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Hormones and Cognitive Functioning During Late Pregnancy and Postpartum: A Longitudinal Study

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Abstract

This longitudinal study investigated the possible influence of estradiol (E_2), progesterone (P), testosterone (T), cortisol (CORT), and prolactin (PRL) levels on cognitive functioning during late pregnancy and the early postpartum period. The performance of 55 pregnant women on a battery of neuropsychological tests, tested once during the third trimester of pregnancy and once during the early postpartum period, was compared with that of 21 nonpregnant controls matched for age and education. Women in the pregnancy group had significantly lower scores than the controls during both the pre- and postpartum visits on tasks of verbal recall and processing speed. CORT levels were significantly associated, in an inverted-U function, with verbal recall scores at both the pregnancy and at postpartum periods and with spatial abilities at postpartum only. During pregnancy, PRL levels were associated in both a linear and an inverted-U function with scores on tests of paragraph recall and in a linear function with scores on tests of executive function. At postpartum, E_2 and CORT were negatively associated in a linear fashion with attention scores. These findings provide new evidence that fluctuating hormone levels during late pregnancy and early postpartum may modulate selected cognitive abilities.

Keywords

pregnancy; postpartum; cognition; steroid hormones; prolactin

During pregnancy and the postpartum periods, a considerable number of women experience some degree of cognitive change that has come to be colloquially called “pregnancy brain.” The symptoms most frequently reported by women during these repro ductive periods are forgetfulness and memory disturbances (Casey, Huntsdale, Angus, & Janes, 1999), poor concentration, increased absentmindedness, and difficulty reading (Parsons & Redman, 1991; Poser, Kassirer, & Peyser, 1986).

The pregnancy and postpartum periods are characterized by the most drastic hormonal fluctuations women experience during their reproductive lives. During pregnancy, levels of some steroid hormones such as estradiol (E_2) and progesterone (P) increase by up to 30- and 70-fold, respectively, in comparison to nonpregnant levels (Tulchinsky, Hobel, Yeager, & Marshall, 1972). Within the first 48 h following delivery, there is a rapid clearance of up to

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80% of placental steroids in the maternal circulation (Bonnar, Franklin, Nott, & McNeilly, 1975; West & McNeilly, 1979). Key steroid hormones affected in this manner are E_2, P, and cortisol (CORT; Bonnar et al., 1975; Willcox, Yovich, McColm, & Phillips, 1985). Other hormones which fluctuate during these periods are testosterone (T) and prolactin (PRL; Bonnar et al., 1975; Pearlman, Crépy, & Murphy, 1967).

Under nonstressful conditions, CORT levels follow a circadian rhythm characterized by highest levels in the morning after awakening followed by a steady decline throughout the day; lowest levels around midnight and a rise again in the early morning hours (Edwards, Evans, Hucklebridge, & Clow, 2001; Weitzman et al., 1971). A distinct feature of the CORT circadian cycle is a marked increase in secretion peaking approximately 30–45 min after awakening, referred to as the CORT Awakening Response (CAR; Pruessner et al., 1997). Although levels of CORT increase throughout pregnancy, the circadian rhythm and CAR are maintained (Cousins et al., 1983; de Weerth & Buitelaar, 2005). Because of its high intraindividual stability, the CAR may be regarded as a reliable marker of the hypothalamus-pituitary-adrenals (HPA) axis reactivity (Schmidt-Reinwald et al., 1999). Because it is not feasible to obtain serial blood samples in the early morning when participants are at home, the CAR is typically measured using salivary samples.

It is interesting to note that many of the hormones that play a key role in the establishment and maintenance of pregnancy have been found to influence selective cognitive functions. For example, higher levels of E_2 have protective effects on specific types of cognitive abilities, such as verbal memory and working memory, in postmenopausal women (Duff & Hampson, 2000; Sherwin, 1988) and in healthy cycling women (Grigorova, Sherwin, & Tulandi, 2006; Maki, Rich, & Shayna Rosenbaum, 2002). There is evidence that higher levels of T may enhance performance on spatial abilities in women who undergo hormone transgender treatments (Slabbekoorn, van Goozen, Megens, Gooren, & Cohen Kettenis, 1999) but may be detrimental to performance on tasks that tend to show a female advantage, such as verbal memory (Schattmann & Sherwin, 2007). A curvilinear relationship has been found between serum levels of T and performance on tests of spatial abilities such that intermediate concentrations of T are optimal in nonpregnant women (Shute, Pellegrino, Hubert, & Reynolds, 1983). A curvilinear relationship has also been observed between levels of CORT and performance on tests of working memory, such that intermediate concentrations of CORT are op timal for performance in young men (Lupien, Gillin, & Hauger, 1999). While few studies have investigated the role of P on cognitive functioning in humans, there is some evidence that higher levels of P may dampen performance on specific cognitive tasks when administered to healthy young women (Freeman, Purdy, Coutifaris, Rickels, & Paul, 1993). On the other hand, higher levels of P have been associated with better performance on a visual reproduction recall task during the luteal phase of the menstrual cycle in young women (Phillips & Sherwin, 1992).

Even more limited information is available concerning the role of PRL on learning and memory. In rats, elevated levels of PRL were associated with facilitated acquisition of avoidance behaviors (Drago, Bohus, & Mattheij, 1982) but had an inhibitory effect on general motor activity and latency to explore (Gonzalez-Mora, Guadalupe, & Mas, 1990; Alvarez & Banzan, 1994). To our knowledge, there are no studies that have investigated the

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role of PRL on cognitive functioning in nonhuman primates or in humans This represents an important gap in the literature because PRL levels increase during pregnancy and gradually decrease during the weeks following childbirth (Battin, Marrs, Fleiss, & Mishell, 1985; Bonnar et al., 1975).

Attempts to objectively measure reported changes in cognitive function during pregnancy and the postpartum period found impairments in selective abilities such as verbal free recall and working memory (for review, see Henry & Rendell, 2007), but inconsistencies abound. In cross-sectional studies, pregnant women performed worse than the controls on tasks of working memory (Janes, Casey, Huntsdale, & Angus, 1999), word fluency, word list learning (de Groot, Hornstra, Roozendaal, & Jolles, 2003), priming tasks, and incidental learning tasks (Sharp, Brindle, Brown, & Turner, 1993). When pregnancy history was taken into account, primiparous women (those pregnant for the first time) but not multiparous women (those pregnant the second or more times) demonstrated impaired implicit memory (Brindle, Brown, Brown, Griffith, & Turner, 1991). Though there is little information avail able concerning differences between primigravid and multigravid women, some have speculated that the brain's response to the physiological changes encountered in subsequent pregnancies may differ (Brindle et al., 1991).

