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# Hormonal Correlates for the Initiation of Breastfeeding in Bangladeshi Women

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## SUMMARY

Hormonal changes that occur prior to or during parturition are known to trigger early postpartum maternal behaviors in many mammals. In humans, little evidence has been found for hormonal mediation of early postpartum maternal behavior. In this paper, we investigate the effects of fetoplacental hormone concentrations in late pregnancy on a specific postpartum maternal behavior—the time from parturition to initiation of breastfeeding. A sample of 91 pregnant rural Bangladeshi women, enrolled in a nine-month prospective study, provided twice-weekly urine specimens and structured interviews. The subjects provided self-reports of time from parturition to initiation of breastfeeding. Specimens were assayed for urinary concentrations of human chorionic gonadotropin (hCG), pregnanediol-3α-glucuronide (PdG, a metabolite of progesterone), and urinary estrone conjugates (E1C). Parametric survival analysis was used to investigate the effects of hCG, PdG, and E1C concentrations and other covariates (mother's age, parity, and child's sex) on the duration from parturition to breastfeeding. Mother's age, parity, the child's sex, hCG, and PdG showed no association with the onset of breastfeeding. Urinary E1C was significantly associated with time to initiation of breastfeeding, explaining about 4% of the variation in the behavior. The relationship was positive so that higher prepartum concentrations of estradiol led to later times to initiation of breastfeeding. The direction of this relationship is opposite that found for many other species of mammals, but is consistent with some recent findings in primates.



**Keywords**: Maternal behavior. Breastfeeding. Bangladesh. Fetoplacental hormones. Estrogen.

Following parturition, mammalian mothers exhibit species-specific behaviors directed to the newborn. Many of these maternal behaviors are learned—acquired as infants, learned by observing other mothers, or learned through participation in the rearing of younger siblings and conspecifics (Pryce, 1993; Fleming et al., 1999). Yet for most mammals in which early postpartum maternal behaviors have been investigated, there is evidence that these behaviors are, to some extent, physiologically preprogrammed. Hormonal changes during pregnancy are involved in establishment of postpartum maternal behaviors in mice, rats, and ewes (reviewed by Fleming and Corter, 1995 and Rosenblatt, 1995) and some primates (Pryce et al., 1988; Pryce et al., 1993; Fite and French, 2000). Hormones identified as playing a role in maternal behavior are those that are elevated or change during pregnancy or at parturition, including estrogens (E), progesterone (P), prolactin (PRL), and oxytocin (Pryce, 1993; Uvnäs-Moberg, 1996; Fleming et al., 1999; Maestripieri, 1999). Additionally, an association has been found between cortisol and postpartum maternal behaviors (Fleming et al., 1990, 1997; Bahr et al., 1998).

In rats, hormonal changes in levels of P, E, and PRL at the end of pregnancy trigger maternal behaviors (Bridges, 1990; Numan, 1994). These effects are demonstrated experimentally by administering exogenous hormones to virgin ovariectomized rats, who immediately display characteristic maternal behaviors toward pups (Bridges et al., 1984, 1994). The dose of exogenous E must be about fivefold higher than peripartum concentrations to be effective, however. Initial priming by E and P for two to three weeks enhances sensitivity to the onset of maternal behaviors. Following an initial priming, E administered at concentrations representative of peripartum levels, combined with a decrease in P, triggers maternal behaviors (Rosenblatt, 1994). Thus, hormones that maintain pregnancy act to prime an eventual maternal response, and hormonal changes at parturition trigger early postpartum maternal behaviors (Rosenblatt, 1994). Once maternal behaviors are activated, E, P, and PRL are not needed to sustain the behaviors (Cohen and Bridges, 1981; Fleming et al., 1999). In fact, maternal behaviors can be acquired without being triggered by pregnancy or exogenous hormones in rats; castrated males, intact males, virgin ovarectomized females, and virgin hypophysectomized females housed with pups initiate maternal behaviors after 5 to 7 days (Rosenblatt, 1967).

Less is known about hormonal priming and activation of early postpartum maternal behaviors in primates. Studies to date have usually involved small sample sizes, or are based on indirect measures of hormones or maternal behaviors. Among new world monkeys, investigations yield equivocal results on the effects of prepartum hormones on postpartum maternal behavior. Tamarin (*Saguinus labiatus*) females that provided competent maternal care during the first postpartum week had higher concentrations of estradiol-17β ($E_2$) than females who provided inadequate maternal care (Pryce et al., 1988). Marmoset (*Callithrix jacchus*) females given pregnancy levels of exogenous E and P showed increased interactions with infants over untreated females (Pryce et al., 1993). Maternal behaviors were not related to prepartum steroid concentrations in another study of *C. jacchus* (Pryce et al., 1995). An investigation in another species of marmoset (*C. kuhlii*) found that high concentrations of prepartum $E_2$ were associated with reduced maternal carrying effort and poor infant survival (Fite and French, 2000). This

finding is unusual because the relationship between prepartum $E_2$ and postpartum maternal behavior was opposite that found in studies of other mammals.

Few studies have directly examined the effects of prepartum hormones and early postpartum maternal behavior in old world primates. Pregnant pigtail macaques (*Macaca nemestrina*) display an increased interest in or interaction with infants of other females that covaries with hormanal changes across pregnancy (Maestripieri and Wallen, 1995; Maestripieri and Zehr, 1998). Ovarectomized rhesus macaques (*M. mulatta*) given exogenous E increased their rate of interactions with infants in one study (Maestripieri and Zehr, 1998), but not in another study (Gibber, 1986). Chimpanzee (*Pan troglodytes*) mothers with larger perineal swellings during pregnancy (a marker for higher estradiol levels) are more likely to exhibit appropriate maternal caregiving (Dahl et al., 1994; Dahl, 1999). In constrast, a study of female gorillas (*N*=8) found no association between postpartum maternal behaviors and prepartum urinary estrone conjugates (E1C), pregnanediol-3α-glucuronide (PdG, a urinary metabolite of progesterone), E1C:PdG ratio, or prepartum changes in these hormones (Bahr et al., 2001).

