an increase on SCL Interpersonal Sensitivity ($r = -.58$, $p = .04$) and SCL Depression ($r = -.58$, $p = .04$). Similar trends ($.1 \geq p > .05$) were apparent on the BDI, the SCL Obsessive–Compulsive, SCL Anxiety and SCL Paranoid Ideation subscales. Decline in P was associated with a decline in the SCL Phobic Anxiety scale ($r = .54$, $p < .05$). Change in cortisol levels did not correlate with change in mood.

4. Discussion

These findings confirm previous reports of peripartal cognitive deficits (Poser et al., 1986; Silber et al., 1990; Brindle et al., 1991; Eidelman et al., 1993; Sharp et al., 1993; Keenan et al., 1997). Specifically, cognitive performance was worse, in certain domains, during pregnancy than relatively shortly after delivery, although performance continued below expected normative values on aspects of verbal memory. Subjects did not report greater mood disturbances after delivery, rather there was minimal evidence for greater mood disturbances during pregnancy. Importantly, the cognitive deficits observed during pregnancy, in comparison to performance after delivery, were statistically independent from the mood disturbances associated with pregnancy.

When pregnant, women demonstrated more difficulty with verbal learning and acquisition and with discriminating relevant from irrelevant responses. In terms of verbal learning characteristics, pregnancy was associated with less effective, more haphazard learning styles. The level of deficits observed is also notable when compared with normative data. While these women performed slightly above average on an intelligence test when pregnant, performance on indices of verbal memory ranged as low as the fifth percentile when compared with women of similar age. While performance improved after delivery, memory performance continued to be below age norms. Subjects also showed a degree of difficulty on tasks requiring speed of cognitive processing and conceptual tracking when performance while pregnant was compared with performance after delivery. When compared with normative samples, performance in these cognitive domains was not below expected performance.

Levels of circulating steroid hormones do not appear to explain the cognitive deficits observed. One possible explanation for cognitive deficits during pregnancy is that the extremely high levels of steroids have a negative effect on cognitive performance, e.g. the relation between a steroid hormone and cognitive performance could be represented as an inverted-u. If this were the case, negative associations between hormone levels and cognitive performance would be expected to emerge at the upper range of the hormone. During pregnancy, significant correlations between hormone levels and cognitive performance were positive, although the number of such associations was limited. Thus, any appreciable positive effects of steroid hormones on cognition, as have been reported across the menstrual cycle (Hampson and Kimura, 1988; Hampson, 1990) and with ERT (Sherwin, 1988; Phillips and Sherwin, 1992a; Kampen and Sherwin, 1994; Robinson et al., 1994; Sherwin and Tulandi, 1996), may be negated during the perinatal period. While it is conceivable that this is due to the elevated levels, given the lack of negative associations between hormones and cognitive performance during pregnancy, it seems more likely that some other unmeasured aspect of pregnancy underlies the cognitive deficit.

Glucocorticoids have been reported to have negative effects on cognition (Lupien et al., 1994). The rise in basal levels of cortisol that occurs in the last trimester of pregnancy could be expected to underlie the cognitive deficits we observed. We found no such role for cortisol during pregnancy, however, there was some suggestion of a positive role after delivery. Our protocol for blood collection was not designed to allow for analysis of diurnal variation, which questions the reliability of our findings.

Analysis of the pattern of cognitive deficits associated with pregnancy may provide some clues as to possible underlying mechanisms. Deficits associated with pregnancy are clearest in learning new verbal information. This could stem from difficulty discriminating relevant from irrelevant stimuli. Cholinergic inputs are argued to mediate the ability to detect, select and encode appropriate stimuli (Hasselmo et al., 1996; Sarter and Bruno, 1997). A muscarinic acetylcholine receptor blocker, scopolamine, impairs the encoding of new information (Drachman, 1977; Vitello et al., 1997). Conversely, when cholinergic activity is increased, memory is enhanced (Sitaram et al., 1978; Furey et al., 1997). Cholinergic disturbances, in the brain, have not been reported in pregnant women. However, our cognitive results are consistent with a cholinergic dysfunction. This need be directly assessed, as do a myriad of other possible hormonal factors associated with pregnancy that may adversely impact memory.