Evidence from prospective studies also supports the idea that changes in cognitive function occur during the pregnancy and postpartum periods, but it is unclear when these impairments occur. For example, impairments on word list learning tasks have been observed during different trimesters and at postpartum (de Groot, Vuurman, Hormstra, & Jolles, 2006; Mickes, Wixted, Sha piro, & Scarff, 2009; Parsons et al., 2004). Furthermore, perfor mance on paragraph recall (Keenan, Yaldoo, Stress, Fuerst, & Ginsburg, 1998), planning (Jarrahi-Zadeh, Kane, Van De Castle, Lachenbruch, & Ewing, 1969), and cognitive speed tasks (Chris tensen, Leach, & Mackinnon, 2010) was worse only in the third trimester. Others have failed to find any differences in scores on objective measures of cognitive functions during pregnancy and postpartum (Casey, 2000; Christensen, Poyser, Pollitt, & Cubis, 1999; Crawley, Dennison, & Carter, 2003; Harris, Deary, Harris Marlene, Lees, & Wilson, 1996; McDowall, 2000), even though participants often reported subjective cognitive difficulties (Christensen et al., 1999; Crawley et al., 2003; McDowall, 2000). It has been suggested that testing in a laboratory setting may underestimate the degree of impairment experienced in day-to-day life (Cuttler, Graf, Pawluski, & Galea, 2011; Rendell & Henry, 2008;). The nature of the testing paradigms and the sensitivity of the measures used are important factors to consider when assessing cognitive abilities in healthy young women.

Although considerable evidence suggests that steroid hormones modulate cognitive functioning in young, cycling women (Grigorova et al., 2006; Maki et al., 2002) and in postmenopausal women (Sherwin & Henry, 2008) these hormone-behavior relationships have not been extensively studied during pregnancy and the post-partum period; to our knowledge, the findings of only three studies are available. In a prospective study, women in the third trimester of pregnancy performed significantly worse on a word-list memory task (verbal memory) and on a task of executive attention compared with their performance at 26 days postpartum (Buckwalter et al., 1999). During pregnancy, higher levels of dehydro-

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epiandrosterone (DHEA) were positively associated with better performance on a line orientation task and CORT levels were negatively associated with perseverative responses on a verbal learning task. During postpartum, levels of DHEA and CORT were positively associated with better performance on tasks of verbal memory and executive function. In a second prospective study, women performed worse on tests of associate learning and reaction time during late pregnancy and early postpartum compared with their own late postpartum performance and to nonpregnant controls (Silber, Almkvist, Larsson, & Uvnäs-Moberg, 1990). No significant correlations were found between hormone levels and cognitive performance throughout the study. Finally, during the third trimester and the early postpartum period, women performed more poorly on a task of verbal recall compared with nonpregnant controls (Glynn, 2010). E_2 levels were negatively associated and CORT levels were positively associated with verbal recall performance during both test times. Thus, although there is some evidence that fluctuating levels of steroid hormones may be associated with changes in cognitive function during pregnancy and the postpartum period, the inconsistency in the findings do not allow any concluding statements at this time.

In this repeated-measures prospective study, women were administered mood and sleep questionnaires and a battery of neuropsychological tests once during the third trimester of pregnancy (weeks 34–38) and once during the early postpartum period (12 weeks after childbirth). Serum and saliva samples were collected at each test time for analysis of steroid and peptide hormone levels. The purpose of the present study was to investigate the changes that may occur in specific cognitive functions during late pregnancy and the early postpartum period, as well as to determine their possible association with fluctuating levels of E_2, P, T, CORT, and the peptide hormone PRL. It was hypothesized that performance on all tests of cognitive functioning would be worse for the pregnancy group compared with nonpregnant controls during both the pre- and postpartum visits. In addition, based on findings from the hormone therapy literature which suggest that lower levels of E_2 are detrimental to selective cognitive abilities in women, we hypothesized that the decrease in test scores in the pregnancy group would be most prominent during the postpartum period, when levels of E_2 are very low. It was further hypothesized that performance on tests of verbal memory and working memory would be positively correlated with levels of E_2, but negatively correlated with levels of P, T, and CORT, whereas scores on visuospatial tasks would be positively correlated with levels of T but negatively correlated with levels of E_2. Because of the lack of information available concerning the effects of PRL on cognition, no hypotheses could be formulated. Observations of possible relationships between PRL and cognitive functioning in this study would thus be novel and exploratory in nature.

Method

Participants

Women between the ages of 22 and 40 years (M = 31.4 years) were recruited from prenatal classes conducted by obstetrical departments of hospitals associated with the McGill University Health Center (Royal Victoria Hospital, Jewish General Hospital and St. Mary's Hospital Centre), Montreal, Canada, as well as from a private organization (Childcare

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Education, Montreal, Canada) and from a public health clinic (Centre de santé et de services sociaux Cavendish, Montreal, Canada).

Inclusion criteria required that the women have a healthy primigravid pregnancy (first full-term pregnancy). Enrollment was restricted to primigravid women in the attempt to control for fatigue levels, which may be more pronounced in women who must also take care of their older children at home following delivery of their newborn. Women were required to be 18 years or older, be fluent in English or French, have a minimum of 12 years of formal education, have been in a stable relationship for the past 12 months, and have had a history of regular menstrual cycles prior to pregnancy. Exclusion criteria included being the primary care-giver of a child (e.g., by adoption or foster care), having experienced more than three prior miscarriages (to control for possible endocrine irregularities), current use of hormonal preparations, chronic medical or neurological disorders, psychiatric illness (e.g., major depressive disorder), current use of psychotropic medications, smoking four or more cigarettes per day, intake of four alcoholic drinks or more a day for 3 years or equivalent, history of head injury that resulted in loss of consciousness or concussion, pregnancy complications (e.g., preeclampsia, cervical insufficiency), and thrombotic problems during late pregnancy or delivery. In addition, women who experienced preterm labor (prior to 37 weeks' gestation) or whose babies spent more than 7 days in the neonatal intensive care unit were removed from the study.

Because it was not possible to recruit women prior to their pregnancy for baseline measurements of cognitive functioning, healthy nulliparous, nonpregnant, nonbreastfeeding women between the ages of 19 and 41 years ($M = 28.8$) were recruited to serve as a control for the possibility of practice effects associated with repeated administration of neuropsychological tests. Inclusion criteria for the control women required that they be 18 years or older, be fluent in English or French, have a minimum of 12 years of formal education and have a history of regular menstrual cycles. Apart from those specific to pregnancy, the exclusion criteria were the same for women in the control group.

Materials

Mood and sleep questionnaires

Edinburgh Postnatal Depression Scale (EPDS): The EPDS (Cox, Holden, & Sagovsky, 1987) is a 10-item self-report scale designed to measure levels of depressive symptoms experienced during the past week. It consists of statements related to different aspects of mood and anxiety; for each, women were required to indicate which of four choices best described how they felt. Higher scores indicate more depressed mood. The EPDS has been validated for use with pregnant women in various countries (Adewuya, Ola, Dada, & Fasoto, 2006; Adouard, Glangeaud-Freudenthal, & Golse, 2005; Bergink et al., 2011; Ji et al., 2011; Murray & Cox, 1990; Rubertsson, Börjesson, Berglund, Josefsson, & Sydsjö, 2011; Su et al., 2007), as well as for use in nonpregnant mothers (Cox, Chapman, Murray, & Jones, 1996). Although we are aware of no studies that have validated the EPDS for nulliparous women, we used it as a subjective mood measure for the control group in order to maintain consistency between groups.

