R40 MC 00305-01: Assessing the Stress/Preterm-Low Birthweight Relationship

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I. Study Aim

Cumulative evidence shows that women who experience high stress levels may be at increased risk of early parturition and other adverse pregnancy outcomes.[1-11] While recent studies suggest that the effects of stress on preterm delivery (PTD) may be mediated by increases in placental secretion of corticotropin-releasing hormone, (CRH) [4,7-8,12-15] no studies have looked at this relationship among working women specifically. The majority of women work during pregnancy (63%) most work full-time.[16-17] While the gender composition of the workforce has diversified, employer policies and federal employment laws often fail to recognize the shared financial responsibilities or reproductive realities of women. [18-19] Our case-control study *Juggling Life and Work During Pregnancy* conducted in Southern California provided the unique opportunity to: 1) examine occupational, socio-demographic, family and lifestyle stressors, maternal perceived stress, CRH levels, and their relationship to PTD/LBW(low birthweight); and 2) investigate whether antenatal leave may be a beneficial intervention for reducing adverse pregnancy outcomes, particularly in higher-risk subgroups.

II. Background and Significance

Although exposure to stressors has been measured inconsistently and often imprecisely,[20] poor birth outcomes have been associated with multiple stressors including acute life events, pregnancy itself as a distressing event, chronic hassles associated with psychosocial and physical conditions of the workplace and the household, lack of social supports, poverty and racial discrimination.[1-11,15,21-22] Studies showing a relationship between high perceived stress and PTD have found a modest association—typically 1.5 to twofold increase[12,21,23]—suggesting that other moderating factors may be involved.

When individuals experience stress, they undergo a cascade of neuroendocrine responses which engage the hypothalamus-pituitary-adrenal axis (HPA) and the sympathetic nervous system. Corticotropin-releasing hormone (CRH) is the major

hypothalamic-regulator of the mammalian stress response.[24] CRH is expressed in the brain and during pregnancy by trophoblasts in the placenta, chorion, amnion and decidual cells. There is an increasing release of placental CRH into both maternal and fetal compartments over the course of gestation. The activation of the fetal hypothalamic pituitary adrenal axis (HPA) may drive a CRH mediated "placental clock" that triggers the onset of labor at term.[25-26] Recent prospective studies suggest that similar HPA axis orchestrated pathways may trigger stress-induced PTD.[14-15] Two studies have shown that compared to women delivering at term, women delivering preterm had CRH levels that were more elevated and rose earlier.[14-15] In one study, elevated levels of CRH as early as 18 to 20 weeks gestation were associated with a greater risk for PTD.[15] In another, CRH concentrations in maternal serum taken at 7 to 23 weeks gestation were higher in women who delivered preterm.[27] Furthermore, CRH measured at delivery in umbilical plasma and in third trimester maternal plasma were far higher in term low birthweight compared to term normal-birthweight fetuses.[28-29]

Whether maternal stress has a direct effect on pregnancy through excessive production of CRH and early onset of labor and/or through the sympathetic nervous system is not well understood. Hobel et al, in a preliminary study of 18 women who had spontaneous preterm delivery matched to 18 full-term controls, found that self-reported maternal stress and state anxiety ascertained prospectively at 18 to 20 weeks gestation predicted a rise in CRH levels at 28-30 weeks gestation.[13-14] Erickson et al in a larger prospective study of pregnant Danish women also found that certain social and behavioral risk factors among women who delivered preterm were associated with higher levels of bound CRH.[27] It appears that the nature, timing and chronicity of the stress measure may affect CRH production and its contribution to preterm delivery and fetal growth.[8] Our study examined perceived stress, CRH, and other social, occupational, and behavioral factors that may be related to delivery of a preterm or term low birthweight infant in working women. We postulated that high levels of CRH and perceived stress are each associated with an increased risk of delivering a preterm or term low birthweight infant; and examined whether CRH mediates a maternal stress-birth outcome relationship; or whether stress in the presence of elevated CRH may have a stronger effect on birth outcomes (moderation effect).

Working women who feel stressed during pregnancy may arrange with their employer to take maternity time off to reduce stress and fatigue. Studies conducted in Mexico, Canada, Spain and France where maternity leave policies protect pregnant working women, indicate beneficial effects of pregnancy leave on reducing the risk of preterm delivery, intrauterine growth retardation and caesarean sections. [30-33] Our study examined the actual patterns of antenatal leave taking and the characteristics associated with leave among pregnant workers from Southern California. It is the first epidemiological study in the US to assess whether state-supported pregnancy leave

may be beneficial for prolonging gestation, increasing birthweight and buffering against C- sections.

