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Pregnancy-Related Sickness in Rural Bangladesh: Symptoms and Their Links with Reproductive Hormones

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ABSTRACT

BACKGROUND We undertook a prospective study in rural Bangladesh examining the association between reproductive hormones and nausea, vomiting and dizziness in pregnancy. METHODS Twice weekly interviews and urine specimens were collected from 203 women across pregnancy. Urinary concentrations of estrone conjugates (E1C), pregnanediol-3-glucuronide (PDG) and hCG were used in a logistic regression to estimate the effect of each hormone on the probability of each symptom. RESULTS Nausea, vomiting and dizziness observations occurred at relatively low frequencies in the sample: the frequency of vomiting in the first 20 weeks of pregnancy was 8%, nausea was 29% and dizziness 53%. Analysis of 1,232 observations from 115 women in the first twenty weeks of pregnancy revealed no association of E1C, PDG or hCG with nausea or vomiting. The only significant association was increased probability of dizziness with higher levels of hCG. CONCLUSIONS Urinary E1C, PDG and hCG were not associated with nausea and vomiting in pregnant Bangladeshi women. Dizziness paralleled the timing of nausea and vomiting in pregnancy in the sample, but occurred at higher frequencies than nausea or vomiting, was positively associated with hCG concentration, and may be an additional symptom of pregnancy-related sickness in Bangladeshi women.

INTRODUCTION

Pregnancy-related sickness (PRS) is a major form of female morbidity, for which the cause is unknown. The prevalence of nausea and vomiting in early pregnancy ranges from 57% to 89% in studies reporting the total percentage of women experiencing nausea and/or vomiting in Western populations (Brandes 1967) (Jarnfelt-Samsioe et al. 1983) (Tierson et al. 1986) (Gadsby et al. 1993) (Weigel and Weigel 1989) (Walker et al. 1985).

The symptoms of PRS include mild to severe nausea, with or without vomiting (Fairweather 1968). Vomiting severe enough to require rehydration and close medical monitoring–hyperemesis gravidarum–is relatively uncommon (0.5-10 cases per 1,000 pregnant women) and may be an extreme manifestation of PRS (Hod et al. 1994). The symptoms of nausea and vomiting are most common in the first trimester of pregnancy, but persist into the second and third trimesters for some women (Lacroix et al. 2000). The onset of nausea and vomiting is typically between four to eight weeks after conception, and begins to decline around the twelfth week, with symptoms disappearing by the twentieth week for most women (Gadsby et al. 1993) (Lacroix et al. 2000) (Whitehead et al. 1992) (Diggory and Tomkinson 1962) (Klebanoff et al. 1985) (Uddenberg et al. 1971). A detailed prospective study in US women that examined symptoms daily throughout pregnancy found that 90% of women experienced onset of symptoms by the 8th week of gestation, and 90% experienced relief of symptoms by the 22nd week (Lacroix et al. 2000).

Changing maternal circulatory levels of human chorionic gonadotropin (hCG), progesterone, and estradiol early in pregnancy have been implicated as causative factors of nausea and vomiting. A variety of mechanisms have been proposed linking reproductive hormones with nausea and vomiting, including stimulation of the emetic center of the brain (Whitehead et al. 1992), and alterations of the hepatic system (Jarnfelt-Samsioe et al. 1985), vestibular system (Black 2002), gastric function (Koch 2002), and taste and olfaction (Heinrichs 2002).

Several indirect lines of evidence have implicated estrogens in producing nausea and vomiting of pregnancy, all pointing to an increased likelihood of symptoms with higher estrogen levels (for a review see (Goodwin 2002)). There have, however, been relatively few studies that have explicitly examined estrogen concentrations in women with and without PRS, and they have not found consistent associations. Two studies of PRS and estradiol reported higher levels of estradiol in symptomatic women (Jarnfelt-Samsioe et al. 1986) (Lagiou et al. 2003) and one study reported no association (Masson et al. 1985). In four studies of hyperemesis gravidarum and estradiol, three found positive associations (Depue et al. 1987) (Goodwin et al. 1992) (Yoneyama et al. 2002) and one found no association (Jordan et al. 1999). Two of these seven studies sampled women twice in pregnancy (second and third trimesters) (Jarnfelt-Samsioe et al. 1986) (Lagiou et al. 2003), and the remainder sampled women once in the first trimester or early in the second trimester.

The pattern of hCG secretion in early pregnancy tends to parallel the timing of PRS symptoms, and has thus been of considerable interest as a potential mechanism triggering nausea and vomiting in early pregnancy. The rise, decline, and plateau of hCG in the first trimester coincides with the onset, peak and decline of PRS symptoms from 4-20 weeks. In addition to this close temporal association, conditions with higher levels of hCG have been linked with a higher risk of nausea and vomiting (for a review see (Goodwin 2002)). On the whole, hormonal studies of women with and without PRS indicate that higher levels of hCG are associated with nausea and/or vomiting: eleven out of fifteen studies have reported a positive association. Four studies found higher hCG levels in women with PRS (Masson et al. 1985) (Jarnfelt-Samsioe et al. 1986) (Mori et al. 1988) (Schoeneck 1942) and one study reported no association (Soules et al. 1980). Seven studies of hyperemesis gravidarum found positive associations between hCG and nausea and/or vomiting (Goodwin et al. 1992) (Yoneyama et al. 2002) (Jordan et al. 1999) (Kauppila et al. 1979) (Leylek et al. 1996) (Leylek et al. 1999) (Al-Yatama et al. 2002). Two studies of hyperemesis found no association with hCG (Depue et al. 1987) (Sekizawa et al. 2001) and one

found a negative association (Fairweather and Loraine 1962). In only two of these studies were women sampled more than once (Jarnfelt-Samsioe et al. 1986) (Fairweather and Loraine 1962).