Mood disturbances were most clearly elevated during pregnancy on a measure of obsessive-compulsiveness. This subscale of the SCL measures ''thoughts, impulses and actions that are experienced as unremitting and irresistible by the individual but are … of an unwanted nature'' (Derogatis, 1983). There also was a trend for an overall elevation on reported symptoms from the SCL during pregnancy. We found no difference in level of depressive symptoms before and after pregnancy, suggesting that depression may be as salient in the antenatal period as the postnatal. In general, mean scores on mood measures were lower after delivery, although the

amount of variance consistently increased after delivery. Further exploration of a range of mood states, including negative thought processes, with equal attention given to the antenatal period, is suggested by these results.

Mood functioning, during and after pregnancy, is strongly related to circulating levels of steroid hormones, although the pattern of associations is markedly different at these two times. During pregnancy, levels of both *P* and DHEA showed a consistent pattern of associations with mood; DHEA with less mood disturbance, *P* with more. After delivery, when *P* levels are greatly reduced, *P* no longer was associated with mood. DHEA levels are also reduced after delivery, and DHEA showed a much less consistent pattern of associations with measures of mood. After delivery, the hormone with the clearest association with mood was T, which was strongly and consistently associated with greater mood disturbances. The lowering of DHEA that occurred from T_1 to T_2 was associated with increases in mood disturbances. The decline in E_2 was associated with some decreases in mood disturbances. This is in contradiction to the suggestion that estrogen withdrawal may contribute to postpartum mood disturbances (O'Hara et al., 1991).

DHEA has been reported to enhance mood during a randomized clinical trial (Morales et al., 1994). Our results suggest that endogenous levels play a similar role particularly during pregnancy. Postnatal mood disturbances may be exacerbated by the decline in DHEA. DHEA supplementation may be a viable treatment for postpartum mood disturbances. Our findings suggest that *p* is a negative factor in mood when levels are elevated, as occurs during pregnancy. Our findings that T is a negative factor in mood only when levels are relatively low is perplexing. T has been reported to be higher in women with PMS (Eriksson et al., 1992). The association with greater mood disturbances after delivery may indicate that T is a factor when other hormones are at a low level. Regardless, the strength and consistency of the correlations between T and mood measures warrants further explorations. Most saliently, T correlated with all three measures of depression after delivery, suggesting it may be a factor in the etiology of post-natal depression. Also of interest is the different roles that the two androgens we measured play in mood functioning, with DHEA clearly associated with less mood disturbances during pregnancy and T with greater disturbances in the postpartum. That two androgens have such different effects on mood may indicate that their mechanisms of action on the brain are not identical.

Our findings confirm a specific cognitive deficit for learning new information that appears to be most profound during pregnancy. Performance improves after delivery but may still be impaired during the time period when we evaluated these women. The cognitive deficits during pregnancy are independent of mood changes that occur during this time period. Mood was not more disturbed after delivery. Steroid hormones appear to play a strong role in mood functioning; it is unclear if they play a role in cognitive performance, during pregnancy and the postpartum. Studies using similar within subjects designs, including testing earlier in pregnancy and later after delivery than was done in our study, are needed to better identify the nature and extent of cognitive and mood changes associated with pregnancy. Also, other hormones that are impacted by reproduction, such as prolactin and oxytocin, should be evaluated.

Acknowledgements

The impetus for this study came from discussions with Caleb E. Finch, Ph.D., and his seminal work on reproduction and senescence. Portions of this study were presented at the International Neuropsychological Society Meeting, Orlando FL, February, 1997 and at the Society for Gynecologic Investigations, San Diego CA, March, 1997.