Hormonal priming and triggering of maternal behaviors in women have been suggested by a number of authors. Nearly all these discussions of the neuroendocrinology or psychobiology of human maternal behavior are based on evidence from animal studies (e.g., Rosenblatt, 1994; Uvnäs-Moberg, 1996; Fleming et al., 1999; Maestripieri, 1999). In fact, there is almost no evidence for hormonal mediation of early postpartum maternal behavior in women. The effect of reproductive hormones on maternal attitude in women was studied by Fleming et al. (1990), who found no association between prepartum plasma $E_2$, and P concentrations on postpartum maternal attitudes throughout pregnancy and at six weeks postpartum. In another study, Fleming et al. (1997) examined maternal attitude and prepartum hormone concentrations, and found that women with high plasma $E_2$ and $E_2$:PdG ratios during pregnancy had lower feelings of attachment and more negative mood states postpartum.

In this paper, we investigate the associations between prepartum hormone concentrations (E1C, PdG and human chorionic gonadotgrophin [hCG]) and a specific postpartum maternal behavior—time from parturition to initiation of breastfeeding, defined here as the first postpartum time the infant is placed at the mother's breast. We prospectively monitored a sample of rural Bangladeshi women across pregnancy and into the early postpartum period, collecting twice weekly urine specimens and reports of postpartum breastfeeding behavior. We found evidence that women with higher concentrations of urinary E1C in the last two weeks of pregnancy initiated breastfeeding at significantly later times. No association was found between onset of breastfeeding and other urinary endocrine measures. This study appears to be the only investigation of the effects of prepartum fetoplacental hormones on a specific early postpartum maternal behavior, and the first to use initiation of breastfeeding as a measure of maternal behavior.

### *Initiation of breastfeeding*

For all mammals, both mother and infant must, to some extent, participate in the initiation of breastfeeding, but the degree of maternal involvement differs among species. In humans, mothers must actively participate in transporting the infant to the breast. A

female rat does not transport her newborn pups, which are blind and deaf at birth, to the nipple. Instead, she assists newborns by assuming a squatting posture that allows them to find the nipple (Blass and Teicher, 1980). Rhesus macaque newborns are typically able to transport themselves to the nipple without active participation of the mother beyond permitting the newborn's actions (Jolly, 1985:325). Among mammals, such specific maternal behaviors directed toward the initiation of breastfeeding and the subsequent onset of lactation (i.e. the start of copious milk production by the mammary glands), are required for infant survival. Once lactation is established, other neuroendocrine mechanisms, experiential learning, and mechanisms for psycho-social attachment may be sufficient to sustain later maternal behaviors (Uvnäs-Moberg, 1996). Thus, initiation of breastfeeding may be one of the primary behaviors targeted and triggered by neuroendocrine changes at parturition.

In humans, early initiation of breastfeeding is beneficial to the newborn through the early transfer of health promoting agents found in colostrum (review by Cunningham, 1995). The health benefits include decreased infant morbidity from the passive immunity conferred through colostrum (Hanson et al., 1994; Hanson, 2000) and by reducing an infant's exposure to pathogens (Hanson et al., 1985a, 1985b). Growth factors in colostrum promote the maturation of gastro-intestional epithelia cells that facilitates nutrient absorption and development of a physical barrier to pathogens (Xu, 1996).

Frequent breastfeeding episodes beginning within an hour or two of delivery leads to an earlier onset of stage II lactogenesis in humans (Chapman and Perez-Escamilla, 1999; Neville and Morton, 2001), and the establishment of longer and more successful breastfeeding (Salariya et al., 1978; Trevathan, 1984; Hill, 1991), and of exclusive breastfeeding (Kurinj and Shiono, 1991). The close physical contact of early breastfeeding allows a mother and infant to learn the olfactory and tactile characteristics needed for mutual recognition (Porter and Winberg, 1999), which is a precursor to an enduring social attachment, and results in a healthy relationship between a mother and her child (Maestripieri, 2001).

# METHODS

### *Subjects and samples*

Data were collected in a nine-month prospective study of birth spacing and fecundity conducted from February through December 1993 in twenty-eight rural Bangladeshi villages (Holman, 1996). The villages were all located in the rural sub-district of Matlab *thana*, about 50 km southeast of Dhaka. Matlab has a population of about 200,000 permanent residents in 149 villages. Participants gave informed consent prior to participation in the study. The study protocol was reviewed and approved by the Pennsylvania State University Office for Regulatory Compliance and the International Centre for Diarrhoeal Disease Research, Bangladesh Research and Ethical Review Committees.

Twice-weekly interviews and urine samples were collected from 494 women in the larger study for at least one month, and as long as nine months.. Women of all

reproductive states were selected by the following criteria: married women living with their spouse in the study area who were not using contraceptive methods, were not menopausal, and were in the age range 18 to 46 years. Participants were typical residents of this rural area of Bangladesh. Few had electricity in their homes. None of the participants was under western-type medical care for their pregnancies. Deliveries occurred in their own residence or that of a relative. Deliveries were attended by midwives or a female relative, as is typical of the area (Croley et al., 1966). Social norms usually prevent medical practitioners from performing gynecological examinations, even during obstetric emergencies (Rozario, 1995).

Urine specimens were collected from subjects by one of eight female Bangladeshi field workers who visited the subjects at home between 6 AM and 3 PM. Specimens were immediately placed in a portable cooler containing ice packs. At the end of a field worker's daily round, the specimens were placed in a large chest cooler in her residence. Every two to three days, the specimens were removed and the coolers were replenished with ice packs. The specimens were transported cold to a rural hospital where they were refrigerated at 4° C. One to three days later, specimens were brought to room temperature, and pH (Horiba C-1 pH meter) and specific gravity (Atago Uricon-N urine specific gravity refractometer) were determined. From each specimen, a 6.5 ml sample was taken, preserved by the addition of 65 µl of 0.17 g/ml boric acid solution, and stored at -20° C. Most samples were frozen within one week of collection; however, occasional freezer space shortages required that some samples be refrigerated for up to four weeks before being frozen. De Medeiros et al. (1991) has shown that intact hCG shows very little decline in immunoreactivity at room temperature or 4°C over a period of 21 days, and Holman (1996) found that PdG show little decline in immunoreactivity at room temperature for 12 days; O'Connor et al. (n.d.) found that PdG and E1C showed little decline in immunoreactivity at room temperature for 8 days using the same assays employed in the present investigation. Frozen samples were shipped to the Pennsylvania State University, and were stored at -20° C until they were assayed for reproductive hormones in 1996.

At the same time a specimen was collected, subjects answered structured questionnaires about menses, pregnancy status, pregnancy outcome, contraception, and breastfeeding behavior. At the first postpartum interview, subjects were queried as to the sex of the child, complications of delivery, whether or not the child was ever breastfed, and if so, the number of hours until the child was first put to the breast.