There are far fewer studies of the association of progesterone with nausea and vomiting of pregnancy, and no specific mechanisms proposed linking this hormone with the etiology of PRS. In one study, lower levels of progesterone were found in emetic subjects (Jarnfelt-Samsioe et al. 1986), but three other studies found no difference in progesterone levels between women who did and did not experience PRS (Lagiou et al. 2003) (Masson et al. 1985) (Soules et al. 1980). In one study, higher levels were found in women with hyperemesis (Yoneyama et al. 2002).

The contradictory results for relationships between reproductive hormones and PRS symptoms may reflect a lack of direct causal association, or they may be a function of variation across studies in sample characteristics, and the limited and varied sampling frames in study design. Differences in sample characteristics that may have contributed to variation among the studies include specimen type tested, assays used, maternal age and parity, and the use of population-based versus clinical samples. Additionally, there is considerable variation across studies in the timing of data collection, ranging between 4 and 38 weeks of gestation, when hormonal levels and symptoms are changing significantly from week to week.

Although not included in the literature as symptoms of PRS, dizziness and vertigo are common complaints in pregnancy (Alley 1984). Motion sickness and other vestibular problems share much in common with the nausea and vomiting of pregnancy, and indirect evidence has linked reproductive hormones with triggering vestibular disturbances leading to nausea and vomiting (Black 2002). We are not aware of any studies that have examined the relationship of reproductive hormones with dizziness in pregnancy.

Our main objective was to conduct a longitudinal observational study of reproductive hormones and nausea and vomiting in a non-Western population, with a detailed sampling frame to control for the varying dynamics of pregnancy sickness symptoms and reproductive hormones. An additional objective

was to evaluate the relationship of dizziness, a common complaint in pregnancy, with reproductive hormone levels. We therefore examined urinary hormones and PRS symptoms in a prospective study in a sample of rural Bangladeshi women.

DATA AND METHODS

Research Site

The research was conducted in 17 villages within Matlab thana, a rural administrative unit in Bangladesh, located 50 km southeast of the capital city of Dhaka. Most of the thana is part of an ongoing large scale survey of demography, health and disease conducted by the International Centre for Diarrhoeal Disease Research in Bangladesh (ICDDR,B). The ICDDR,B has maintained a demographic surveillance survey (DSS) in the Matlab study area since 1966. At the time of data collection in 1993, the DSS covered about 200,000 people in 143 villages. One half of the villages were part of a Maternal, Child Health and Family Planning intervention area, and the other half of the villages were in a non-intervention area (ICDDRB 1992). The villages included in the study reported here were selected from the non-intervention area, and constitute a largely natural fertility population.

Study Participants

In February 1993 a sample of 3,290 women were interviewed once as part of a screening survey for a longitudinal study of fetal loss (Holman 1996). All resident married women between the ages of seventeen and forty-six years who were present in the households visited during the survey period were interviewed. From this sample, 708 women were selected for follow-up in a 9 month prospective survey in which twice-weekly urine specimens and interviews were obtained. Women of all reproductive states who were married, living with their spouse in the study area, not using contraceptive methods, not menopausal, and in the age range 17 to 46 years, were eligible for the study. At each interview women were asked if they believed they were pregnant. Women who identified themselves as pregnant were then asked about symptoms of PRS at that and each subsequent interview.

None of the participants were under western-type medical care for their pregnancies. Participants gave informed consent prior to participation in the study. No monetary compensation was provided for participation. 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.

Interview and Specimen Collection

In the ethnographic literature of Bangladesh, it is clear that PRS is a well-recognized phenomenon (Maloney et al. 1981). We used a focus group in Matlab thana to ascertain the local names and common characteristics of PRS. This information was then used in question design for the PRS component of reproductive interviews with Bangladeshi women, conducted by female Bangladeshi field workers. In the interviews, women were asked if they were currently pregnant, and then asked if they had experienced nausea, vomiting or dizziness since the last interview. In a separate section of the interview we asked women about illness and disease-related nausea and vomiting.

Urine specimens were collected from participants in their homes at the time of the interview. Urine specimens were 'spot specimens' collected at whatever time of the morning was convenient for the participants. The majority of specimens were collected before noon but some were collected in the afternoon. Immediately after collection, the urine specimens were placed in coolers with ice packs and transported within two days to a research hospital (Holman 1996). Specimens were kept at 4ºC for up to one week and then brought to room temperature to determine pH (Horiba C-1 pH meter) and specific gravity (Atago Uricon-N urine specific gravity refractometer). A 6.5 ml sample of each specimen was taken, preserved with 17 g/L boric acid solution, and stored at -20°C. The preserved specimens were transported via frozen air freight to the US and stored at -20°C until they were assayed for reproductive hormones in 1997. The specimens underwent two to five freeze-thaw cycles, and variable times at refrigerated (never more than 2 weeks) or ambient temperatures (never more than 1 day). These

collection and storage conditions are not likely to have significantly affected the stability of the urinary steroid metabolites (O'Connor et al. 2003) or urinary hCG (de Medeiros et al. 1991).