California is one of five states at the forefront of providing paid pregnancy leave. Leave is generally paid for up to four weeks before birth, and up to six weeks after a vaginal delivery or eight weeks after a c- section. Cash benefits, averaging $293/week in 2003, derive from temporary state-sponsored non-occupational disability insurance funded through employee payroll deductions.[34] Women working for public or private employers with five or more employees are covered. In other states, the more restrictive federal Family and Medical Leave Act (FMLA) prevails. FMLA allows parents to take up to 12 weeks of *unpaid* job protected leave around the birth of a child or to provide family care.[35] The law only applies to full-time employees working for at least one year in companies with 50 or more employees. FMLA covers less than half of the workers in the private sector; part-time employees and those working in informal labor markets do not benefit. While studies show increases in family leave uptake since the law was enacted in 1993, because leave is unpaid, many FMLA-eligible employees cannot afford to take leave, even if they are stressed and tired. [36]

III. Study Design, Sampling, Measures and Data Collection Procedures

Participants were from a case-control study, *Juggling Work and Life During Pregnancy*, designed to examine the relationship between stress, CRH, antenatal leave and pregnancy outcomes. All women participated in the California Department of Health Services expanded alpha fetoprotein Prenatal Screening Program (XAFP) in three Southern California counties (Orange, Imperial and San Diego). Women delivering live births between July 2002 and December 2003 were eligible for contact if they were at least 18 years old, delivered within 6.5 months of the interview date, had a singleton birth without congenital anomalies, and had a U.S. mailing address. Live birth records were matched to XAFP records corresponding to the regional lab serving these three counties, yielding 38,383 women with linked data in our sampling frame.[41] Sampled women included all women delivering preterm (PTD) or low-birthweight (LBW) infants (n=3,361) according to last menstrual period and birthweight from birth records registered between July 2002 and August 2003, and a random sample of controls delivering normal weight at term (≥ 37 weeks gestation) (n=3,366) frequency-matched on race and month-of-birth , as well as 504 unmatched low birthweight cases registered between September and December 2003, included to improve study power for LBW analyses.

Sampled potential participants were mailed an introductory letter one to six months after delivery and subsequently prescreened by telephone to ascertain that they had worked 20 hours or more per week during the first two trimesters of pregnancy or through the date of prenatal testing. Telephone prescreening was attempted for 6,506 women who were within the eligibility time period and had telephone contact

information from prenatal screening records. Among women invited to participate in the 45 minute postpartum telephone interview, 3,655 women were successfully contacted. Out of the 3,655 successful contacts, 740 women (20%) refused participation and 1592 (44%) were not eligible because they were not working at least 20 hours per week during the designated period. Of the remaining 1,323 eligible women, 109 were unable to complete the interview, yielding 1,214 completed interviews. The response rate among women eligible for the study was 73%. Work eligibility and refusal rates were identical among women delivering preterm or term LBW infants and control women.

Banked maternal serum from blood drawn at the time of XAFP testing between 15-20 weeks gestation was analyzed for CRH by radioimmunoassay. Two specimens were unavailable for use, 11 had blood draws outside the 15-20-week range, and 39 were excluded because of birth defects.

During the post-partum interview conducted one to 6.5 months after delivery, participants were queried about antenatal leave arrangements, work and family stress; stressful life events; lifestyle, occupational and demographic characteristics; obstetric risks and birth outcomes. Bilingual Spanish-English interviewers used CATI (Computer Assisted Telephone Interviewing) software to enter the responses into a database and offered $10 gift cards to participants in return for a completed interview. The study protocol was approved by the Committees for the Protection of Human Subjects at the University of California, Berkeley (No. 2003-5-115) and by the California Health and Human Services Agency (No.02-10-18.)

*Key o*utcomes included *preterm delivery(PTD)* defined as less than 35 completed weeks gestation , near term delivery at 35-36 weeks gestation, and *term low birthweight*, defined as delivery at 37 weeks or beyond and infant weighing <2500 grams. We characterized PTD in this way because these subgroups have overlapping yet distinct etiologies and younger gestational ages represent more severe cases. [37] We classified cases based on the gestational age dates used by the prenatal screening program, instead of gestational age dates from birth records as was used for sampling, in order to improve accuracy; in 62% of records, early ultrasound dating was employed. The final sample included 441 cases (359 PTD, 82 term LBW) and 721 term normal birthweight controls. We also examined gestational age as a continuous variable when assessing the effects of antenatal leave.