### *Assay Methods*

Urinary hCG was quantified in duplicate by an immunoenzymetric assay (IEMA) that uses two capture monoclonal antibodies directed against intact hCG and the β-subunit of hCG, and a biotinylated monoclonal detection antibody which binds to the ß subunit of intact or dissociated hCG (O'Connor et al., 1988). Optical density was measured on a microtiter plate reader (Dynatech MR7000; Dynex Technologies, Chantilly, VA). The limit of detection (mean + 3 SE above the zero standard) for the IEMA was 3.1 IU/L. Inter and intra-assay coefficients of variation (CV) were 12.4% and 14.9%. The IEMA has less than 1% cross-reactivity with human lutenizing hormone (O'Connor et al., 1988).

Concentrations of urinary steroids were measured in duplicate using microtiter plate-based enzyme immunoassays (EIAs). Tracers were horseradish peroxidase conjugated to Estrone 3-glucuronide and PdG. The estrone conjugate assay (E1C EIA) used the 155B3 monoclonal antibody which cross-reacts with free estrone, estrone sulfate and estrone glucuronide (Kohen and Lichter, 1986). The pregnanediol glucuronide assay (PdG EIA) used the Quidel 330 monclonal antibody, which cross-reacts with pregnanediol-3-alpha-glucuronide and 20-alpha-hydroxy-4-pregnen-3-one (O'Connor et al., n.d.). The limits of detection (mean +3 SE above the zero standard) were 21 nmol/L for the PdG EIA and 0.27 nmol/L for the E1C EIA (O'Connor et al., n.d.). Inter- and intra-assay variance components for high concentration control pools were 8% and 13%, respectively, for the PdG EIA, and 10% and 10%, respectively, for the E1C EIA.

Urine specimens were spot samples, taken opportunistically, rather than first morning voids. Creatinine excretion was low and highly variable for this sample, and the amount of creatinine excreted changes significantly by reproductive status (Holman, 1996). Therefore, we did not correct hormone concentrations by creatinine. Instead, hormone concentrations were normalized using the specific gravity method of Alfthan et al. (1993), correcting raw hormone concentration $x_{raw}$ as : $x_{corrected} = x_{raw} \times (SpG_{target} - 1)/(SpG_{sample} - 1)$, where $SpG_{sample}$ is the specific gravity of the specimen, and $SpG_{target}$ is a target specific gravity. We used 1.015 as the target specific gravity reflecting the generally low density of Bangladeshi urine specimens compared to those of Western populations (Holman, 1996).

### *Statistical Methods*

Survival analysis was used to estimate the distribution of times to initiation of breastfeeding, as well as the effects of covariates on the time to initiation of breastfeeding. Previously, we found that times to initiation of breastfeeding in this sample were well approximated by a negative exponential distribution (Holman and Grimes, 2001). A negative exponential distribution for the initiation of breastfeeding is consistent with idea that these women are initiating breastfeeding without strong culturally-mediated delays in establishing breastfeeding like refusing to feed colostrum to the newborn or an imposed pattern of maternal-child separation after parturition (see Holman and Grimes, 2001, n.d.).

We assume that an underlying negative exponential probability density function, $f(t) = \lambda_i e^{-\lambda_i t}$, properly describes the distribution of times from parturition to initiation of breastfeeding. The parameter $\lambda_i$ is a function of the covariates and the underlying baseline hazard $\lambda$ as $\lambda_i = \lambda \exp(\mathbf{x}_i'\boldsymbol{\beta})$, where $\mathbf{x}_i$ is a $N \times m$ matrix with $m$ different covariates for $N$ subjects, and $\boldsymbol{\beta}$ is a $1 \times m$ array of parameters to be estimated. The value $x_{ij}$ is the $j$-th measured covariate for the $i$-th subject. Thus, an array of $m$ covariates is constructed for the $i$-th subject as $\mathbf{x}_i'\boldsymbol{\beta} = x_{i1}\beta_1 + x_{i2}\beta_2 + \ldots + x_{im}\beta_m$. Maximum likelihood was used to estimate parameters $\lambda$ and $\boldsymbol{\beta}$.

Covariates included in analyses were the log of the subject's urinary concentrations of *hCG*, *PdG*, and *E1C* taken closest to parturition, as well as the derived variable *E1C:PdG* ratio. The prepartum day on which the urine specimen was collected differed among subjects, but was always within the last three weeks of pregnancy. Other

covariates included in analyses were child's *sex*, mother's *age* and mother's *parity*. Parity was coded as primaparous or multiparous during the index pregnancy with the idea that maternal behavior may be associated with prior maternal experience, as is found in other primates (Holman and Goy, 1995; Pryce et al., 1988).

The outcome variable is the number of hours until an infant was first breastfed. This durration was reported to the nearest hour by most mothers. For a few observations, the time to onset of breastfeeding was either right censored, when a subject was lost to follow-up prior to the initiation of breastfeeding, or interval censored, when a breastfeeding subject did not report the number of hours to initiation of breastfeeding (Holman and Grimes, 2001). The resulting likelihood for all types of observations is

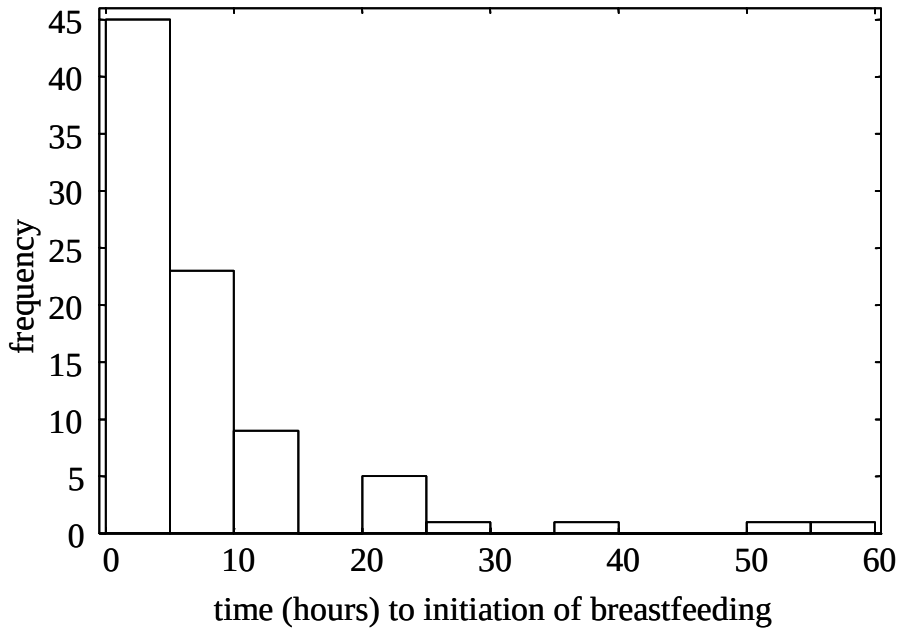
$$L = \prod_{i \in \text{exact}} \lambda_i e^{-\lambda_i t_i} \prod_{i \in \text{interval censored}} e^{-\lambda_i t_{f_i}} - e^{-\lambda_i t_{s_i}} \prod_{i \in \text{right censored}} e^{-\lambda_i t_{c_i}} \qquad (1)$$