Laboratory Assays

Urinary hCG was quantified with a microtiter plate immuno-enzymometric assay (IEMA) that used two monoclonal antibodies directed against both intact and β-subunit hCG, and a biotinylated monoclonal detection antibody specific to the β-subunit of intact and dissociated hCG (O'Connor et al. 1988). The limit of detection (mean + 3 SE above the zero standard) 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 luteinizing hormone (O'Connor et al. 1988).

Urinary PDG and E1C concentrations were determined in microtiter plate-based enzyme immunoassays (EIAs). The assays are described in detail elsewhere (O'Connor et al. 2003). Briefly, the E1C EIA used the 155B3 monoclonal antibody which cross-reacts 100% with free estrone, estrone sulfate and estrone glucuronide. The pregnanediol glucuronide assay (PDG EIA) used the Quidel 330 monclonal antibody, which cross-reacts 100% with pregnanediol-3-alpha-glucuronide and 119% with 20-alpha-hydroxy-4-pregnen-3-one. 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. Inter- and intra-assay CVs for high concentration urine control pools were 10% and 9% for the PDG EIA, and 11% and 7% for the E1C EIA.

Urine specimens were assayed in duplicate, and were added to the assays neat, or pre-diluted for higher concentration specimens. Absorbance was measured with a Dynatech MR7000 Plate Reader (test wavelength 405 nm, reference wavelength 570 nm). Hormone concentrations were estimated from optical density using a four parameter logistic model (Rodbard 1974) in Biolinx 1.0 Software (Dynex Laboratories, Inc., Chantilly, VA, USA). Standards (5β-pregnane-3α, 20α-diol glucuronide, Sigma Catalog No. P3635; Estrone-ß-D-glucuronide, Sigma Catalog No. E1752; CR 127 provided by J. O'Connor, Columbia University, USA) and in-house urine controls were run in duplicate. Hormone

concentrations were normalized using specific gravity (Miller et al. 2004), with 1.015 as the target specific gravity.

Statistical Methods

We used logistic regression to estimate the probability of each PRS symptom (nausea, vomiting, dizziness) occurring given the concentrations of three hormones (E1C, PDG, hCG), maternal age, parity and the number of previous pregnancy losses. The hormone concentrations were measured from urine samples collected twice weekly from each individual. For the i-th woman, there were m_i twice-weekly observations.

The outcomes are a series of m_i symptoms (either vomiting, nausea or dizziness) $\mathbf{v}_i = (v_{i1}, v_{i2}, \ldots, v_{im})$ for the i-th individual with an array of n covariates, $\mathbf{x}_{ik} = (x_{i1k}, x_{i2k}, \ldots, x_{ink})$, for the i-th woman (i from 1 to N) for the k-th observation (k from 1 to m_i). A series of $n + 1$ parameters were estimated, including β_0 that defines the baseline probability of the symptom occurring, and $\boldsymbol{\beta} = (\beta_1, \beta_2, \ldots, \beta_n)$ that quantifies the effects of covariates on the probability of experiencing the symptom. The effect of covariates for the i-th individual was modeled on the probability of experiencing the symptom as $p_{ik}=1/[1+\exp(\beta_0+\mathbf{x}_{ik}'\boldsymbol{\beta})+z]$. Since we have repeated measures on each individual, z is a random effect term that controls for correlations among repeated measures. We assume that z is distributed among individuals as a normal distribution, $g_z(z|0, \sigma_z)$, with a mean of zero and a variance (σ_z^2) that can be estimated from the observations. The resulting likelihood is taken as an expectation over the distribution of $g_z()$. The likelihood for the series of observations taken from N individuals, each with m_i observations is

$$L = \prod_{i=1}^{N} \int_{-\infty}^{\infty} g_z(z \mid 0, \sigma_z) \prod_{k=1}^{m_i} \left\{ \left[\frac{1}{1+e^{\beta_0 + \mathbf{x}_{ik}'\boldsymbol{\beta} + z}} \right]^{\delta_{ik}} \left[1 - \frac{1}{1+e^{\beta_0 + \mathbf{x}_{ik}'\boldsymbol{\beta} + z}} \right]^{1-\delta_{ik}} \right\} dz ,$$

where δ_{ik} is 1 if the symptom occurs at observation *k* for subject *i*, and 0 if the symptom does not occur. Values of β_0, $\boldsymbol{\beta}$, and σ_z that maximize this equation are the maximum likelihood estimates of these parameters.

Initially, parameters for all covariates were included in the regression. Covariates were eliminated sequentially and the model re-estimated until all models were found. The model with the most parsimonious set of parameters was selected using the Bayesian Information Criterion (BIC) (Raftery 1995). This criterion penalizes models for having an excess number of parameters and poor fit to the data. The final model included the set of parameters that minimized BIC. The procedure introduces a new variance component into our estimates known as *model-selection uncertainty*. One way to incorporate this uncertainty is to use Bayesian model averaging to provide estimates for all parameters averaged over all models and weighted by the estimated probability of each model. A weighted standard error term can then incorporate the model-selection uncertainty (Raftery 1996) (Raftery 1995) (Burnham and Anderson 1998). We report results for both the best fitting (or most probable) model selected by BIC, and the parameter estimates averaged over all models and weighted by the estimated probability that each model is the correct model.

