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Gestational hormone profiles predict human maternal behavior at 1-year postpartum

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ABSTRACT

In many non-human species, including primates, gestational reproductive hormones play an essential role in the onset of maternal motivation and behaviors. We investigated the associations between prepartum estradiol and progesterone and maternal behavior at 1-year postpartum in 177 women. Blood was obtained at five gestational time points and an index of quality of maternal care was determined using a well-validated mother-child interaction protocol. Women who exhibited higher quality maternal care at 1-year postpartum were characterized by unique gestational profiles of estradiol, progesterone and the estrogen to progesterone ratio; specifically by slower accelerations and levels of these hormone trajectories beginning in midgestation. Further, it appeared that both fetal sex and parity moderated these findings, with first time mothers and mothers of females showing stronger associations. In sum, these data document persisting associations between prepartum hormone profiles and human maternal behavior. More broadly, these findings add to the growing literature highlighting the perinatal period as one of critical neurodevelopment in the lifespan of the human female.

1. Introduction

Human offspring are vulnerable and require intensive and prolonged parental care. Further, humans produce relatively few offspring over the course of the lifespan. As such, it is not surprising that some evolutionary biologists have argued that the development of maternal behaviors represents one of the primary forces shaping evolution of the mammalian brain (Hrdy, 1999; MacLean, 1990). In addition, because historically, the human father was often absent, others have argued that the burden has fallen on the female nervous system to care for our vulnerable young (Kinsley and Amory-Meyer, 2011). To meet the complex and varied challenges of motherhood, the female nervous system exhibits a remarkable neuroplasticity as a result of pregnancy, parturition, lactation and offspring exposure (Hillerer et al., 2014; Kinsley, 2008). In a range of non-human mammals, compelling evidence further suggests that the perinatal endocrine milieu plays a role in this extensive neurological transformation, setting the stage for maternal motivation and responsiveness (Bridges, 1984; Terkel and Rosenblatt, 1968, 1972).

A rich and well-articulated non-primate animal literature describes the important role of sex steroid hormones in the onset and maintenance of maternal behaviors (Brunton and Russell, 2008; Numan and Insel, 2003; Saltzman and Maestripieri, 2011; Bridges, 2015). Across many species during gestation, predictable and dramatic increases in estrogens and progesterone are observed. These sex steroids are synthesized by the gonads, adrenal cortex and placenta and act on target tissues throughout the body including the brain. Among non-human primates, prepartum estrogens and the ratio of estradiol to progesterone have been linked to responsiveness to infants and rates of interaction with unrelated infants during gestation (Maestripieri and Wallen, 1995; Maestripieri and Zehr, 1998; Ramirez et al., 2004). Among nulliparous, reproductively-suppressed female marmosets, endocrine treatment that simulates the estradiol and progesterone profile of late pregnancy will result in more bar pressing to obtain visual access to a replica of an infant marmoset and to turn off an audio recording of infant distress compared to untreated females (Pryce et al., 1993). Persisting associations between gestational sex steroid levels and postpartum maternal behaviors also have been observed in non-human primate models. Late pregnancy estradiol concentrations have been linked to postpartum maternal behaviors and infant survival in tamarins, marmosets, titi monkeys, macaques and baboons (Bardi et al., 2003; Fite and French, 2000; French et al., 2004; Jarcho et al., 2012; Pryce et al., 1988).

To our knowledge, only one previous study has examined the link between gestational reproductive hormone exposures and postnatal maternal behavior in humans. Fleming et al. (1997) examined estradiol and progesterone levels four times across gestation as predictors of mothers' reports of attachment to their infants at 4-days postpartum. Mothers who exhibited higher levels of estradiol at both 5 and 7 months' gestation reported lower feelings of attachment to their infants in the early postpartum period. This same inverse association was observed

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for the estrogen to progesterone ratio. To date, it is not known whether or not prepartum sex hormone profiles predict maternal behavior or attachment beyond the immediate postpartum period.

The current study, which utilizes data from a large, prospective cohort of women, examines whether or not associations between gestational hormone profiles and observations of human maternal behavior can be detected as late as the end of the first postpartum year (no existing study has examined this question beyond 1-month postpartum).

2. Materials and methods

2.1. Participants

Participants included 177 women and their infants (97 boys and 80 girls) enrolled in a large, longitudinal study of early life influences on development. Mothers were recruited early in pregnancy from a large university medical center based on the following criteria: 1) singleton pregnancy 2) over the age of 18 3) English speaking 4) non-smoking 5) absence of any condition that could dysregulate neuroendocrine function. Exclusion criteria for the present study also included: 1) attended <3 prepartum visits 2) missing data at the 12 month postpartum visit. Demographic characteristics of the participants can be seen in Table 1. The women who met the inclusion criteria for this study did not differ from the larger sample in terms of race/ethnicity, maternal age, education level, income, cohabitation with the baby's father or parity. It was the case however, that women who had delivered preterm were less likely to have been included in the present sent of analyses. This research was approved by the University of California, Irvine, institutional review board, carried out in accordance with The Code of Ethics of the World Medical Association for experiments involving humans and all participants provided informed consent.