where $t_i$ is an exact time to the start of breastfeeding, $[t_f, t_s)$ is the half-open interval during which breastfeeding was initiated (for interval censored cases), and $t_c$ denotes the time at right-censoring (Holman and Grimes, 2001). Parameter estimates were found as those that numerically maximize likelihood (1).

The most parsimonious combination of covariates was selected using minimum Akike's information criterion (AIC) (Akike, 1973, Burnham and Anderson, 1998). This criterion balances the tradeoff between goodness-of-fit and the fewest number of parameters to include in the model.

Because some of the observations were interval- or right-censored, it is not possible to find least-squares estimates for correlation coefficients between the time to onset of breastfeeding and urinary hormone concentrations. Instead, we generate product-moment correlations using a method described in the Appendix.

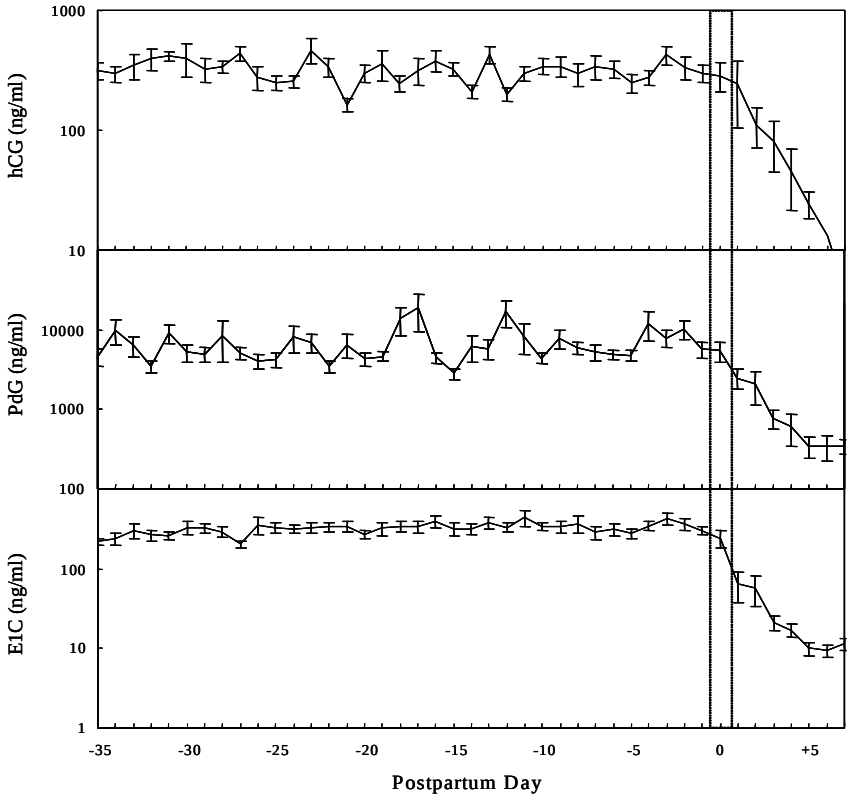
Figure 1. Distribution of times (hours) to initiation of breastfeeding in 86 rural Bangladeshi women; five interval- or right-censored observations are not shown.



# RESULTS

Of the 494 subjects in the prospective birth-spacing study, 91 gave birth to a singleton (46 girls and 45 boys), provided a urine specimen during the last 3 weeks of pregnancy, and provided at least one postpartum interview. Descriptive statistics for the subset of 91 subjects are given in Table 1. Ten mothers delivered their first child. The empirical distribution of times to initiation of breastfeeding for the complete observations (Figure 1) clearly shows a pattern consistent with a negative exponential distribution for times to initiation of breastfeeding.

Figure 2. Average (± SE) concentrations of E1C, PdG, and hCG over the last five weeks of pregnancy and the first postpartum week (parturition is day 0).




Mean urinary hormone concentrations over the last five weeks of pregnancy and through the first week postpartum are shown in Figure 2. Because each subject provided specimens twice-weekly, the mean hormone concentrations in Figure 2 are based on roughly 20 subjects for each day before parturtion, and about 10 subjects for each day on and after parturition. Systematic increases or declines in hormone concentrations were not seen over the prepartum period, so that we included all subjects who provided at least one urine specimen collected during the three weeks prior to parturition. For most subjects, the specimen was taken during the last week of pregnancy, although one specimen was collected as early as 20 days before parturition. This distribution is shown in Figure 3. Individual times to initiation of breastfeeding, plotted against urinary hormone concentrations are shown in Figure 4. The vertical lines denote times to initiation of breastfeeding that are right- or interval-censored between the endpoints.

Table 1. Characteristics of the 91 Bangladeshi women and prepartum endocrine measures.

| | age (yr) | Parity[a] | Sample day, prepartum | hCG (ng/ml) | PdG (ng/ml) | E1C (ng/ml |
|---|---|---|---|---|---|---|
| Mean | 28.7 | 4.2 | 3.5 | 346 | 8268 | 341 |
| Std. Dev. | 6.35 | 2.3 | 3.0 | 313 | 13,647 | 276 |
| Minimum | 18.9 | 1 | 1 | 1.1 | 4.2 | 9.7 |
| Maximum | 47.7 | 10 | 20 | 1978 | 112,113 | 1571 |