Parameter estimates were found by maximizing numerically evaluated likelihoods using the *mle* programming language (Holman 2003). Numerical integration was done by a closed trapezoidal approximation over 80 points. Standard errors of the parameter estimates were found from the inverse of the observed Fisher's information matrix.

Separate analyses were done for the first 20 weeks of pregnancy and across the entirety of pregnancy.

RESULTS

Urine specimens and interviews were collected from a total of 199 pregnant women, spanning from day 10 to day 279 of pregnancy (from estimated day of ovulation, using subject reports of last menses). Individual women contributed as little as 1 and up to as many as 112 paired urine/interview observations. Concentrations for all three reproductive hormones were available for 3,664 paired urine sample/interview observations across pregnancy. The frequencies of paired urine/interview observations distributed across pregnancy are shown in **Figure 1**. Descriptive statistics for the variables examined in the analyses are shown in Table I for the full sample, and in Table II for the first twenty weeks of gestation only. The frequency of vomiting observations in the full sample was relatively low at 4%; nausea is slightly higher at 16% and dizziness is much higher at 45% (Table I). In the first twenty weeks of gestation, the frequencies of symptom observations were higher, as would be expected: 8% vomiting, 29% nausea and 53% dizziness (Table II).

The probabilities (number of observations with symptoms/number of observations on that day) of each of the PRS symptoms by gestation day are shown in **Figure 2**. Nausea and vomiting were highest in the first 15-20 weeks of pregnancy, and declined to sustained lower levels throughout the remainder of pregnancy (Figure 2). Interestingly, dizziness was also highest in the first 15-20 weeks of pregnancy, and declined slowly thereafter (Figure 2). Unlike nausea and vomiting, however, dizziness continued at comparatively high frequencies throughout pregnancy (Figure 2).

The averaged concentrations of hCG, E1C and PDG across pregnancy (derived from 3,664 specimens from 199 women) are shown in **Figure 3**. They show patterns typical of pregnancy, although there was surprisingly high variability in PDG in the second and third trimesters.

Since there were six covariates incorporated in the full model, we fitted 64 (2^6) different combinations of covariates to select the final model. Table III shows the results of the logistic regression analysis for the best fitting model for each symptom for the first twenty weeks of pregnancy. The only significant association was a higher probability of experiencing dizziness with higher levels of hCG.

When examining the relationship of hormones with symptoms across all of pregnancy, we found that the probability of experiencing nausea or vomiting was significantly higher for lower levels of estrogen and higher levels of hCG (Table IV). The probability of dizziness was increased for higher levels of hCG, and lower maternal ages, but was not associated with E1C, PDG, parity or previous losses (Table IV). Age, parity, PDG concentrations and previous pregnancy losses were not associated with the probability of nausea or vomiting (Table IV).

DISCUSSION

This study is the first to prospectively examine reproductive hormone levels and PRS symptoms using repeated biological sampling and interviews across pregnancy in a large sample of women. It is also the first to examine the association of dizziness with reproductive hormone levels in pregnancy. Our study differs from previous work in using a non-clinical, population sample of women from a rural area of a developing country. Finally, our data and statistical approach are unique in that they compare hormone levels on days (at twice weekly intervals) with and without symptoms, rather than comparing only women with and without symptoms. We did not attempt to identify or differentiate cases of hyperemesis gravidarum within our sample, and we included all cases in our analysis regardless of pregnancy outcome.

We did not find any significant associations of nausea or vomiting with E1C, PDG or hCG in the first 20 weeks of gestation in our sample. Our results corroborate the consistent finding of no association of progesterone with nausea or vomiting in three of four previous studies (Soules et al. 1980; Masson et al. 1985; Lagiou et al. 2003). Our results are not, however, consistent with findings from eleven out of fifteen previous studies which found an association of higher levels of hCG with nausea and vomiting in pregnancy (Schoeneck 1942; Kauppila et al. 1979; Masson et al. 1985; Jarnfelt-Samsioe et al. 1986; Mori et al. 1988; Goodwin et al. 1992; Leylek et al. 1996; Jordan et al. 1999; Leylek et al. 1999; Al-Yatama et al. 2002; Yoneyama et al. 2002). On the other hand, our data agree with those from three previous studies which found no association with hCG (Soules et al. 1980; Depue et al. 1987; Sekizawa et al. 2001). Our

results are not consistent with five of seven studies that found a positive association between estradiol and nausea and vomiting of pregnancy (Jarnfelt-Samsioe et al. 1986; Depue et al. 1987; Goodwin et al. 1992; Yoneyama et al. 2002; Lagiou et al. 2003), but agree with two that found no association (Masson et al. 1985; Jordan et al. 1999).

Our analyses across the entirety of pregnancy showed that higher levels of hCG and lower levels of E1C significantly increased the probability of nausea and vomiting in pregnancy. Because we did not find these relationships in the analysis of the first 20 weeks of pregnancy, we believe that the findings across all of pregnancy may be a statistical artifact of the higher frequencies of symptoms in the first part of pregnancy, when hCG levels were high and E1C levels low, and the lower frequencies of symptoms toward the end of pregnancy when hCG levels were lower and E1C levels much higher. Although this same general relationship holds for PDG and symptoms across pregnancy (low PDG, high symptoms early in gestation, higher PDG and lower symptoms later), we did not find any significant associations between PDG and nausea, vomiting or dizziness in this analysis. We attribute this to high variability in PDG in later pregnancy (see Figure 3), compared to hCG and E1C.