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Pittsburgh Sleep Quality Index (PSQI): The PSQI (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) is a 10-item self-report instrument that measures the quality and patterns of sleep. It differentiates seven areas of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction over the last month. For each item, women chose one of four statements. Higher scores indicate more sleep disturbances. The validated French form (Blais, Gendron, Mimeault, & Morin, 1997) was used for French-speaking participants.

Neuropsychological Tests

Vocabulary (Wechsler Adult Intelligence Scale – III)—This subtest measures expressive vocabulary and verbal knowledge that is purported to be a good estimate of crystallized intelligence and general intelligence (Wechsler, 1997).

Rey Auditory and Verbal Learning Test (Rey AVLT)—The Rey AVLT (Schmidt, 1996) is a test of rote verbal learning and memory. After hearing a list of 15 concrete, unrelated words, participants were asked to recall as many words as they could. The same list was read five consecutive times. The dependent variables of interest were scores on learning Trial 1 and Trial 5, immediate recall following an interference list, delayed recall following a 30-min delay, and recognition of the previously learned words from a list of distracter words. Alternate forms of all the tests of verbal memory were used for each test session.

Logical Memory (Wechsler Adult Intelligence Scale–III)—This subtest (Wechsler, 1997) measures the immediate and delayed contextual recall of short stories. Participants were read a standardized short story and were asked to recall the paragraph verbatim immediately following presentation and again, following a 30-min delay.

Verbal Paired Associates (Wechsler Adult Intelligence Scale–III)—This test (Wechsler, 1997) assesses the learning and retention of associated and unassociated word pairs. Participants were read a list of 10 word pairs, 3 consecutive times. Immediately following each presentation, the examiner provided the first word of a pair and participants were required to provide the second word. A delayed recall trial was administered following a 30-min delay.

Digit Span (Wechsler Adult Intelligence Scale–III)—This a task of attention and working memory (Wechsler, 1997). The examiner read aloud sequences of numbers at a rate of one per second. The sequences increased by one digit until the participants failed two consecutive learning trials. The forward portion, mea suring attention skills, required participants to repeat sequences the same order as presented. The reverse portion, which measures working memory abilities, required the participants to recall the numerical sequence in the reverse order.

Letter-Number Sequencing subtest (Wechsler Adult Intelligence Scale–III)—In this test of working memory (Wechsler, 1997), the examiner read aloud a combination of

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numbers and letters and participants were required to recall the numbers first, ascending order, followed by the letters in alphabetical order.

Tower of London (TOL)—The TOL (Culbertson & Zillmer, 2000) measures problem-solving and planning skills. Participants were required to replicate different combinations of colored beads on pegs using the least number of moves as possible.

Mental Rotations Test—The Mental Rotations Test (Vanden berg & Kuse, 1978) measures the ability to quickly and accurately mentally rotate three-dimensional figures. Participants were shown a series of rotated geometric figures and were asked to determine which 2 out of 4 rotated figures corresponded to a target figure One point was awarded for each item in which both alternatives were correctly identified, thereby reducing the likelihood that the participants guessed correctly. Alternate forms were used for each test session.

Block Design (Wechsler Adult Intelligence Scale–III)—This test (Wechsler, 1997) assesses the ability to analyze and synthesize abstract visual stimuli. Participants were presented with a series image designs and were required to reconstruct each image using 3-dimensional, two-colored blocks.

Spatial Span (Wechsler Adult Intelligence Scale–III)—This test (Wechsler, 1997) measures spatial attention and spatial working memory in which the examiner taps a sequence of blocks at rate of one per second. The sequences increase by one digit until the participants fail two consecutive learning trials. The forward portion, associated with attention skills, required participants repeat sequences in the same order as presented. The reverse portion, associated with working memory abilities, required the participants to recall the sequence in the reverse order.

Cancellation Task (Montreal Neurological Institute)—In this test of attention and visual scanning, the participants were required to scan a page filled with similar designs and cross out the target shapes as fast as they could.

Digit Symbol (Wechsler Adult Intelligence Scale–III)—This subtest (Wechsler, 1997) assesses visuomotor scanning and attention. Using an answer key, participants were required to draw symbols corresponding to target numbers as fast as possible.

Procedure

Contact information for women in the pregnancy group was acquired through sign-up sheets presented to attendees of prenatal classes at the designated clinics and hospitals. Brochures were handed out during the prenatal visits and placed in the waiting rooms of the Obstetrics and Gynecology departments of the participating hospitals. The control group responded to notices posted at the university and to newspaper advertisements. Women who expressed interest in the study were contacted by telephone to complete a confidential screening questionnaire to ensure that they met all selection criteria. The study was approved by the Institutional Review Board, Faculty of Medicine, McGill University, Montreal, Canada; by the Research Ethics Board, Royal Victoria Hospital, McGill University Health Centre,

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Montreal, Canada; and by the Research Ethics Committee, St. Mary's Hospital Center, Montreal, Canada. Written informed consent was obtained from all participants.

Participants from the pregnancy group were also invited to sign an authorization form, approved by the Research Ethics Board, Faculty of Medicine, McGill University, which provided permission for the researchers to obtain information from their obstetrical medical charts on their health during their pregnancy and postpartum periods, on their delivery procedures and interventions, on medication use and health of the infant. The initial test session for women in the pregnancy group was scheduled between their 34th and 38th week of gestation, and the second test session was - scheduled approximately 12 weeks after delivery. The control participants were scheduled to be tested once during the midluteal phase of their menstrual cycle and once during the menstrual phase of their cycle. The two phases of the menstrual cycle were chosen . to parallel the hormonal profiles experienced by the pregnancy group during their visits (i.e., high levels of E_2 and P during pregnancy and the midluteal phase and low levels of these hormones at postpartum and the menstrual phase). The two testing sessions for the controls were scheduled at an interval of 16 weeks apart to ensure that the interval between test sessions was identical to that of the pregnancy group. The order of test sessions for the control group was randomly counterbalanced according to cycle phase so that at Visit 1, half of the women were tested during the midluteal phase and half were tested during the menstrual phase. Women were tested during the alternate phase at Visit 2.

Prior to their testing sessions, women were provided with saliva collection kits (Phoenix Bio-Tech Corp, Mississauga, Ontario) for assay of CORT levels and measurement of their CAR. They were instructed to collect two saliva samples on two consecutive days during the four days prior to their visit to the lab. The first sample was obtained upon awakening, and the second, 30 minutes after awakening. Women were instructed to place the vials in their home freezer and bring them to the laboratory when they attended their test sessions.

All participants were tested in the Psychoendocrine Laboratory at McGill University. Blood samples were drawn by a certified blood technician at the beginning of each session for measurement of E_2, P, T, PRL and SHBG. The EPDS was then filled out and the battery of neuropsychological tests was administered. Each test session lasted approximately two hours. A 15-min break was given half way through the session and snacks and beverages were offered to the participants. Women were compensated $30 per session to cover travel expenses.

Participants completed the PSQI at home at their convenience during the week following each test session. The questionnaire was returned by mail in preaddressed, stamped envelopes.