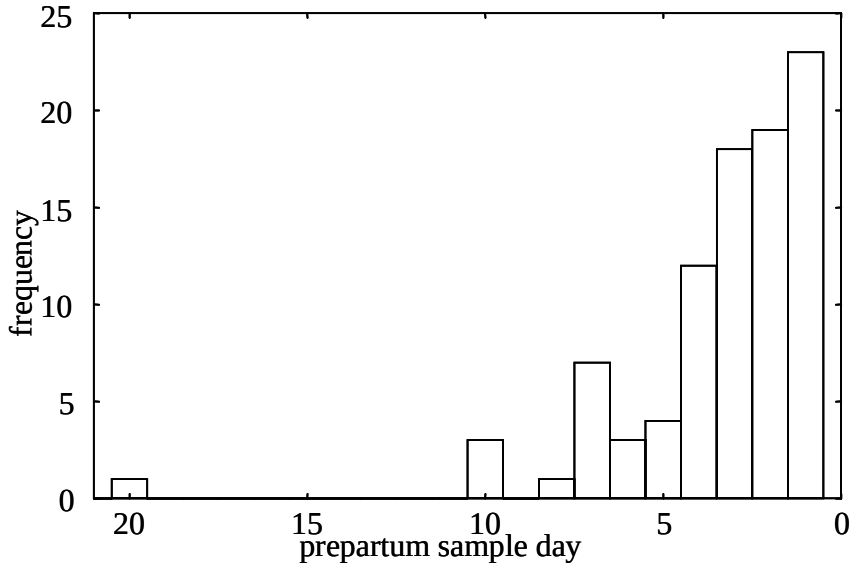
[a]Parity includes the child in the focal pregnancy.

The effects of child's sex, mother's age, mother's parity, hCG concentration, PdG concentration, and E1C:PdG ratio were not significant. Parameter estimates for a subset of the models (all those that include *E1C*, *PdG* and *hCG* as a covariate) are shown in Table 2, including a full model with all three hormones included as covariates. As assessed by minimum AIC, the most parsimonious model only included *E1C* concentration as a covariate (model 7). Adding any other covariate (*PdG*, *hCG*, *E1C*:*PdG*, *sex*, *age*, *parity*) alone or in combination to model 7, did not improve the fit. By two other criteria, the results are mixed: by a likelihood ratio test, the fit of model 7 over model 8 is not statistically significant ($\Lambda = 3.64 \sim \chi^2$, 1 d.f., $p \leq 0.06$); by a Wald test, model 7 fits significantly better than model 8 ($W = 6.79 \sim \chi^2$, 1 d.f., $p \leq 0.01$).

The negative value for $\beta_{E1C}$ means that higher concentrations of E1C increased the time to initiation of breastfeeding. That is, the effect of higher concentrations of E1C was to delay the onset of breastfeeding. The product-moment correlations (SE) between time to initiation of breastfeeding and hormone concentration were 0.199 (0.093) for E1C, 0.108 (0.123) for PdG, and 0.147 (0.107) for hCG. Only the correlation for E1C is significantly different from zero ($p<0.05$). The correlation of 0.199 suggests that about 4 percent of the variation in the timing to initiation of breastfeeding is associated with urinary E1C concentration.

The magnitude of the effect of E1C on time to initiation of breastfeeding can be

Figure 3. Distribution of days prior to parturition for which urine specimens were collected for 91 Bangladeshi subjects.



seen in Figure 5. Mean time to initiation of breastfeeding, computed over the observed range of *E1C* values as $1/[\lambda\exp(\beta_{E1C}\times E1C)]$, roughly doubles from just over 5 hours at the lowest values of *E1C* to nearly 11 hours at the highest values of *E1C*.

## DISCUSSION

Prepartum concentrations of E1C were significantly correlated with time to initiation of breastfeeding. Rural Bangladeshi women who had higher concentrations of E1C within three weeks before parturition had a longer latency from parturition to initiation of breastfeeding. Previous studies in non-primate mammals have firmly established that high prepartum estrogen concentrations are associated with improved early postpartum maternal behaviors (see Fleming and Corter, 1995; Rosenblatt, 1995). The present study is consistent with previous research in finding that early postpartum maternal behaviors are affected by prepartum concentrations of E. The pattern, however, is the reverse of that found in studies of most other mammals because the higher E1C concentrations were associated with delayed initiation of breastfeeding.

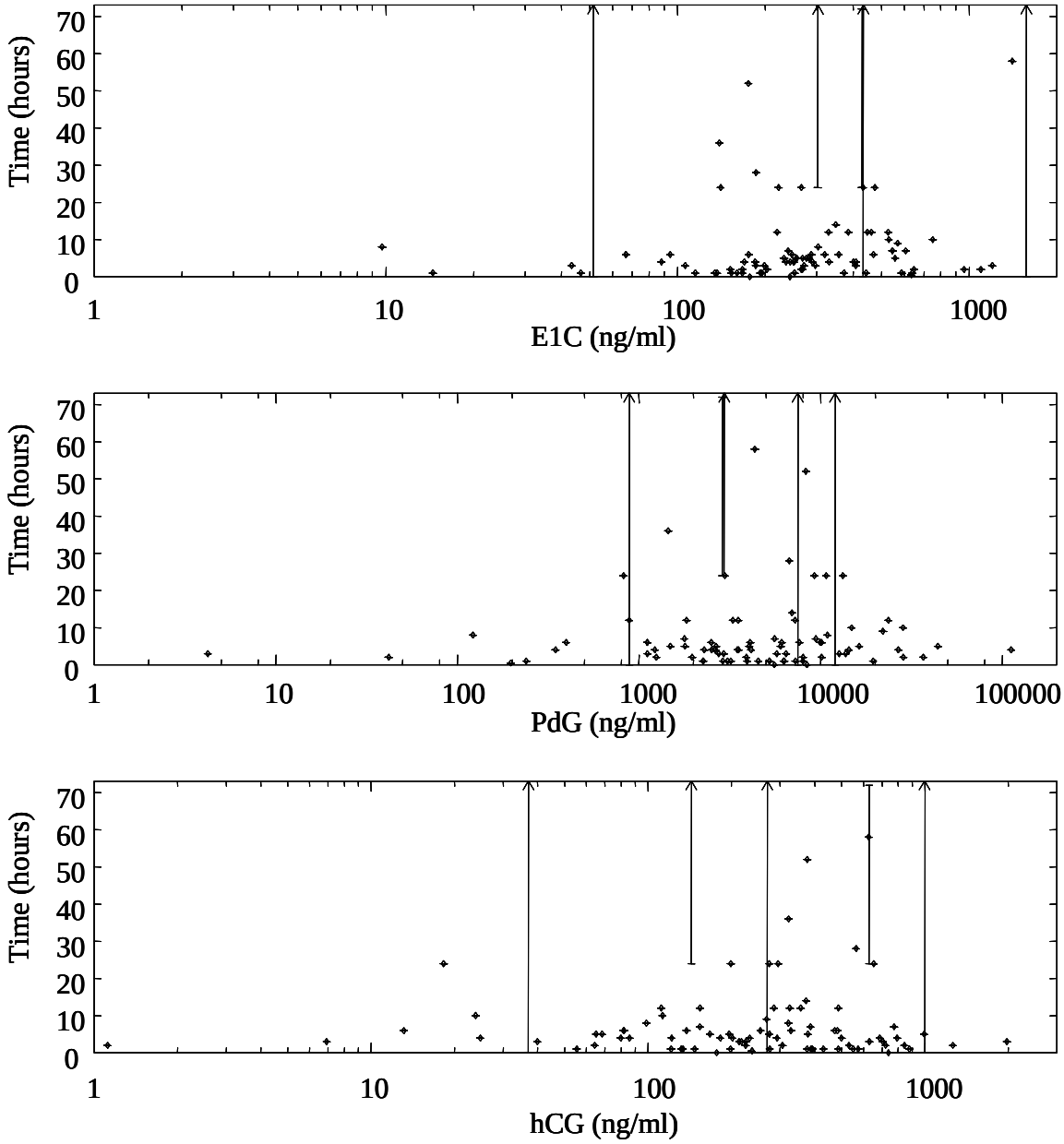
Investigations in primates have produced mixed results on the relationship between prepartum E and postpartum maternal behaviors. Table 3 summarizes the findings in four callithricid species, two cercopithid species, and three hominoid species studied to date. Within the Callitrichidae, most studies find that a higher concentration of E is associated with increased measures of maternal function. The Fite and French (2000) study is the exception in finding a strong and significant result in the opposite direction. In macaques, one study found no association, and the remaining studies found a positive association between E and increased measures of maternal function. Investigations within Hominoidea have been mixed, finding no association between prepartum steroids and maternal behavior, (Fleming et al., 1990; Bahr et al., 2001), finding a positive