In analyses across all of pregnancy and in the first twenty weeks, we found that higher levels of hCG were significantly associated with an increased probability of dizziness in pregnancy. These results support a link between levels of hCG and the probability of dizziness independent of gestational age. The pattern of dizziness across pregnancy suggests that it may be an additional symptom of pregnancy-related sickness. Although there were higher levels of dizziness in the first 20 weeks of gestation, and a steady slow decline thereafter, comparatively high and sustained levels occurred throughout pregnancy. The frequency of observations with dizziness was considerably higher than nausea or vomiting (Tables I and II). Dizziness is a common complaint in pregnancy, yet we are not aware of any other studies that have examined dizziness across pregnancy. Dizziness and vertigo, such as occur in motion sickness, are closely associated with nausea and vomiting and disrupted vestibular function (Black 2002). We suggest that dizziness may be a more common and more benign symptom of pregnancy sickness than nausea and

vomiting. Further work is needed to evaluate dizziness in pregnancy, and its association with nausea and vomiting, in additional population samples.

We propose two possible explanations for why our results differ from the trend toward positive associations between nausea/vomiting and reproductive hormones, particularly hCG. First, we hypothesized that the preponderance of positive associations in most studies between symptoms and hCG and estrogens was the result of bias introduced by not comparing women matched for gestational age; thus, women sampled early in gestation before the onset of symptoms might have lower hCG and estrogens than women sampled later in the first trimester when symptoms are more likely to be present and hormone levels higher. This would be particularly a problem for hCG since this bias could occur before and after the peak, and thus increase the likelihood of positive associations. However, this explanation is not likely as most of the studies do attempt to control for gestational age (e.g. (Jarnfelt-Samsioe et al. 1986) (Masson et al. 1985) (Schoeneck 1942) (Jarnfelt-Samsioe et al. 1986)).

A second possible explanation is that hormone levels may be associated with nausea and vomiting only above a certain threshold of hormone level for those women destined to have symptoms. Western women tend to have higher levels of steroid reproductive hormones across the ovarian cycle (O'Connor et al 2003; Vitzthum et al 2004) and may have higher levels of these hormones during pregnancy, and higher hCG as well. We hypothesize that it is only at the levels present in Western women that hormone concentrations affect the likelihood of nausea and vomiting, and that a significant proportion of Bangladeshi women are below this threshold. Moreover, if dizziness is a more benign symptom of PRS, produced by the same mechanisms causing nausea and vomiting but at a lower threshold, this explanation would also account for our finding of a positive association of hCG with dizziness. Further work is needed to evaluate these possibilities.

The lack of association between hormones and nausea and vomiting may also be related to the compromised nutritional and health status of the women in our sample, as well as a low prevalence of PRS symptoms. The majority of women in Bangladesh suffer from chronic under-nutrition and infectious

disease, and have limited access to healthcare (Holman and O'Connor 2003). The average body mass index (BMI) for a large random sample of non-pregnant women between 15-45 years of age in 1992 in Matlab, Bangladesh was 18.8 ±1.9 (Ahmed et al. 1998). This is considerably lower than an average BMI of 26.5 in US women in 2003 (CDC 2003). Additionally, the women in our sample had very limited access to clinics or hospitals, or to any type of medical care aside from rehydration therapy and traditional medical practicioners (Holman and O'Connor 2003).

Although we were able to obtain mean frequency of observations of symptoms in our sample (Tables I and II), there are no comparable data in the published literature with which to compare these frequencies. Other studies report frequencies of women with symptoms, not frequency of days of observations with symptoms. As a result of right censoring, interval censoring and left truncation, we could not obtain unbiased estimates of the prevalence of nausea, vomiting and/or dizziness in the prospective sample. We do, however, have prevalence estimates of each of the symptoms from our cross-sectional screening survey from which we drew our prospective sample for the reproductive hormone study (O'Connor et al, unpublished data). These estimates are largely retrospective, and refer to symptoms in the most recent pregnancy for a woman; about 10% of the 3,290 women were pregnant at the time of the cross-sectional interview. The prevalence (number of women with symptom/number of total women) of each symptom was low in that data set: 36% reported nausea, 36% vomiting, and 42% dizziness in their most recent or current pregnancy. The total frequency of nausea and/or vomiting was 42% and all three symptoms together occurred at 51%. It is possible that low BMI and low hormone levels may be related to both a lower prevalence of symptoms and lack of association of hormones with nausea and vomiting. Future research should directly address these issues.

CONCLUSIONS

Reproductive hormones were not significantly associated with the symptoms of nausea and vomiting in Bangladeshi women. Dizziness roughly paralleled the timing of nausea and vomiting in

pregnancy in our sample, occurred at higher frequencies, was positively associated with hCG concentration, and may be an additional but more benign symptom of pregnancy-related sickness.