2.2. Overview of study design

Pregnant participants were recruited by a research nurse during the first trimester of pregnancy. Each woman then participated in a study visit at 14–16 ($M = 15.31$, $SD = 0.92$), 24–26 ($M = 25.55$, $SD = 0.93$), 30–32 ($M = 30.96$, $SD = 0.77$), 36+ weeks' gestation ($M = 36.7$, $SD = 0.83$) and also at 12-months postpartum ($M = 13.23$, $SD = 0.53$). At each prepartum visit, an interview was conducted and a blood sample obtained. At the postpartum visit, structured interviews were conducted, a blood sample was collected in a subset of women (N = 116) and maternal behaviors were observed and coded.

Table 1
Participant characteristics (N = 177).

Race/ethnicity (%)	
Latina	27
Non-Hispanic White	51
Asian	8
Other	14
Maternal age (mean years)	30.0
Education (%)	
High school or less	38
Associates or vocational degree	18
4-Year college degree	25
Graduate degree	19
Annual household income (mean US Dollars)	61,203
Parity (% primiparous)	41.8
Length of gestation (mean weeks)	39.2
Infant sex (% female)	45.2
Infant age at assessment (mean months)	12.2
Maternal sensitivity composite (mean)	9.6
Depression (mean)	4.1

Note: The range of possible scores for the maternal sensitivity composite is 3 to 12 and the range for depression is 0 to 27.

2.3. Endocrine measures

In the afternoon, blood samples (20 ml/draw) were withdrawn by antecubital venipuncture into red top vacutainers for serum collection. Blood samples sat at room temperature until clotted. Samples were then centrifuged at 2000 ×*g* (15 min). Serum was decanted into polypropylene tubes and stored at −80 °C until assayed.

17β-Estradiol levels were determined by a microtiter well competitive binding enzyme immunoassay. Serum samples were diluted 10-fold prior to testing and mixed well. Diluted samples (25 μl) were incubated with enzyme conjugate (200 μl) for 2 h at room temperature in each well. After decanting and rinsing wells with diluted wash solution three times (400 μl per well), substrate reagent (100 μl) was added to the blotted wells and incubated for 15 min at room temperature. Within 10 min after addition of stop reagent (50 μl), absorbance readings were taken at 450 nm. The assay has <0.2% cross-reactivity with estriol and estrone, and non-detectable cross-reactivity with 17α-estradiol, progesterone and 25 other naturally occurring steroids. Reported inter- and intra-assay coefficients of variance are <10% and 7%, respectively, with analytical sensitivity at 9.71 pg/ml.

Progesterone levels were determined quantitatively by competitive binding enzyme immunoassay. Thawed and thoroughly mixed serum samples were diluted 10-fold prior to assay. Diluted samples (25 μl) were dispensed into wells and incubated with enzyme conjugate (200 μl) for 1 h at room temperature. Decanted microtiter plates were washed 3 times with diluted wash solution (400 μl per well). Substrate reagent (200 μl) was added to each well and incubated for 15 min at room temperature. Enzymatic reaction was stopped with stop solution (50 μl) and absorbance readings were taken at 450 nm within 10 min. Cross reactivity of this assay is reported as 1.1% with 11-desoxycorticosterone; <0.4% with pregnenolone, 17α –OH progesterone, corticosterone; and <0.1% with estriol, 17β-estradiol, cortisol, and 3 other naturally occurring steroids. Inter-and intra-assay coefficients of variance are reported as <10% and 7% respectively with analytical sensitivity at 0.045 ng/ml.

In addition, because in humans and other species the balance of sex steroids appears to play a role in the onset of maternal behavior (Fleming et al., 1997; Jarcho et al., 2012; Maestripieri and Zehr, 1998; Rosenblatt et al., 1988), the ratio of estrogen to progesterone (E/P) was calculated and also used as a predictor of maternal behavior.

2.4. Assessment of maternal behavior

Mothers were videotaped interacting with their infants in a semi-structured 10-minute play episode when the infant was 12-months of age. From these videotapes maternal behavior coded using a laboratory protocol developed for the NICHD Study of Early Child Care and Youth Development (NICHD Early Child Care Research Network, 1999a). During this play interaction, mothers were given a standard set of age-appropriate toys and told to play with their infant as they would at home.

Categories of maternal behavior were scored on a 4-point global rating scale (1 = not at all characteristic to 4 = highly characteristic). Following the NICHD procedure, a composite rating of maternal sensitivity was created by summing ratings of sensitivity to nondistress, positive regard, and intrusiveness (reverse-coded). Coding was done by intensively trained and reliable teams of coders. All coders were blind to other data gathered on study participants. Twenty percent of sessions were selected at random, without coder knowledge, and coded again by a second independent coder to obtain an index of inter-rater reliability. Reliability for each of the three subscales comprising the composite were: sensitivity to nondistress (90%), intrusiveness (90%), and positive regard (93%).

This paradigm is an objective, behaviorally-based laboratory assessment tool for studying maternal sensitivity with standardized procedures for coding behavior. It was developed for a large NICHD