Table 2. Parameter estimates for an exponential survival model of time to initiation of breastfeeding.

| Model | $\lambda$ (SE) | $\beta_{E1C}$ (SE) | $\beta_{PdG}$ (SE) | $\beta_{hCG}$ (SE) | Loglikelihood (AIC) |
|---|---|---|---|---|---|
| 1 | 0.655 | -0.247 | 0.0368 | -0.106 | -262.50 |
| | (0.523) | (0.111) | (0.0976) | (0.100) | (533.00) |
| 2 | 0.718 | -0.224 | | -0.090 | -262.56 |
| | (0.463) | (0.106) | | (0.084) | (531.13) |
| 3 | 0.287 | | -0.0271 | -0.111 | -263.93 |
| | (0.222) | | (0.1099) | (0.097) | (533.86) |
| 4 | 0.501 | -0.243 | -0.0027 | | -262.94 |
| | (0.379) | (0.098) | (0.0804) | | (531.89) |
| 5 | 0.248 | | | -0.126 | -263.97 |
| | (0.119) | | | (0.080) | (531.94) |
| 6 | 0.230 | | -0.0734 | | -264.43 |
| | (0.181) | | (0.0916) | | (532.85) |
| 7[a] | 0.495 | -0.245 | | | -262.95 |
| | (0.269) | (0.094) | | | (529.89) |
| 8 | 0.125 | | | | -264.77 |
| | (0.010) | | | | (531.54) |

[a] The most parsimonious model as assessed by AIC.

Figure 4. Concentrations of urinary E1C, PdG, and hCG by times (hours) to initiation of breastfeeding in 91 subjects. Points show exact times to initiation of breastfeeding; vertical lines show interval or right-censored times to breastfeeding. The display of one right censored and three interval censored observations is truncated at 73 hours.




association (Dahl, 1999), or finding a negative association (Fleming et al., 1997; present study).

Table 3 . Investigations in primates of the relationship between prepartum measures of estradiol and maternal behaviors.

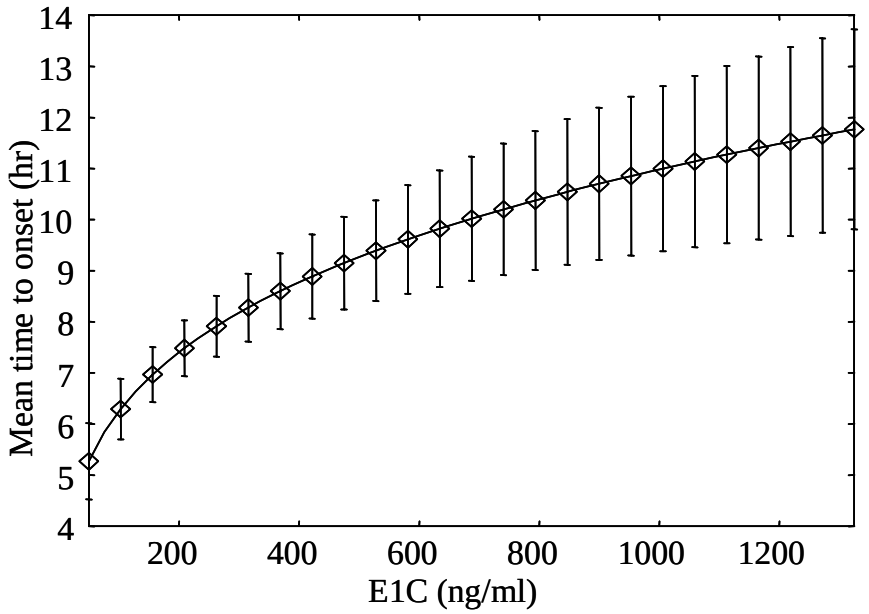
| Species[a] | Study | *N* | Measures of E | Maternal behavior(s) | Relationship[b] | Comments |
|---|---|---|---|---|---|---|
| *C. kuhlii* | Fite & French, 2000 | 6, w/2 delieveies | Prepartum urinary $E_2$, $E_2$:PdG | Carrying effort, infant survival | – | $r$=-0.63 for carrying effort and $E_2$ |
| *C. jacchus* | Pryce et al., 1995 | 8 | Urinary $E_2$, HPO[c] | Six proxy behaviors | 0 | |
| *C. jacchus* | Pryce et al., 1993 | 4 | Plasma $E_2$ | Changes in operant maternal behavior across pregnancy | + | |
| *C. jacchus* | Pryce et al., 1993 | 3 | Exogenous $E_2$ and P | Changes in operant maternal behavior | + | Positive for high $E_2$:P |
| *S. labiatus* | Pryce et al., 1988 | 12 | Urinary $E_2$ from 1 to 5 weeks prepartum | Infant survival | + | Positive for $E_2$ during last week of pregnancy for inexperienced mothers; none for experienced mothers. |
| *M. mulatto* | Gibber, 1986 | 11 | Behavioral changes across pregnancy | Infant contact in 2-week intervals over the course of pregnancy | 0 | |
| *M. mulatto* | Maestripieri & Zeher, 1998 | 5 treated, 6 controls | Exogenous E | Infant handling | + | |
| *M. nemestrina* | Maestripieri & Zeher, 1998 | 8 | Plasma $E_2$ and P | Infant handling in each eight-week trimester. | + | Positive in third trimester, $r$=0.81 for $E_2$, $r$=0.84 for $E_2$:P |
| *M. nemestrina* | Maestripieri & Wallen, 1995 | 24 | Behavioral changes across pregnancy | Interaction with or interest in infants | + | |
| *P. troglodytes* | Dahl, 1999 | 107 | Perineal swelling across pregnancy. | Appropriate maternal caregiving | + | Positive for some measures. |
| *G. gorilla* | Bahr et al., 2001 | 8 | Prepartum urinary E1C, E1C:PdG ratio. | Nine infant-directed behaviors | 0 | 1 nearly significant: $r$=-0.69, $p$<0.1 |
| *H. sapiens* | Flemming, 1990 | 30 | Prepartum plasma $E_2$ | Maternal-attitude constructs | 0 | |
| *H. sapiens* | Flemming et al., 1997 | 29 | Prepartum plasma $E_2$ and $E_2$:P | Self-reported feelings of maternal attachment postpartum in primaparas | – | E:P: $r$=-0.45 @ 5 months; $r$=-0.5 @ 7 months |
| *H. sapiens* | Present study | 91 | Prepartum urinary E1C | Initiation of breastfeeding | – | $r$=0.2 for E1C |