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TABLES

Table I. Sample Characteristics for the Full Sample

Variable	**Mean (SD)**	**Min**	**Max**	**N of observations**
Age	27.3 (5.8)	17.2	47.7	3913
Parity	2.75 (2.1)	0	9	3844
Prev Losses[a]	0.41 (0.83)	0	6	3914
Nausea	0.16 (0.37)	0	1	3882
Vomiting	0.04 (0.20)	0	1	3883
Dizziness	0.45 (0.50)	0	1	3884
hCG (nmol/L)[b]	6.2632 (7.6667)	0.00035	121.9834	3787
PDG (μmol/L)[b]	11.1216 (24.5086)	0.00604	553.7414	3893
E1C (μmol/L)[b]	0.4437 (0.4594)	0.000115	7.355972	3906

[a] Number of previous miscarriages and stillbirths

[b] Hormone concentrations are specific gravity adjusted

Table II. Sample Characteristics for the First Twenty Weeks Sample

Variable	**Mean (SD)**	**Min**	**Max**	**N of observations**
Age	26.7 (5.5)	17.2	40.7	1353
Parity	2.54 (1.76)	0	7	1335
Prev Losses[a]	0.38 (0.71)	0	4	1353
Nausea	0.29 (0.46)	0	1	1346
Vomiting	0.08 (0.27)	0	1	1346
Dizziness	0.53 (0.50)	0	1	1347
hCG (nmol/L)[b]	8.3334 (10.7193)	0.00035	121.9834	1281
PDG (μmol/L)[b]	5.9122 (10.2114)	0.015505	109.3254	1348
E1C (μmol/L)[b]	0.21726 (0.20984)	0.000115	2.40818	1348

[a] Number of previous miscarriages and stillbirths

[b] Hormone concentrations are specific gravity adjusted

Table III. Logistic regression results of the association of hormones with symptoms in the first twenty weeks of pregnancy[a]

Parameter	Best Model Estimate (SE)	BMA Averaged Estimate (SE)	Best Model Estimate (SE)	BMA Averaged Estimate (SE)	Best Model Estimate (SE)	BMA Averaged Estimate (SE)	N of estimates (models) averaged
	Nausea[b]		Vomiting[b]		Dizziness[c]		
Sigma z	1.94	1.93 (0.25)	1.59 (0.27)	1.59 (0.27)	3.96 (0.51)	3.92 (0.50)	64
Baseline	1.38	1.32 (0.32)	3.14 (0.27)	3.062(0.37)	0.41 (0.43)	-0.09 (0.76)	64
Age		0.04 (0.04)		0.05 (0.04)		0.00 (0.12)	32
Parity		0.13 (0.12)		0.16 (0.13)		0.49 (0.24)	32
Prev Losses		0.64 (0.34)		0.29 (0.35)		1.43 (0.68)	32
hCG		-0.28		-0.29 (0.16)	-0.59 (0.23)	-0.59 (0.23)	32
PDG		-0.00		-0.00 (0.02)		0.02 (0.02)	32
E1C		1.01 (1.04)		1.08 (1.36)		1.26 (1.44)	32

[a] A negative coefficient indicates a positive association

[b] *N*=1,248 observations

[c] *N*=1,249 observations

Table IV. Logistic regression results of the association of hormones with symptoms across all of pregnancy[a]

Parameter	Best Model Estimate (SE)	BMA Averaged Estimate (SE)	Best Model Estimate (SE)	BMA Averaged Estimate (SE)	Best Model Estimate (SE)	BMA Averaged Estimate (SE)	N of estimates (models) averaged
	Nausea		Vomiting		Dizziness		
Sigma z	2.07 (0.19)	2.07 (0.19)	1.58 (0.39)	1.57 (0.21)	4.26 (0.39)	4.24 (0.39)	64
Baseline	2.24 (0.22)	1.72 (0.86)	3.65 (1.59)	3.62 (0.30)	-3.8 (1.59)	-2.76 (2.33)	64
Age	-	0.08 (0.04)	-	0.02 (0.03)	0.19 (0.06)	0.19 (0.06)	32
Parity	-	-0.08 (0.19)	-	-0.00 (0.08)	-	0.18 (0.29)	32
Prev Losses	-	0.40 (0.25)	-	0.34 (0.26)	-	0.36 (0.43)	32
hCG	-0.43	-0.43 (0.12)	-0.51 (0.15)	-0.51 (0.15)	-0.59 (0.18)	-0.59 (0.18)	32
PDG	-	0.01 (0.01)	-	0.02 (0.02)	-	0.00 (0.00)	32
E1C	2.21 (0.39)	2.18 (0.39)	2.66 (0.79)	2.69 (0.79)	-	0.98 (0.36)	32