References

Baker, E.R., Best, R.G., Manfredi, R.L., Demers, L.M., Wolf, G.C., 1995. Efficacy of progesterone vaginal suppositories in alleviation of nervous symptoms in patients with premenstrual-syndrome. Journal of Assisted Reproduction Genetics 12, 205–209.

Benton, A., deS Hamsher, K., Varney, N.R., Spreen, O., 1983. Judgment of Line Orientation. Oxford University Press, New York.

Brindle, P.M., Brown, M.W., Brown, J., Griffith, H.B., Turner, G.M., 1991. Objective and subjective memory impairment in pregnancy. Psychology and Medicine 21, 647–653.

Brown, L., Sherbenou, R.J., Johnsen, S.K., 1990. Test of Nonverbal Intelligence Pro-Ed, Austin, TX.

Carroll, B.J., Feinberg, M., Greden, J.F., 1981. A specific laboratory test for the diagnosis of melancholia. Archives of General Psychiatry 38, 15–22.

Cassidenti, D.L., Vigod, A.G., Stanczyk, F.Z., Lobo, R.A., 1990. Short-term effects of smoking on the phamacokinetic profiles of micronized estradiol in postmenopausal women. American Journal of Obstetrics and Gynecology 163, 1953.

Delis, D.C., Kramer, J.H., Kaplan, E., Ober, B.A., 1987. The California Verbal Learning Test. The Psychological Corporation, New York.

Derogatis, L.R., 1983. SCL-90-R Manual II. Clinical Psychometric Research, Towson, MD.

Ditkoff, E.C., Crary, W.G., Cristo, M., Lobo, R.A., 1991. Estrogen improves psychological function in asymptomatic postmenopausal women. Obstetrics and Gynecology 78, 991–995.

Dorgan, J.F., Stanczyk, F.Z., Longcope, C., Stephenson, H.E., Chang, L., Miller, R., Franz, C., Falk, R.T., Kahel, L., 1994. Relations of serum DHEA, DHEAS, and 5-androstene-3β,17β-diol to risk of breast cancer in postmenopausal women. Cancer Epidemiology and Biomarkers Prevention 3, 177.

Drachman, D.A., 1977. Memory and cognitive function in man: does the cholinergic system have a specific role? Neurology 27, 783–790.

Eidelman, A.I., Hoffman, N.W., Kaitz, M., 1993. Cognitive deficits in women after childbirth. Obstetrics and Gyncology 81, 764–767.

Eriksson, E., Sundblad, C., Lisjo, P., Modigh, K., Andersch, B., 1992. Serum levels of androgens are higher in women with premenstrual irritability and dysphoria than in controls. Psychoneuroendocrinology 17, 195–204.

Fink, G., Sumner, B.E.H., Rosie, R., Grace, O., Quinn, J.P., 1996. Estrogen control of central neurotransmission-effect on mood, mental state, and memory. Cellular Molecular Neurobiology 16, 325–344.

Freeman, E.W., Purdy, R.H., Coutifaris, C., Rickels, K., Paul, S.M., 1993. Anxiolytic metabolites of progesterone: correlation with mood and performance measures following oral progesterone administration to healthy female volunteers. Neuroendocrinology 58, 478–484.

Furey, M.L., Pietrini, P., Haxby, J.V., Alexander, G.E., Lee, H.C., Van Meter, J., Grady, C.L., Shetty, U., Rapoport, S.I., Schapiro, M.B., Freo, U., 1997. Cholinergic stimulation alters performance and task-specific regional blood flow during working memory. Proceedings of the National Academy of Science USA 94, 6512–6516.

Goebelsmann, U., Arce, J.J., Thorneycroft, I.H., Mishell, D.R. Jr, 1974. Serum testosterone concentrations in women throughout the menstrual cycle and following hCG administration. Journal of Obstetrics and Gynecology 119, 445–452.