Women in the pregnancy group were welcome to bring their baby to the postpartum test session if they were unable to arrange babysitting services. A baby swing and a bassinette were available in the lab.

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Hormone Assays

Blood samples—A 10-ml blood sample was collected via venipuncture from the antecubital space using Vacutainer tubes. The blood was immediately centrifuged and the serum separated and stored at −50 °C for subsequent assay. Serum levels of E_2, P, T, PRL, and albumin were assayed in the Biochemistry Laboratory of the Royal Victoria Hospital, MUHC. Serum levels of E_2 were assayed by automated competitive immunoassay direct chemiluminescence using the ADVIA Centaur Estradiol-6 III kit (Bayer Corporation). The minimum sensitivity and range of this assay was 25.7–3670 pmol/L. Serum P levels were assayed by automated competitive immunoassay direct chemiluminescence using the ADVIA Centaur Progesterone kit (Bayer Corporation). The sensitivity and range of this assay was 0.48–190.8 nmol/L. T levels were assayed by automated competitive immunoassay direct chemiluminescence using the ADVIA Centaur Testosterone kit (Bayer Corporation). The sensitivity and range of this assay was 0.35–52.1 nmol/L. PRL levels were determined by automated competitive immunoassay direct chemiluminescence using the ADVIA Centaur Prolactin kit (Bayer Corporation, U.S.A.). The sensitivity and range of this assay was 0.3–200 ng/ml and the interassay coefficient of variance (CV) was 6.4%. Albumin levels were determined using biochromatic digital endpoint using the Albumin Assay kit (Beckman). The sensitivity and range of this assay was 10–70 g/L, and the interassay CV was 2.3%. Assays of SHBG were conducted at the Endocrine Laboratory, Hôtel Dieu Hospital, Montreal, Quebec. SHBG levels were determined by electrochemiluminescence immunoassay using the ELECSYS SHBG kit (Roche, Switzerland). The sensitivity of this test is 2.0 nmol/L. Levels of free T were estimated by computing the free androgen index (FAI) calculated by the equation 100T/SHBG and has been demonstrated to be a reliable estimate of bioavailable T (Ivison, Robinson, & Diver, 2002; Nanjee & Wheeler, 1985).

Saliva samples—The saliva samples were stored in our laboratory at −50 °C for subsequent assay. Assays of free CORT were conducted for each saliva sample in the laboratory of Dr. D. Walker, Douglas Mental Health University Institute, Montreal, Quebec. Salivary CORT concentrations were measured using a sensitive enzyme immunoassay kit (Salimetrics, State College, PA). The limit of detection of this assay was 0.012 μg/dl with a range of 0.012–3.0 μg/dl. The intra- and interassay coefficient of variation was 2.14% and 2.86% respectively. Two ratios for area under the curve (AUC) of CAR were calculated using the trapezoidal method (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). The first, AUC with respect to ground (AUCg) is associated with relative hormonal output whereas the second, AUC with respect to increase (AUCi), is associated with the change over time which is considered to represent the sensitivity of the system.

Statistical Analyses

Statistical analyses were conducted using the PASW statistical package software (version 18). Independent-samples *t* tests were conducted to determine whether group (pregnancy vs. control) differences were present on various demographic measures. Univariate analyses of variance (ANOVAs) were used to determine whether differences in hormone levels were present between groups at each visit. Repeated measures ANOVAs were used to determine whether differences in hormone levels were present between visits for each group. A

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Principal Component Analysis (PCA) was performed using the standardized z-scores of the cognitive tasks. The principle axis method was used to extract the components followed by a varimax (orthogonal) rotation. Only components displaying eigenvalues greater than 1 were retained. Based on the results of the PCA, the z-scores of highly loading variables were summed to form composite scores. Two-way mixed designed multivariate analyses of covariance (MANCOVA) procedures were performed between raw scores of cognitive tasks forming specific PCA components. Group (pregnancy vs. control) served as the between subjects factor, Time (Visit 1 vs. Visit 2) as the within-subject factor and mood (EPDS) and sleep (PSQI) scores as the covariates. Significant main effects and interaction effects were further explored with univariate analyses and Tukey post hoc tests. Hierarchical regressions, controlling for the effects of mood and sleep, were then used to examine the relationship between hormone levels and composite scores of neuropsychological tests. The presence of curvilinear relationships was tested with the addition of quadratic terms to the regression models. Thus, each component score was first regressed on mood and sleep in Step 1, followed by the linear term for the hormonal variables of interest in Step 2 and finally on the quadratic term for the hormonal variables of interest in Step 3. Values for the two visits were entered as different regressions. Square root or log transformations were used for highly skewed data.

Results

A total of 305 women initially expressed interest in the study, of whom 109 met selection criteria and were enrolled. Fifty-five women from the pregnancy group concluded the study (see Table 1 for reasons of noncompletion). The mean interval between Visit 1 and Visit 2 was 18.1 week. At the postpartum visit, an average of 14.0 weeks following delivery, 28 women (50.9%) were breast-feeding and not using hormonal contraceptives, eight women (14.5%) were breastfeeding and using a hormonal contraceptive (norethindrone), 12 women (21.8%) were breastfeeding but did not report whether or not they were using hormonal contraceptives, four women (7.2%) were formula-feeding and not using hormonal contraceptives, and three women (5.4%) were formula-feeding and using a hormonal contraceptive (cyproterone acetate and ethinyl estradiol; levonorgestrel and ethinyl estradiol; norgestimate and ethinyl estradiol). Thirty-four women (61.8%) had a vaginal delivery, 17 women (30.9%) had delivery by cesarean section and type of delivery information was not available for four women (7.2%). Twenty-two women (40.0%) delivered girls, 29 women (52.7%) delivered boys and information was not available for four women (7.2%).

A total of 113 nonpregnant women expressed interest in the study. Of these, 45 women met the selection criteria and were enrolled and 21 women completed the study (see Table 1 for reasons of noncompletion). The mean interval between Visit 1 and Visit 2 for controls was 18.7 weeks.

Participant Characteristics

There were no significant differences in age, years of education, or vocabulary scores between the pregnancy and control groups (Table 2). All women were well educated, with

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an average of 18 years of formal education and mean vocabulary scores fell well within the average range.

No significant differences in cognitive performance scores were observed between women who were breastfeeding and those who were not. A comparison of the cognitive scores of women who brought their infants to the test session to scores of women who did not bring their infants found no significant visit by group interactions indicating that the infants' presence did not significantly influence performance on the cognitive tests. Therefore, data from all subgroups of pregnant women were collapsed for the analyses.

Mood and Sleep

Multivariate analyses (MANOVA) on the EPDS mood scores demonstrated no significant effect of group, $F(1, 74) = 0.08$, $p = .78$; visit, $F(1, 74) = 0.09$, $p = .76$; or visit by group interaction, $F(1, 74) = 0.01$, $p = .91$; Table 3). Mean mood scores for both groups fell well within the normal range at both visits. The MANOVA of PSQI scores indicated no significant effect of group, $F(1, 74) = 0.12$, $p = .73$; visit, $F(1, 74) = 0.12$, $p = .72$; or visit by group interaction, $F(1, 74) = 0.01$, $p = .94$. Mean sleep scores of both groups reveal only mild sleep difficulties.