Stress Exposures. Perceived stress was assessed with a standard measure which uses a single question, i.e. “how often did you feel stressed during the second trimester of pregnancy?” [38] It was categorized as never, seldom, often or always and responses were collapsed into a 3 level variable, always, often, and seldom/never stressed. Evidence from a prospective study suggests that a single assessment in second trimester may be sufficient to assess stress response.[39]

Because perceived stress was assessed postpartum, we examined recall bias. Women interviewed up to 16 weeks postpartum (median time) were as likely to report high stress as women interviewed later, suggesting that reporting of stress was not strongly biased by duration of recall, a non-differential misclassification error. The relationship between perceived and objective measures of stress (e.g. having children under age five, a married status, high exposure to physical stressors at work and/or home) was consistent between cases and controls, suggesting that stress reporting was not exaggerated among cases. However, differential misclassification error cannot be ruled out.

CRH levels were evaluated in maternal sera stored at-20ºC between 339 to 915 days (mean=638) after extraction by laboratory technicians who were blind to case-control status. We followed the same extraction method of CRH using methanol (3.5 mL) from serum (0.5 mL) as Holzman et al.[40] and measured CRH using the sensitive radioimmunoassay procedure described by Siler Khodr et al.[41] Log CRH increased linearly with day of gestation at blood draw. To adjust for this relationship, log-transformed CRH was regressed on gestational age at blood draw among controls, and residuals for cases and controls obtained from the resulting regression formula, were then added to the overall mean CRH value. We examined log CRH with respect to birth outcomes using non-parametric smoothes from generalized additive models [42] for visual comparison with linear and quadratic models. We chose the quadratic model if the Akaike Information Criterion (AIC) indicated it was a better fit to the data.

Other independent variables included in the analyses consisted of *socio-demographic* variables: maternal age; parity; maternal race/ethnicity; marital status; annual household income; highest educational attainment at the time of delivery; type of health insurance, whether private or public; the number of children under age five, and type of occupation. *Occupational stressors* included: work shift; flexibility in setting one's own work schedule; job fulfillment; commuting time to- and- from work; the imbalance between work efforts and rewards; and, exposure to a number of physical stressors including bending at least ten times per hour, standing for more than 4 hours, carrying or lifting heavy things weighing more than 15 pounds on a daily basis, operating heavy machinery, and exposure to high levels of noise or uncomfortable temperatures.

We measured *housework exertion* as lifting of items or children weighing more than 15 pounds each day, and hours of standing for at least 4 hours while doing housework. Exposure to the two physical stressors at home were combined with the six physical stressors at work into one measure similar to Mamelle's occupational fatigue index [3] in which each stressor was scored as 1=exposed or 0=unexposed. Women exposed to 3 or more physical stressors, a sensitive cutoff for PTD in this dataset, were classified as high.

Behavioral/social variables included smoking during the three months prior and during pregnancy, trimester of prenatal care initiation and number of adverse life events. The latter was evaluated with the Life Events Inventory (LEI) modified for use with pregnant populations.[6] Participants were asked about 23 life events that they may have experienced during pregnancy or that happened to someone close to them.

Antenatal leave was measured by self-report and refers to an arrangement whereby women take pregnancy leave with the expectation of returning to their job or employer sometime after giving birth.

Obstetric risks were determined by a history of previous adverse outcomes (spontaneous abortions, low birthweight and/or preterm deliveries), pre-pregnancy body mass index (BMI), and height (<5 feet vs. ≥5).

IV. Main Findings and Statistical Techniques Employed

A. Psychosocial Stress, CRH, Preterm Delivery and Term Low Birthweight

We explored whether: (i) social, occupational and behavioral factors in addition to perceived prenatal stress and second-trimester CRH levels are related to delivery of a preterm or term low birthweight infant in our sample; (ii) CRH levels in maternal blood at 15-20 weeks gestation are associated with second trimester perceived prenatal stress; (iii) CRH mediates a maternal stress-birth outcome relationship; and (iv) stress in the presence of elevated CRH may have a stronger effect on birth outcomes (moderation effect).

We performed bivariate analyses using SAS to examine the sociodemographic, occupational, housework and behavioral characteristics, obstetric risks, CRH levels and perceived stress by case status. Odds ratios adjusted for matching of cases and controls on race and month of birth and 95% confidence intervals were calculated to examine the relationship between the two exposures (CRH and perceived stress) among controls and between each exposure and each outcome (PTD <35 weeks, PTD 35-36 weeks and term LBW). Due to frequency matching of controls on race/ethnicity and month of delivery, all odds ratios were adjusted for these factors using logistic regression (i.e. strata adjusted). Odds ratios were further adjusted in multivariable regression models that included candidate covariates that met one of the following criteria: 1) shown to be important determinants of birth outcomes in the literature (i.e. age, height and BMI); 2) associated with outcome at $p<.10$ in unadjusted analyses; or 3) adjustment changed the odds ratios for stress or CRH by at least 5%.[43] Covariates were then eliminated from multivariate logistic models if they were no longer predictive of outcome or their exclusion did not alter the odds ratios by 5%. In separate logistic models, we explored interactions between perceived stress, and CRH on the odds of each adverse outcome.