[a] *C. = Callithrix, M = Macaca, S. = Saguinus, H. = Homo, P. = Pan, G. = Gorilla*.

[b] A plus sign (+) means that a higher measure (or proxy measure) for E was significantly associated with a greater degree of maternal behavior (or proxy measure), – denotes a significant negative association was found, and 0 means no significant association was found.

[c] Hydroxypregnanolone

Figure 5. The mean time (±1 SE) to initiation of breastfeeding expected for mothers with a given concentration of prepartum urinary E1C, based on parameter estimates for model 7 in Table 2.




Taken as a whole, then, the phylogenetic pattern seen in these studies can be interpreted in a number of ways. For the moment, we will not consider the Fite and French (2000) results. The first possible explanation is that most primate groups, except for the Hominoidia (apes and humans), share a primitive mammalian mechanism for neuroendocrine regulation of early postpartum maternal behaviors. The exception found in the Hominoidea is a reversal of the relationship between prepartum E and early postpartum maternal behaviors. The one study that is inconsistent with this explanation, Dahl's (1994, 1999) investigation in chimpanzees, used perineal swelling as a proxy for E concentrations across pregnancy. However, since little perineal swelling occurs during the third trimester (Dahl, 1999) perineal swelling may not provide a good marker for E near parturition. Additionally, the findings of no effect of E on maternal behavior in one of the three human studies (Flemming, 1990) and the gorilla study (Bahr et al., 2001) might reflect the small sample sizes and the relatively weak effect of E on maternal behavior as found in the present investigation.

The second possible explanation is that the primitive mammalian pattern holds for all primates, including most hominoids, except humans. Under this explanation, the gorilla results would show a positive relationship between E and maternal behavior given a larger sample size. This explanation is more parsimonious because it is consistent with the results of Dahl (1994, 1999), but with the research published to date, it is not possible to differentiate between these first two explanations.

Primates are characterized by relatively precocial newborns that can actively participate in finding a nipple. Compared to other primates, human infants are relatively altricial in their neuromotoric capabilities at birth. Of all the anthropoid primates, the large-bodied hominoids (*Pan*, *Gorilla*, *Pongo*, and *Homo*) are the least precocial at birth, with newborn *H. sapiens* being the most altricial of this group with respect to motor

skills (reviewed by Martin and MacLarnon, 1990). This trend in Hominoidea probably coincided with the emergence of longer life spans, slower rates of development, and brain expansion. In *Homo* this condition is exaggerated through further brain expansion under the constraints of bipedality (Martin and MacLarnon, 1990; Portmann, 1990; Martin, 1983). The result in humans (and probably all Hominoidea) is a mosaic of altricial neuromotor skills and precocial cognitive skills (Clancy et al., 2001).

As a consequence, behaviors expressed by more precocial primate newborns at births are not possible in humans because the neural structures responsible for facilitating such behaviors are not fully developed at birth as they are in most other primates (Martin and MacLarnon, 1990). The human mother has the primary responsibility for transporting her infant to the breast—a task that is not required of most non-hominoid primate mothers. Thus, the evolution of secondary altricial characteristics in humans, and perhaps hominoids more generally, may have coincided with novel changes in the preexisting neuroendocrine mechanism that regulate early postpartum maternal behaviors. These changes may have resulted in a reversal of the primitive mammalian pattern for the mediation of early postpartum maternal behaviors by fetoplacental hormones.

Other explanations for our findings are possible. One of our assumptions is that delayed breastfeeding is associated with lower "maternal function" or reflects lower maternal motivation. It is possible that this assumption is incorrect. The most motivated mothers may delay breastfeeding for reasons such as postpartum cleaning, grooming, or for some other reason that is associated with higher maternal care. We have no evidence that this is true, but we also have no information with which to further examine this issue.

The correlation between E1C and time to initiation of breastfeeding was only about 0.2, suggesting that most (96%) of the variability in time to initiation of breastfeeding is explained by non-hormonally mediated factors. It is clear that maternal behaviors in mammals are, to a great extent, learned (reviewed in Fleming et al., 1999). In humans, behavioral norms and social learning probably play an even larger role in determining when breastfeeding is initiated, leaving a small role for hormonally-mediated pre-programmed behaviors.