Hormone Levels

Univariate ANOVA analyses for hormone levels during Visit 1 show significant differences between the pregnancy and control groups (Table 4). Levels of E_2, $F(1, 68) = 41.83$, $p < .001$; P, $F(1, 69) = 569.74$, $p < .001$]; T, $F(1, 71) = 51.88$, $p < .001$]; PRL, $F(1, 71) = 103.48$, $p < .001$; CORT AUCg, $F(1, 74) = 6.68$, $p = .012$; and SHBG, $F(1, 71) = 216.23$, $p < .001$, were significantly higher in pregnant women compared with controls, whereas FAI, $F(1, 71) = 27.76$, $p < .001$, levels were significantly lower in pregnant women. Levels of CORT AUCi, $F(1, 74) = 0.027$, $p = .34$, were not significantly different between groups at Visit 1. During Visit 2, levels of E_2, $F(1, 69) = 32.12$, $p < .001$; P, $F(1, 69) = 20.30$, $p < .001$; T, $F(1, 69) = 30.76$, $p < .001$; and FAI, $F(1, 69) = 13.53$, $p < .001$, were lower in pregnant women compared with controls, whereas levels of PRL, $F(1, 69) = 14.39$, $p < .001$, were significantly higher in pregnant women. Trends for CORT AUCg, $F(1, 71) = 3.84$, $p = .054$, and CORT AUCi, $F(1, 71) = 3.58$, $p = .062$, were obtained showing that levels tended to be lower in the pregnancy group. There were no significant differences between groups for SHBG, $F(1, 69) = 0.096$, $p = .76$, at Visit 2.

Repeated measures ANOVAs showed that for the pregnancy group, levels of E_2, $F(1, 49) = 113.34$, $p < .001$; P, $F(1, 50) = 2537.49$, $p < .001$; T, $F(1, 52) = 244.98$, $p < .001$]; PRL, $F(1, 52) = 176.95$, $p < .001$; CORT AUCg, $F(1, 52) = 57.26$, $p < .001$; and SHBG, $F(1, 52) = 865.76$, $p < .001$, were significantly higher during Visit 1 (pregnancy) compared with Visit 2 (postpartum). Levels of FAI, $F(1, 52) = 23.97$, $p < .001$, were significantly lower during Visit 1, whereas no differences were present for CORT AUCi, $F(1, 52) = 0.333$, $p = .57$. Repeated measures ANOVAs showed that for controls, FAI, $F(1, 15) = 5.77$, $p = .03$, levels were significantly lower during Visit 1 compared with Visit 2. No significant differences were obtained for levels of E_2, $F(1, 15) = 0.000$, $p = .098$; P, $F(1, 15) = 0.001$, $p = .97$; T, $F(1, 15)$

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= 3.65, $p = .08$; PRL, $F(1, 15) = 0.37$, $p = .55$; CORT AUCg, $F(1, 19) = 0.02$, $p = .90$; CORT AUCi, $F(1, 19) = 0.001$, $p < .97$; and SHBG, $F(1, 15) = 0.431$, $p = .052$.

Neuropsychological Tests

The mean scores and standard deviations for neuropsychological tests are seen in Table 5. Results of the principal component analysis indicated that the first five components, accounting for 71.8% of the total variance, displayed eigenvalues greater than 1 and therefore only these components were retained. Cognitive tasks and corresponding factor loadings are presented in Table 6. When interpreting the rotated factor pattern, an item was considered to load on a given component if the factor loading was 0.40 or greater (boldface in Table 6). If an item loaded on more than one component, it was retained only within the component for which its loading was the highest. Using these criteria, seven items were found to load on the first component labeled “Verbal Memory,” four items loaded on the second component labeled “Spatial Ability,” two items loaded on the third component labeled “Paragraph Recall,” three items loaded onto the fourth component labeled “Executive Functions,” and one item loaded onto the fifth component labeled “Attention.”

Component 1: Verbal Memory

For the completion of MANCOVA, missing values were replaced by group means. MANCOVA analyses for Verbal Memory demonstrated no significant effect of visit, $F(7, 64) = 0.86$, $p < .54$; or visit by group interaction, $F(7, 64) = 0.31$, $p < .94$. However, multivariate analyses indicated a significant effect of group, $F(7, 64) = 4.99$, $p < .001$. Significant univariate group effects were present for the Rey AVLT Trial 1, $F(1, 70) = 18.91$, $p < .001$; Rey AVLT Immediate Recall, $F(1, 70) = 4.51$, $p = .04$; and Paired Associates immediate recall, $F(1, 70) = 6.44$, $p = .01$. Trends were also observed for Rey AVLT Trial 5, $F(1, 70) = 3.84$, $p = .054$; and Rey AVLT delayed recall, $F(1, 70) = 3.39$, $p = .070$. Women in the pregnancy group performed significantly worse than the controls on these tests of verbal memory at both visits. The overall regression model performed to examine the linear (Step 2) and quadratic (Step 3) effects of hormone levels on verbal memory, controlling for mood and sleep (Step 1), was not significant for Visit 1 or 2. However, a moderate negative correlation was observed between Verbal Memory component scores and CORT AUCg-quadratic levels during the pregnancy ($r = −0.32$, $p = .01$) and postpartum visits ($r = −0.35$, $p = .005$).

Component 2: Spatial Ability

MANCOVA results for Spatial Ability showed no significant effect of visit, $F(4, 67) = 0.98$, $p = .42$. Strong trends were observed for visit by group interaction, $F(4, 67) = 2.42$, $p = .056$; and effect of group, $F(4, 67) = 2.47$, $p = .053$, but failed to reach conventional levels of significance. Examination of means indicate that women in the pregnancy group tended to perform worse on the Mental Rotations task compared with controls. Regression analyses examining the effects of hormone levels on Spatial Ability, demonstrated that EPDS scores ($\beta = −0.34$, $p = .04$) entered in Step 1 explained 17.7% of the variance, $F(2, 49) = 5.05$, $p = .01$, during the pregnancy visit. Although the overall regression model was not significant for Visit 2, a moderate negative correlation was observed between Spatial Ability component scores and CORT AUCg-quadratic levels ($r = −0.34$, $p = .004$).

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Component 3: Paragraph Recall

MANCOVA analyses for Paragraph Recall demonstrated no significant effect of visit, $F(2, 69) = 0.46$, $p = .63$; group, $F(2, 69) = .87$, $p = .42$; or visit by group interaction, $F(2, 69) = 0.87$, $p = .42$. At Step 3 of a regression performed to examine the effects of pregnancy hormone levels on Paragraph Recall, P-quadratic ($\beta = -6.18$, $p = .001$), P-linear ($\beta = 5.91$, $p = .001$), PSQI ($\beta = -0.73$, $p = .002$), and EPDS ($\beta = -0.65$, $p = .003$) explained 49.9% of the variance, $F(14, 49) = 6.58$, $p = .01$. However, the zero-order correlations between these factors and the dependent variable were weak and nonsignificant. Moderate negative correlations were observed between the Paragraph Recall component scores and PRL-linear ($r = -0.32$, $p = .008$) and PRL-quadratic ($r = -0.31$, $p = .01$). The overall regression model was not significant for Visit 2.