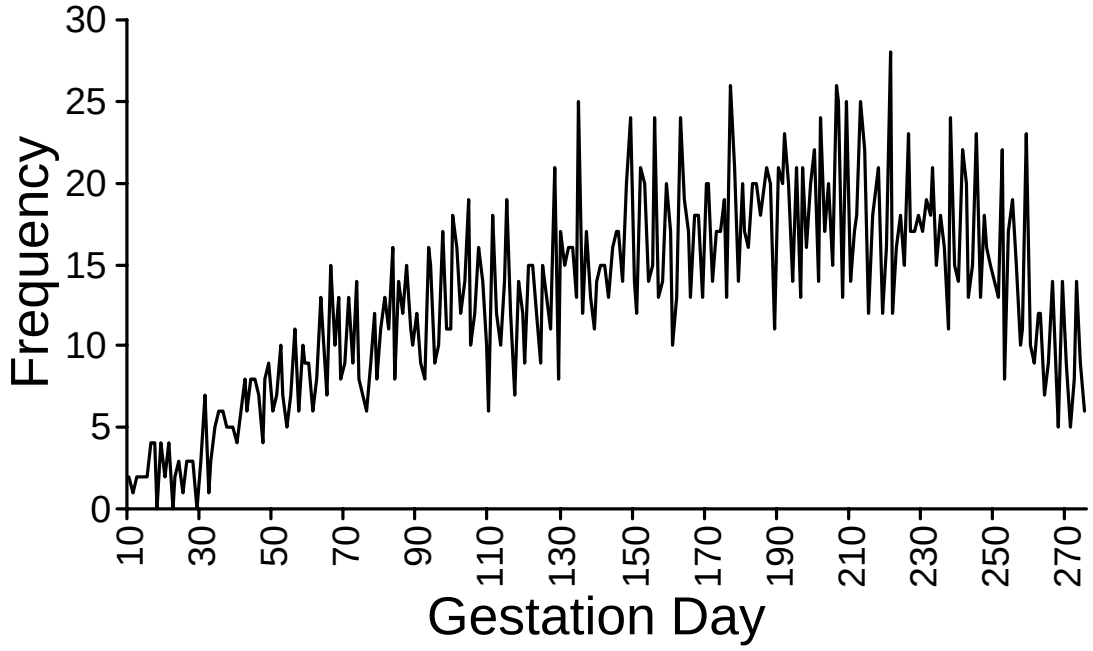
[a] A negative coefficient indicates a positive association, *N*=3,664 observations for each symptom