Halbreich, U., Endicott, J., Goldstein, S., Nee, J., 1986. Premenstrual changes and changes in gonadal hormones. Acta Psychiatrica Scandinavica 74, 576–586.

Hampson, E., 1990. Estrogen-related variations in human spatial and articulatory-motor skills. Psychoneuroendocrinology 15, 97–111.

Hampson, E., Kimura, D., 1988. Reciprocal effects of hormonal fluctuations on human motor and perceptual-spatial skills. Behavioural Neuroscience 102, 456–459.

Harris, B., 1980. Maternity blues. British Journal of Psychiatry 136, 520–521.

Harris, B., Lovett, L., Newcombe, R.G., Read, G.F., Walker, R., Riad-Fahmy, D., 1994. Maternity blues and major endocrine changes: Cardiff puerperal mood and hormone study II. British Medical Journal 308, 949–953.

Hasselmo, M.E., Wyble, B.P., Wallenstein, G.V., 1996. Encoding and retrieval of episodic memories: role of cholinergic and GABAergic modulation in the hippocampus. Hippocampus 6, 693–708.

Heidrich, A., Schleyer, M., Spingler, H., Albert, P., Knoche, M., Fritze, J., Lanczik, M., 1994. Postpartum blues: relationship between not-protein bound steroid hormones in plasma and postpartum mood changes. Journal of Affective Disorders 30, 93–98.

Janowsky, J.S., Oviatt, S.K., Orwoll, E.S., 1994. Testosterone influences spatial cognition in older men. Behavioural Neuroscience 108, 325–332.

Kampen, D.L., Sherwin, B.B., 1994. Estrogen use and verbal memory in healthy postmenopausal women. Obstetrics and Gynecology 83, 979–983.

Keenan, P.A., Yaldoo, D., Ginsburg, K., Stress, M., Fuerst, D., 1997. Society of Neuroscience Abstracts 23, 1581.

Kennerly, H., Gath, D., 1986. Maternity blues reassessed. Psychology and Development 1, 1–17.

Kortepeter, C., MacMillan, N., Ferrell, R., 1992. Possible short-term-memory loss associated with nefarelin acetate. Annals in Pharmacotherapy 26, 169–171.

Lupien, S., Lecours, A.R., Lussier, I., Schwartz, G., Nair, N.P.V., Meaney, M.J., 1994. Basal cortisol levels and cognitive levels in human aging. Journal of Neuroscience 14, 2893–2903.

Morales, A.J., Nolan, J.J., Nelson, J.C., Yen, S.S.C., 1994. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. Journal of Clinical Endocrinology and Metabolism 78, 1360–1367.

Newton, C., Slota, D., Yuzpe, A.A., Tummon, I.S., 1996. Memory complaints associated with the use of gonadotropin-releasing-hormone agonists: a preliminary study. Fertility and Sterility 65, 1253–1255.

Nott, P.N., Franklin, M., Armitage, C., Gelder, M.G., 1976. Hormonal changes and mood in the puerperium. British Journal of Psychiatry 128, 379–383.

O'Hara, M.W., 1986. Social support, life events, and depression during pregnancy and the puerperium. Archives of General Psychiatry 43, 569–573.

O'Hara, M.W., Neunaber, D.J., Zekoski, E.M., 1984. A prospective study of postpartum depression: prevalence, course and predictive factors. Journal of Abnormal Psychology 93, 158–171.

O'Hara, M.W., Schlecte, J.A., Lewis, D.A., Wright, E.J., 1991. Prospective study of postpartum blues: biologic and psychosocial factors. Archives of General Psychiatry 48, 801–806.

O'Hara, M.W., Zekoski, E.M., Phillips, L.H., Wright, E.J., 1990. A controlled prospective study of postpartum mood disorders. Journal of Abnormal Psychology 99, 3–15.