Component 4: Executive Function

MANCOVA analyses for Executive Functions (working memory and processing speed) indicated a significant effect of visit, $F(3, 68) = 3.34$, $p = .02$, and group, $F(3, 68) = 2.88$, $p = .04$, but no significant visit by group interaction, $F(3, 68) = 0.48$, $p = .69$. Univariate visit effect was significant only for Digit Symbol, $F(1, 70) = 5.90$, $p = .02$, showing that women in both the pregnancy and control groups performed better during visit two, suggesting that their improved performance occurred because of a practice effect. In the same vein, the univariate group effect was significant only for Digit Symbol, $F(1, 70) = 7.41$, $p = .01$, such that women in the pregnancy group performed worse than the controls at both visits. In a regression performed to examine the effects of pregnancy hormone levels on Executive Function, entry of EPDS ($\beta = -0.44$, $p = .004$) in Step 1 explained 17.8% of the variance, $F(2, 46) = 4.75$, $p = .01$. Furthermore, entry of P-quadratic ($\beta = -3.59$, $p = .052$), P-linear ($\beta = -3.55$, $p = .05$), EPDS ($\beta = -0.76$, $p = .001$) and CORT AUCi-quadratic ($\beta = -0.35$, $p = .03$) in Step 3 explained 49.0% of the variance [$F(14, 46) = 2.20$, $p = .03$]. However, the zero-order correlations between these factors and Executive Function scores were weak and nonsignificant. A moderate negative correlation was observed between Executive Function scores and PRL-linear levels ($r = -0.34$, $p = .008$). The overall regression model was not significant for Visit 2.

Component 5: Attention

MANCOVA results demonstrated no significant effect of visit, $F(1, 70) = 1.39$, $p = .24$; group, $F(1, 70) = 0.39$, $p = .53$, or visit by group interaction, $F(1, 70) = 0.10$, $p = .75$. In a regression performed to examine the effects of postpartum hormone levels on Attention, entry of E_2 ($\beta = -0.51$, $p = 0.24$; $r = -.39$, $p = .002$) and CORT AUCi-linear ($\beta = -0.30$, $p = .03$; $r = -.35$, $p = .005$) in Step 2 explained 33.0% of the variance, $F(8, 51) = 2.65$, $p = .19$, and were moderately correlated with Attention scores. The overall regression model was not significant for Visit 1.

Discussion

The goal of this prospective study was to examine the cognitive changes that occur during late pregnancy and the early postpartum period, as well as their possible association with fluctuating hormone levels. Our first hypothesis that women in the pregnancy group would

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perform significantly worse than women in the non-pregnant control group was partially supported; this occurred on two tests of verbal recall (Rey AVLT and Paired Associates) and on a task of processing speed (Digit Symbol). Our prediction that a decrease in scores would be most prominent in the postpartum period was not supported.

Contrary to our second hypothesis, only few associations were found between hormone levels and cognitive performance scores. Regression analyses revealed negative linear associations between attention scores and E_2 levels and between attention scores and CORT levels during the postpartum visits such that lower levels of both E_2 and CORT were associated with better performance. In addition, moderate negative quadratic correlations were observed between CORT levels and verbal recall scores during both pregnancy and the postpartum periods indicating that lower and higher levels of CORT were associated with poorer performance, whereas moderate levels were associated with better performance. The negative quadratic correlation between CORT and spatial abilities only occurred at the postpartum visit. Quadratic PRL levels were negatively correlated with Paragraph Recall scores during pregnancy, whereas linear PRL levels were negatively correlated with both Paragraph Recall and Executive Functions scores during the same visit.

Our findings that women from the pregnancy group performed worse than those in the nonpregnant control group on some, but not all, verbal memory tasks is consistent with those of other studies. A persistent impairment on verbal list recall during all trimesters of pregnancy and up to 32 weeks postpartum has been previously observed (Buckwalter et al., 1999; de Groot, et al., 2003; 2006). During late pregnancy, women displayed less effective learning strategies (Buckwalter et al., 1999). In a cross-sectional study, multigravid women scored significantly worse than controls on verbal list recall following a brief delay, but similar to the present findings, no differences were observed between pregnant women and controls on a recognition task (Sharp et al., 1993). Other studies have failed to find an impairment of verbal recall during pregnancy and the postpartum period (Brindle et al., 1991; Vanston & Watson, 2005), but the use of different memory tests as well as lack of conformity between participant characteristics (e.g., week of gestation, pregnancy history) may account for some of these differences. Taken together, these results suggest that memory encoding and retrieval, but not recognition memory are negatively affected during the last trimester of pregnancy.

Consistent with previous findings, we observed worse performance on word paired-associative learning, a test of verbal memory, during the third trimester of pregnancy and the early postpartum period compared with nonpregnant controls. When women were asked to remember pairs of meaningless syllables, they displayed poorer performance during late pregnancy and up to 12 weeks' postpartum, but this was no longer the case at six and 12 months after delivery (Silber et al., 1990). In a more recent study, performance on a paired-associate task was worse only during the second and third trimesters of pregnancy compared with controls (Glynn, 2010). It therefore appears that the increased difficulties in learning word-pair associations may be restricted to the second and third trimesters of pregnancy and the impairment endures until sometime between 12 and 20 weeks' postpartum.

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Our failure to find impairments on the paragraph recall test in the pregnancy group is consistent with some pregnancy studies (Crawley et al., 2003; Harris et al., 1996) but not with others that had a small sample size (Keenan et al., 1998) and tested only during the first few days postpartum (Eidelman, Hoffman, & Kaitz, 1993). The evidence to date suggests that, during pregnancy and the postpartum period, women may experience difficulties in the encoding and retrieval of unrelated verbal information but not of contextual information.

Compared with verbal abilities, visuospatial abilities may be less affected by gestational and postpartum events. In the present study, no significant differences were observed between the pregnant women and the nonpregnant women on tasks of visuospatial abilities, although women tended to have lower scores on the Mental Rotations (a spatial task) compared with controls. While there is some inconsistency, most studies found no differences in performance between pregnant women and nonpregnant controls on spatial tasks (Brussé, Duvekot, Jongerling, Steegers, & De Koning, 2008; Eidelman et al., 1993; Glynn, 2010; Sharp et al., 1993).

In contrast to previous studies, women in the pregnancy group performed more poorly on a processing speed task compared with the controls (de Groot, et al., 2003; de Groot, et al., 2006; Harris et al., 1996; Vanston & Watson, 2005). A factor that may account for the inconsistency is the use of different time intervals for completion of processing speed tasks. Since women in our pregnancy group did not make more errors, but completed fewer items, it may be that performance decreases after a certain amount of sustained effort. While our data did not allow us to make this distinction, this would be worth investigating.