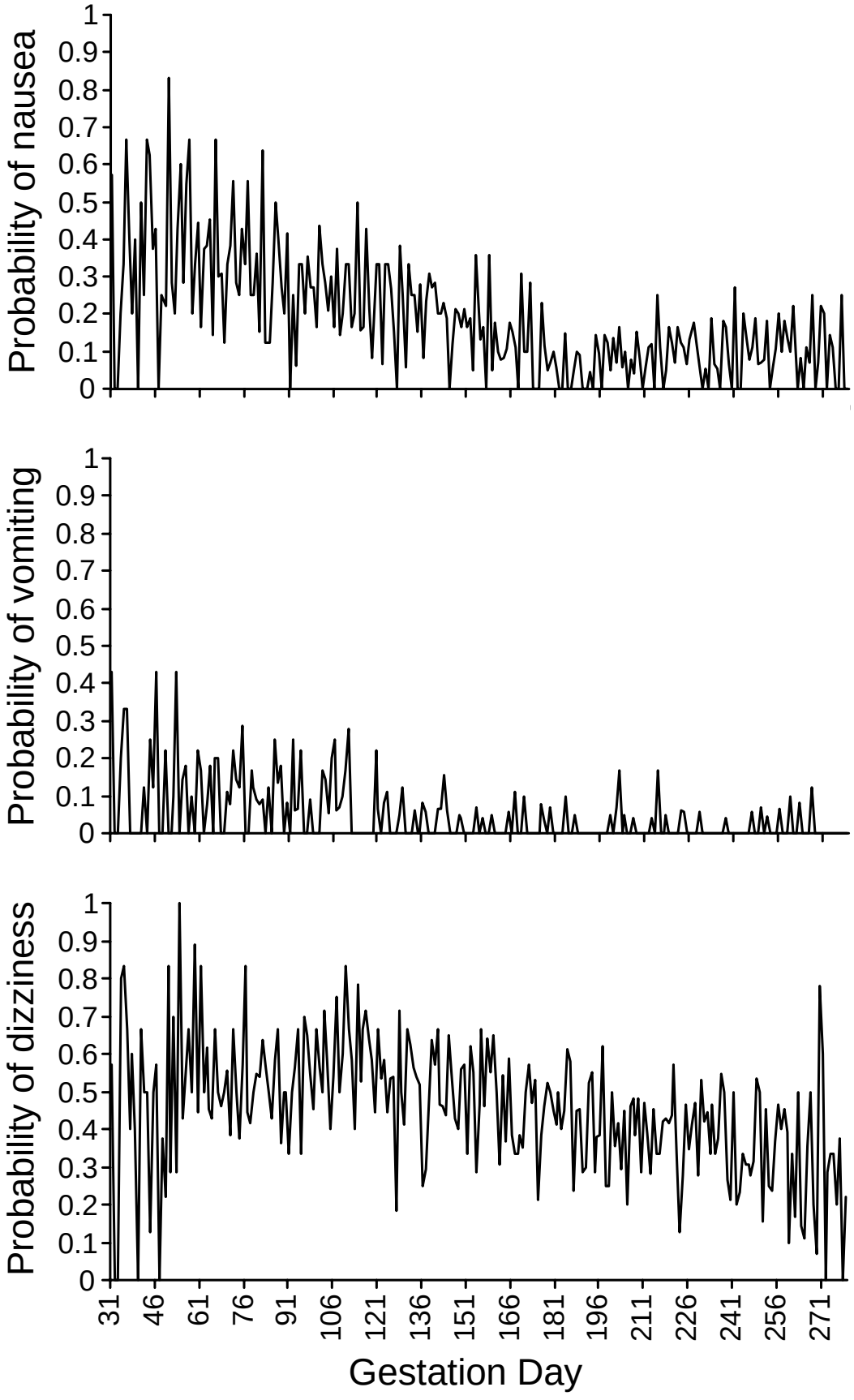
FIGURE LEGENDS

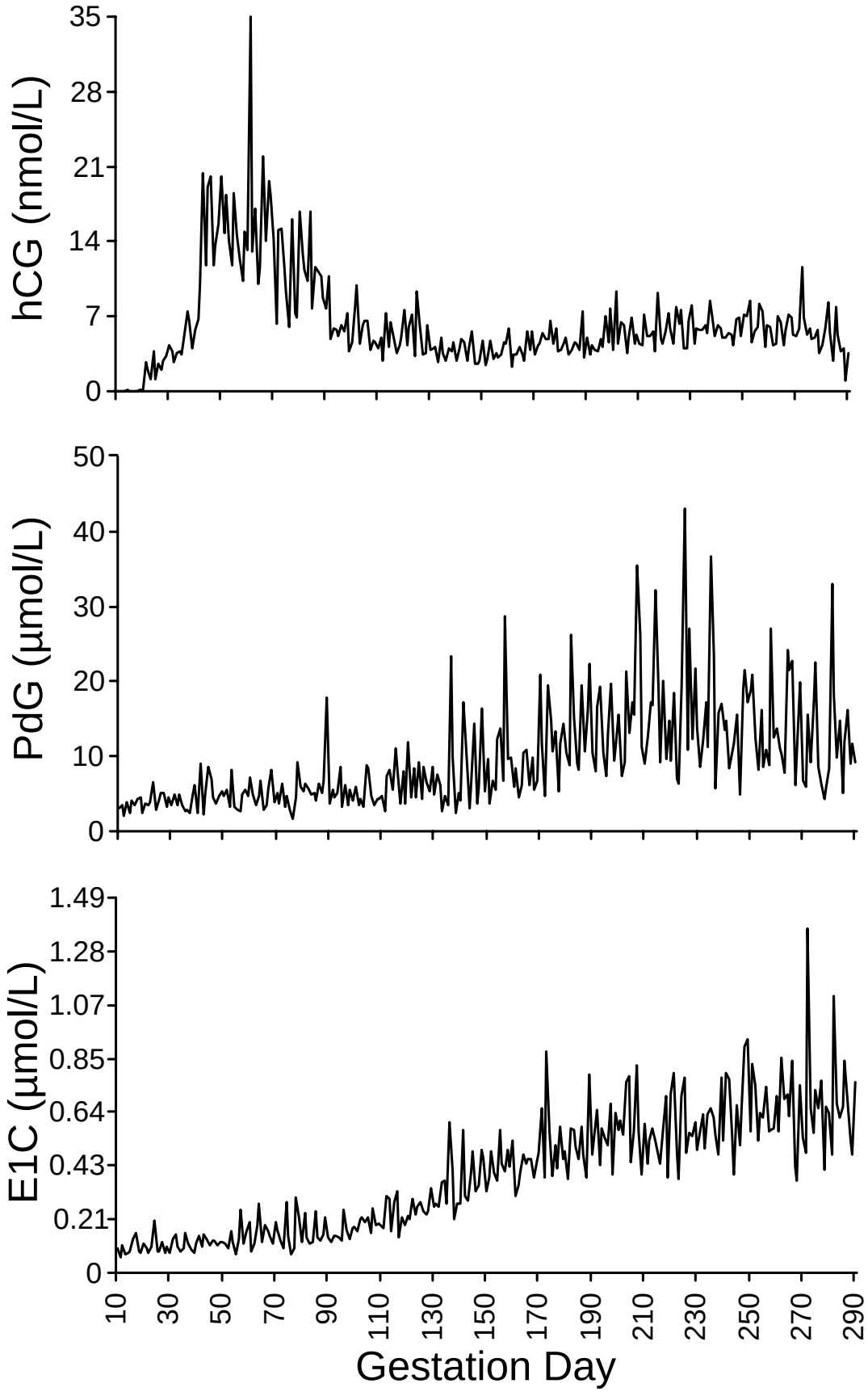
Figure 1. Frequency of paired urine sample/interview observations (3,664) across pregnancy from 199 women.

Figure 2. Probability of nausea, vomiting and dizziness across pregnancy by gestation day. Only days with 4 or more observations are shown.

Figure 3. Unsmoothed averaged concentrations of hCG, E1C and PDG across pregnancy in the Bangladesh sample (N=3,664 specimens from 199 women)


Frequency
30
25
20
15
10
5
0
10
30
50
70
90
110
130
150
170
190
210
230
250
270
Gestation Day


Probability of nausea
Probability of vomiting
Probability of dizziness
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
31
46
61
76
91
106
121
136
151
166
181
196
211
226
241
256
271
Gestation Day


hCG (nmol/L)
35
28
21
14
7
0
PdG (µmol/L)
50
40
30
20
10
0
E1C (µmol/L)
1.49
1.28
1.07
0.85
0.64
0.43
0.21
0
10
30
50
70
90
110
130
150
170
190
210
230
250
270
290
Gestation Day