Phillips, S.M., Sherwin, B.B., 1992a. Effects of estrogen on memory function in surgically menopausal women. Psychoneuroendocrinology 17, 485–495.

Phillips, S.M., Sherwin, B.B., 1992b. Variations in memory function and sex steroid hormones across the menstrual cycle. Psychoneuroendocrinology 17, 497–506.

Poser, C.M., Kassirer, M.R., Peyser, J.M., 1986. Acta Neurologica Scandinavica 73, 39–43.

Pritchard, D.B., Harris, B., 1996. Aspects of perinatal psychiatric illness. British Journal of Psychiatry 169, 555–562.

Redei, E., Freeman, E.W., 1995. Daily plasma estradiol and progesterone levels over the menstrual cycle and their relation to premenstrual symptoms. Psychoneuroendocrinology 20, 259–267.

Robinson, D., Friedman, L., Marcus, R., Tinklenberg, J., Yesavage, J., 1994. Estrogen replacement therapy and memory in older women. Journal of the American Geriatrics Society 42, 919–922.

Sands, R., Studd, J. (1995) Exogenous androgens in postmenopausal women. American Journal of Medicine, 98 (supplement 1A), S76–9.

Sarter, M., Bruno, J.P., 1997. Cognitive functions of cortical acetylcholine: toward a unifying hypothesis. Brain Research Reviews 23, 28–46.

Scott, J.Z., Stanczyk, F.Z., Goebelsmann, V., Mischell, D.R. Jr, 1978. A double-antibody radioimmunoassay for serum progesterone using progesterone-3-oximino-[^{125}I]-histamine as radioligand. Steroids 31, 393–405.

Sharp, K., Brindle, P.M., Brown, M.W., Turner, G.M., 1993. Memory loss during pregnancy. British Journal of Obstetrics and Gynaecology 100, 209–215.

Sherwin, B.B., 1988. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. Psychoneuroendocrinology 13, 345–357.

Sherwin, B.B., Gelfand, M.M., 1985. Sex steroids and affect in the surgical menopause: a double-blind, cross-over study. Psychneuroendocrinology 10, 325–335.

Sherwin, B.B., Tulandi, T., 1996. Add-back estrogen reverses cognitive deficits induced by a gonadotropin-releasing-hormone agonist in women with leiomyomata uteri. Journal of Clinical Endocrinology and Metabolism 81, 2545–2549.

Silber, M., Almkvist, O., Larsson, B., Kerstin, U.M., 1990. Temporary peripartal impairment in memory and attention and its possible relation to oxytocin concentration. Life Sciences 47, 57–65.

Sitaram, N., Weingartner, H., Caine, E.D., Gillin, J.C., 1978. Choline: selective enhancement of serial learning and encoding of low imagery words in man. Life Sciences 22, 1555–1560.

Spreen, O., Strauss, E.A., 1991. Compendium of Neuropsychological Tests. Oxford University Press, NewYork.

Stanczyk, F.Z., Shoupe, D., Nunez, Y., Macias-Gonzales, P., Vijod, M.A., Lobo, R.A., 1988. A randomized comparison of normal estradiol delivery in postmenopausal women. American Journal of Obstetrics and Gynecology 159, 1540–1548.

Vitello, B., Martin, A., Hill, J., Mack, C., Molchan, S., Martinez, R., Murphy, D.L., Sunderland, T., 1997. Cognitive and behavioral effects of cholinergic, dopaminergic, and serotonergic blockade in humans. Neuropsychopharmacology 16, 15–24.

Wechsler, D., 1981. The Wechsler Adult Intelligence Scale—Revised. The Psychological Corporation, New York.

Wolkowitz, O.M., Reus, V.I., Roberts, E., Manfredi, F., Chan, T., Raum, W.J., Ormiston, S., Johnson, R., Canick, J., Brizendine, L., Weingartner, H., 1997. Dehydroepiandrosterone (DHEA) treatment of depression. Biological Psychiatry 41, 311–318.