The negative quadratic relationship between CORT levels and verbal memory is consistent with the hypothesis that CORT influences cognitive abilities following an inverted-U function whereby high and low levels of CORT are detrimental to performance whereas moderate levels are optimal for performance (for review, see de Kloet, Oitzl, & Joëls, 1999; Lupien & McEwen, 1997), although one study reported a positive relation between serum CORT levels and performance on tasks of verbal memory during pregnancy (Glynn, 2010). The fact that the inverted-U function occurred both during the pregnancy and postpartum periods in the present study, even though CORT levels differed significantly at those two points in time, suggests that the body accommodates to the changes in hormonal levels over the course of pregnancy.

To our knowledge, this is the first study to find a relationship between PRL levels and cognitive functioning in young healthy pregnant women. The negative linear association between PRL levels and Executive Function scores suggests that higher levels of PRL are detrimental to executive function abilities. The negative linear and quadratic associations between PRL and Paragraph Recall scores (verbal memory) suggests that high and low levels of PRL are detrimental to verbal memory whereas moderate levels are optimal. Although the mechanism by which PRL may influence cognitive function is unknown, it is possible to speculate that it may be associated with the known inhibitory effects of dopamine (DA) on PRL (Ben-Jonathan & Hnasko, 2001). Indeed, in studies of nonpregnant women, PRL levels are taken as an indirect index of DA function (Kim et al., 2009), where high levels of PRL are indicative of lower levels of DA and vice versa. In human imaging studies,

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a negative relationship between dopamine receptor ligand binding and performance on working memory tasks in both healthy humans and in patients with schizophrenia occurred (Aalto, Brück, Laine, Någren, & Rinne, 2005; Abi-Dargham et al., 2002) indicating that higher levels of DA activity were associated with better performance. In addition, higher DA receptor binding potential was positively correlated with better performance on verbal memory tasks (Takahashi et al., 2007), but these effects may be specific to list learning since a second study failed to observe such associations in paragraph recall and paired associates tasks (Lumme et al., 2010). However, caution must be taken in generalizing these findings to our current results as associations between PRL levels and cognitive functioning were observed only during pregnancy when PRL levels were very high and the regulation of PRL by DA may be different during pregnancy.

Contrary to our hypothesis, no consistent associations were observed between performance scores and levels of E_2, P or T during either visit. The negative linear correlation with attention scores during the postpartum visit was the only association observed with E_2 levels, consistent with others (Buckwalter et al., 1999). However, higher levels of E_2 were positively associated with attention scores in non pregnant women (Portin et al., 1999) and women who had higher levels of E_2 early in gestation had poorer performance on verbal memory (Glynn, 2010).

Cognitive changes during pregnancy and the postpartum period may also be related to gestational and postpartum neuronal plasticity. In female rats, spine density in the CA1 region of the hippocampal formation was significantly higher during late pregnancy and lactation compared with nulliparous female rats (Kinsley et al., 2006). There is also evidence that hippocampal neurogenesis is modulated by reproductive history. For example, postpartum primiparous rats showed fewer and shorter dendritic branch points in the CA1 and CA3 hippocampal regions compared with nulliparous and multiparous rats, whereas multiparous females had higher spine density in the CA1 hippocampal region (Pawluski & Galea, 2006). In addition, during the early postpartum period, primiparous and multiparous rats experienced a decrease in cell proliferation in the dentate gyrus compared with nulliparous rats (Pawluski & Galea, 2007; Leuner, Mirescu, Noiman, & Gould, 2007). Although there is evidence that exposure to pup stimulation has modulating effects on neurogenesis, findings are inconsistent. In one study, a decrease in cell survival in the dentate gyrus was present in the primiparous rats regardless of exposure to pups (Pawluski & Galea, 2007). Conversely, a second study observed that suppression of cell proliferation was prevented by the removal of nursing pups (Leuner et al., 2007). The decrease in cell proliferation was also found to be dependent on elevated corticosterone levels associated with nursing pups, suggesting that changes in adrenal steroids related to pup stimulation may inhibit neurogenesis in adult female rats. Furthermore, treatment with gestation or gestation-like levels of E_2 + P or with PRL in rats results in an increase in spine density in the CA1 region of the hippocampus (Kinsley et al., 2006), cell proliferation in the subventricular zone (Furuta & Bridges, 2005; Shingo et al., 2003) and a larger medial preoptic area (Keyser-Marcus et al., 2001). In humans, a reduction in brain size has been observed in pregnant women compared with prepregnancy volumes (Oatridge et al., 2002). Investigations of the permanency of brain changes during reproductive periods suggest that some changes may be transitory and return to prepregnancy levels following birth and

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lactation, whereas others may be more permanent (Keyser-Marcus et al., 2001; Oatridge et al., 2002; Bodensteiner, Cain, Ray, & Hamula, 2006; Love et al., 2005; Gatewood et al., 2005). The underlying mechanisms and the relationship between neuronal changes and cognitive functioning remain unclear.

A limitation of this study is that participants were tested only during the third trimester of pregnancy. The interpretation of our results is also limited by our relatively small sample size. Although the number of women initially recruited into the study met our requirement for the desired effect size, the attrition rate was higher than anticipated. The majority of participants in the pregnancy group brought their infants with them during Visit 2 as most were breastfeeding and could not make arrangements for childcare. Although this is a confounding factor, it was consistent across the majority of participants. Because participants in the present study were highly educated and in stable relationships, results from this study cannot be generalized to women with a lower level of education or to those who are not in a stable relationship. Finally, hormonal measurements were taken from serum and saliva samples and their correlation with hormone levels in different brain regions is unknown. The strength of this study is that we tested the same women during the third trimester of pregnancy and postpartum and had a nonpregnant group to control for possible practice effects of administering a battery of neuropsychological tests on two occasions.

In summary, the major findings of the present study were that women in the pregnancy group performed worse than nonpregnant controls on tasks of verbal memory and processing speed but no differences in their pregnancy versus postpartum test scores were apparent. Moreover, all mean performance scores fell within the average range in both groups, indicating that the women were not clinically impaired at any time. The inverted-U functions between cortisol levels and verbal memory and spatial abilities suggest that very high and very low levels of CORT are associated with poorer performance in certain cognitive domains. Finally, to our knowledge, the demonstration of the negative effects of too high or too low PRL levels on executive functions and paragraph recall in healthy pregnant women is a novel finding. No consistent associations were observed between levels of E_2, P and T and performance scores.

Future studies are needed to investigate the timeframe of the onset and the duration of changes in cognitive function during pregnancy and the postpartum period that we observed. Examination of the effect of breastfeeding on cognitive change during the postpartum period is also needed. Finally, further studies are needed to more clearly explicate the relationship between PRL and DA levels on cognitive changes during pregnancy.