The final explanation for the phylogenetic pattern in Table 3 is that offered by Fite and French (2000), that there may be a complex relationship between endocrine status and maternal behavior. In other words, species-specific differences in the maternal behavior system may have arisen. This idea can explain the inconsistent findings within Callithricidae and Hominoidea. Even so, this is a complex explanation since it entails at least two reversals in the primitive mammalian pattern.

One of the difficulties in identifying how hormones affect postpartum maternal behavior across species is that many different criteria have been used as proxy measures to quantify maternal behavior, including infant survival, nesting and retrieving behaviors, grooming behaviors, and interactions with infants, to name a few. Some maternal behaviors are species-specific, and make cross-species comparisons difficult. The most fruitful maternal behaviors to consider are those expressed shortly after parturition, in light of findings that maternal behaviors, once activated, may persist in the absence of reproductive steroids for a limited period of time (Fleming et al., 1996). Time to the initiation of breastfeeding would seem to be an ideal proximate maternal behavior to investigate in non-experimental studies.

Breastfeeding is a life history trait with deep mammalian roots, so that initiation of breastfeeding is likely to be closely tied to infant survival.[1] Thus, maternal behaviors that promote the start of breastfeeding may be one of the primary behaviors targeted by pregnancy hormones. Once physical contact, suckling, and lactation are established, a cascade of other mechanisms including neuroendocrine changes (e.g., oxytocin release), experiential learning, and psychological attachment sustain further maternal-infant interactions.

There are some disadvantages to using time to initiation of breastfeeding as a marker of maternal function. In many human societies, initiation of breastfeeding is delayed by the use of drugs in medically assisted births, or by institutional norms that impose a period of separation between the newborn and its mother. In other cultures, breastfeeding is delayed because of cultural beliefs about colostrum or prelacteal feeding rituals (Morse et al., 1990). In other primates, births tend to occur nocturnally for diurnal species, and diurnally for nocturnal species, so that initiation of breastfeeding may be hard to observe (although observations consisting of intervals within which breastfeeding started can be usefully analyzed by the methods used in this study). Finally, the statistical analysis of times to events is more difficult when some observations are right-censored. The right-censored cases cannot be dropped from the analysis without biasing results, so parametric or non-parametric survival analysis must be used to analyze the data (Elandt-Johnson and Johnson, 1980).

In conclusion, we have provided evidence that an early postpartum maternal behavior in women is, in part, mediated by fetoplacental hormones. Our findings are consistent with some recent studies demonstrating that higher prepartum E is associated with lower early postpartum maternal performance (Fite and French, 2000) and lower feelings of maternal attachment (Fleming et al., 1997), but are inconsistent with established findings in other mammals and some primates. This study appears to be the first to examine endocrine correlates of this particular maternal behavior, and the only investigation to find a significant relationship between prepartum fetoplacental hormones and an early postpartum maternal behavior in women. Additional research in humans and other primates will be needed to further clarify the role of prepartum hormones in triggering postpartum maternal behaviors, and phylogenetic differences in the way hormones mediate postpartum maternal behavior.

## APPENDIX

Some of the observations were interval- or right-censored, so that least-squares estimates for correlations between the time to onset of breastfeeding and urinary hormone concentrations cannot be used. Here we describe the method we used to compute the

[1] An alternative measure of maternal competence is infant survival. This measure, which is closely tied to maternal fitness, has been used in previous studies (Pryce et al., 1988; Fite and French, 2001). The difficulty with using infant survival is its complex nature. Infant survival is determined not only by early postpartum maternal behaviors, but later postpartum maternal behaviors, learned behaviors, intrinsic biological factors (biological frailty, congenital defects), and extrinsic environmental factors (disease, predation) that can be unrelated to maternal competence. Additional problems arise in using neonatal or infant mortality as a marker of maternal competence in humans. Ethical considerations preclude some study designs. Additionally, neonatal and infant mortality is low in contemporary humans, so that prospective endocrine studies would need to be very large to detect a correlation between pregnancy hormones and mortality.

correlation coefficients. The definition of a product-moment correlation coefficient is $\sigma_{tx}/(\sigma_t\sigma_x)$, where $\sigma_{tx}$ is the covariance between random variables $T$ and $X$, $\sigma_t$ is the standard deviation of $T$, and $\sigma_x$ is the standard deviation of $X$. For this application, $T$ is the time to initiation of breastfeeding and is distributed as $f(t|\lambda, \beta, x)$, where $\lambda$ is the parameter of a negative exponential distribution and $\beta$ is the regression coefficient for the effect of log hormone concentration ($x$) on $t$. The distribution of log hormone concentration is $\phi(x|\mu, \sigma)$, where $\phi()$ is a normal distribution with parameters $\mu$ and $\sigma$. The covariance between $t$ and $x$ was found by numerically computing

$$\sigma_{tx} = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty}[t - E(t)][x - E(x)]\, f(t \mid \hat{\lambda}, \hat{\beta}, x)\phi(x \mid \hat{\mu}, \hat{\sigma})dxdt \qquad (2)$$

at the maximum likelihood parameter estimates ($\hat{\lambda}$, $\hat{\beta}$, $\hat{\sigma}$, and $\hat{\mu}$). Equation (2) is taken directly from the definition of a covariance (e.g. Harris and Stocker, 1998:806). Expectations were numerically computed as

$$E(t) = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} t\, f(t \mid \hat{\lambda}, \hat{\beta}, x)\phi(x \mid \hat{\mu}, \hat{\sigma})dxdt\,, \qquad (3)$$

and

$$E(x) = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} x\,\phi(x \mid \hat{\mu}, \hat{\sigma})\, f(t \mid \hat{\lambda}, \hat{\beta}, x)dtdx\,, \qquad (4)$$

The variance of $t$, denoted $\sigma_t^2$, and the variance of $x$, denoted $\sigma_x^2$, were found numerically as

$$\sigma_t^2 = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty}[t - E(t)]^2\, f(t \mid \hat{\lambda}, \hat{\beta}, x)\phi(x \mid \hat{\mu}, \hat{\sigma})dxdt \qquad (5)$$

and

$$\sigma_x^2 = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty}[x - E(x)]^2\,\phi(x \mid \hat{\mu}, \hat{\sigma})\, f(t \mid \hat{\lambda}, \hat{\beta}, x)dtdx\,, \qquad (5)$$

respectively. All integration was performed using 200 point open trapezoidal approximations. Standard errors of the correlations coefficients were computed by the delta method (Elandt-Johnson and Johnson, 1980:69) using numerical estimates for the partial derivatives of the likelihood with respect to the parameters.

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