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Table 1

Reasons Participants Did Not Complete Test Sessions

Pregnancy		Control	
Reason	***N***	**Reason**	***N***
Total originally recruited	109	Total originally recruited	45
No longer interested	18	No longer interested	14
Lost contact	18	Lost contact	5
Gave birth before scheduled visit 1	8	Began use of hormonal contraceptive	3
Medical complications	5	Out of town	1
Out of town	2	Menstrual complication	1
Baby born prematurely	1		
Baby in quarantine	1		
Colicky baby	1		
Total who completed the study	55	Total who completed the study	21

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Table 2

Mean (±SD) Age, Education, and Vocabulary Score

	Pregnancy	Control	*p*
Age (years)	31.4 (4.1)	28.8 (5.6)	.077
Education (years)	18.5 (3.1)	18.4 (2.4)	.917
Vocabulary (scaled scores)	11.3 (2.5)	12.5 (3.8)	.176

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Table 3

Mean (±SD) Mood and Sleep Scores

	Visit 1		Visit 2	
	Pregnancy (*n* = 55)	**Controls (*n* = 21)**	**Pregnancy (*n* = 55)**	**Controls (*n* = 21)**
EPDS	6.5 (3.9)	6.9 (4.5)	6.4 (4.1)	6.7 (5.1)
PSQI	6.3 (3.0)	6.5 (1.1)	6.5 (2.7)	6.7 (2.0)

Note. EPDS = Edinburgh Postnatal Depression Scale; PSQI = Pittsburgh Sleep Quality Index.

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Table 4

Mean (±SD) Serum and Saliva Hormone Levels

	Visit 1		Visit 2	
	Pregnancy (*n* = 55)	**Controls (*n* = 21)**	**Pregnancy (*n* = 55)**	**Controls (*n* = 21)**
E_2 (pmol/L)	82,357.8 (52,879.3) *†	443.9 (433.3)	104.9 (91.7) †	376.5 (282.4)
P (nmol/L)	851.3 (320.1) *†	17.8 (20.4)	4.02 (6.76) †	13.5 (15.8)
T (nmol/L)	2.63 (0.98) *†	0.87 (0.53)	0.57 (0.28) †	1.07 (0.39)
FAI	0.8 (0.4) *†	1.9 (1.2) *	1.5 (1.3) †	2.6 (1.1)
PRL (ug/L)	199.6 (79.2) *†	11.7 (10.1)	44.2 (35.7) †	10.7 (4.4)
CORT AUCg	14.7 (5.9) *†	11.1 (4.9)	9.3 (3.7)	11.4 (4.6)
CORT AUCi	1.2 (2.8)	1.9 (2.9)	0.9 (1.7)	1.9 (2.4)
SHBG (nmol/L)	336.6 (81.6) *†	53.6 (21.3)	49.8 (23.2)	47.8 (19.7)

Note. E_2 = estradiol; P = progesterone; T = testosterone; FAI = free androgen index; PRL = prolactin; CORT AUCg = cortisol area under the curve ground; CORT AUCi = cortisol area under the curve increase; SHBG = sex hormone binding globulin.

† $p < .001$ Pregnancy compared with controls during same visit.

* $p < .001$ Visit 1 compared with Visit 2 within groups.

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Table 5

Mean (±SD) Scores of Neuropsychological Tests

	Visit 1		Visit 2	
	Pregnancy (*n* = 55)	**Controls (*n* = 21)**	**Pregnancy (*n* = 55)**	**Controls (*n* = 21)**
Rey AVLT Trial 1	6.2 (1.4)†	7.6 (1.7)	6.7 (1.6)†	8.0 (1.9)
Rey AVLT Trial 5	12.5 (1.6)	13.1 (1.4)	12.9 (1.7)	13.7 (1.7)
Rey AVLT Immediate Recall	11.0 (1.9)†	11.9 (2.2)	11.3 (2.3)†	12.4 (2.2)
Rey AVLT Delayed Recall	10.8 (2.1)	11.5 (2.2)	11.1 (2.1)	12.2 (2.6)
Rey AVLT Total Recognition	39.1 (3.4)	38.4 (4.6)	38.9 (4.2)	39.0 (5.2)
Logical Memory Immediate	15.8 (4.5)	17.0 (4.6)	16.5 (4.3)	17.5 (5.2)
Logical Memory Delayed	13.9 (4.5)	14.5 (5.2)	14.3 (4.5)	15.7 (5.4)
Paired Associates Immediate	34.0 (4.5)†	36.7 (5.9)	31.9 (6.4)†	35.3 (6.3)
Verbal Paired Associates Delayed	13.2 (1.2)	13.2 (1.5)	12.3 (2.3)	12.5 (2.13)
Digit Span Backward	7.4 (2.4)	8.0 (2.5)	7.8 (2.4)	8.1 (2.4)
Letter-Number Sequencing	11.4 (2.5)	11.7 (2.2)	11.3 (2.7)	11.3 (2.3)
Tower of London	5.0 (2.2)	3.9 (2.5)	5.4 (2.3)	5.7 (2.5)
Mental Rotations	4.7 (2.6)	6.1 (2.9)	4.6 (2.9)	6.3 (2.9)
Block Design	12.3 (2.7)	12.6 (2.7)	12.6 (2.3)	13.1 (2.9)
Spatial Span Backward	7.9 (1.8)	8.1 (1.7)	7.8 (1.7)	8.8 (1.5)
Cancellation	135.5 (4.4)	134.7 (6.1)	136.3 (4.4)	135.8 (6.8)
Digit Symbol	82.4 (12.4)†*	93.5 (14.3)†*	88.1 (16.5)	95.6 (19.8)

Note. Rey AVLT = Rey Auditory and Verbal Learning Test.

† $p < .05$ Pregnancy compared with controls during same visit.

* $p < .05$ Visit 1 compared with Visit 2 within groups.

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Table 6

Rotated Component Matrix and Communality Estimates From Principle Component Analysis of Cognitive Tasks

	Components					
Items	**Verbal memory**	**Spatial ability**	**Paragraph recall**	**Executive functions**	**Attention**	**Communality estimates**
Rey AVLT delayed recall	**0.899**	0.154	0.187	0.028	0.023	0.868
Rey AVLT immediate recall	**0.882**	0.172	0.108	−0.008	−0.042	0.822
Rey AVLT trial 5	**0.831**	0.165	0.025	0.100	−0.074	0.734
Rey AVLT total recognition	**0.762**	−0.061	−0.068	0.198	0.039	0.631
Rey AVLT trial 1	**0.669**	−0.220	0.231	0.194	−0.086	0.594
Paired Associates immediate	**0.617**	0.219	0.423	0.023	0.303	0.700
Paired associates delayed	**0.558**	0.327	0.117	0.043	0.361	0.564
Block design	0.083	**0.757**	0.314	0.264	−0.005	0.748
Mental rotations	0.158	**0.722**	0.275	0.219	−0.092	0.678
Spatial span backward	0.224	**0.705**	0.031	0.235	0.070	0.609
Tower of London	−0.087	**0.705**	−0.060	−0.130	0.264	0.594
Logical memory delayed	0.179	0.144	**0.915**	0.078	−0.048	0.898
Logical memory immediate	0.143	0.111	**0.896**	0.225	−0.058	0.890
Letter-number sequencing	0.172	0.191	0.280	**0.797**	0.080	0.786
Digit span backward	0.125	0.134	0.287	**0.710**	0.389	0.772
Digit symbol	0.116	0.474	−0.256	**0.580**	−0.205	0.681
Cancellation	−0.012	0.058	−0.097	0.118	**0.777**	0.631

Note. Rey AVLT = Rey Auditory and Verbal Learning Test. Boldface indicates that the factor loading was retained in this specific component.

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