Sample Characteristics
Compared to Controls (no PTD or LBW)

- **Women who delivered preterm at <35 weeks gestation were more likely to:** be overweight or underweight, have had a previous adverse outcome, a lower annual household income ($25,000 to $50,000 vs. > $75,000), to be fulfilled at work, to perceive prenatal stress often or always in the second trimester, and experience at least 3 life events during pregnancy.
- **Women who delivered at 35-36 weeks gestation were more likely to:** be underweight, have a history of adverse birth outcomes, not be married, have a post-graduate education, rank in the top tertile for CRH, and experience stress often or always.
- **Women who delivered term low birth weight infants were more likely to:** have had one previous birth, experience a commute of over 90 minutes to/from work, be underweight, of short stature, rank in the second or third tertile for CRH and to report always feeling stressed during the second trimester of pregnancy. .

CRH and Stress

We found no evidence that high log CRH was associated with high perceived stress. The odds ratio for the top tertile for CRH and high perceived stress (defined as often or always) in the control group was 0.79 [95%CI=0.57, 1.10], and was similar across the outcome specific subgroups of cases (among PTD OR_{CRH} =0.74 [95%CI=0.48, 1.12]); among TLB OR_{CRH}=0.62 [95%CI=0.25, 1.54].

Log CRH and Birth Outcomes

The shape of the association between log CRH levels and PTD <35 weeks was linear, as was the association between log CRH levels and term low birthweight . However, a quadratic model more adequately fit the association between log CRH levels and near term deliveries at 35-36 weeks with no discernable relationship until log CRH levels reached 4.0 log CRH pg/mL, which corresponds to the 50th percentile.

- Women with higher log CRH levels showed higher odds of PTD <35 weeks gestation in a strata adjusted model (OR=1.32 [95%CI=0.96,1.83]). This association was strengthened after multivariate adjustment (OR=1.46 [95%CI=1.04, 2.07]).

- There was no association of CRH with PTD 35-36 weeks at levels below 4.0 in strata adjusted models (OR=0.77[95%CI=0.39,1.53]), however at log CRH levels above 4.0 the OR for CRH was 2.38[95%CI=1.38,4.10]. This elevated risk remained after multivariate adjustment.

- The linear association of log CRH was even stronger with term low birthweight than with PTD in the strata adjusted model (OR=1.74 [95%CI=1.14, 2.66]) and

remained similar after further adjusting for covariates (OR=1.77 [95%CI=1.13, 2.77]).

Perceived Stress during the Second Trimester and Birth Outcomes

- The risk of delivery at <35 weeks gestation was higher among women who perceived stress as occurring often and always as shown in the strata adjusted model (OR=2.08 [95%CI=1.43, 3.04] and OR=2.36 [95%CI=1.23, 4.51] respectively). This dose-response relationship with risk of delivery at <35 weeks remained elevated after multivariate adjustment (OR=2.04 [95%CI=1.35, 3.08] and OR=2.76 [95%CI= 1.35, 5.64] respectively).

- Near term delivery at 35-36 weeks gestation was also associated with having perceived stress often (OR=1.34 [95%CI=0.95, 1.89]) and always (OR=1.79 [95%CI=0.98, 3.25]) in strata adjusted models and followed a dose-response pattern. These relationships were strengthened after further adjusting for covariates (OR=1.40 [95%CI=0.98, 2.0] and OR=1.96 [95%CI= 1.04, 3.69] respectively).

- Only women who always perceived stress in the second trimester were at increased risk for term low birthweight as shown in the strata adjusted model (OR=2.74 [95%CI=1.30, 5.77]). This stress association grew even stronger after controlling further for covariates (OR=3.19 [95%CI=1.39, 7.37]).

Mediation and Moderation Models

- The odds ratios for CRH were unaffected by adding perceived stress to the model and vice versa No interactions were found between CRH and race or life events for any birth outcomes. Among near term deliveries at 35-36 weeks gestation, the relationship between perceived stress and the outcome was evident only in the presence of high life events (3+) [OR=2.28;95%CI=1.30, 3.98]) vs. low life events [OR=0.96;95%CI=0.61, 1.52]

B. Utilization of Pay-In Antenatal Leave

To examine antenatal leave arrangements among pregnant workers and the occupational, demographic and well-being characteristics associated with leave taking, we first estimated the take-up rates of antenatal leave, quitting, no leave, and other time off. Chi-square tests were used to compare occupational, demographic and well-being characteristics among the main study groups: leave takers, quitters and no leave takers. We used logistic regression to estimate adjusted odds ratios and their 95% confidence intervals of a) taking antenatal leave versus no leave, b) antenatal leave versus quitting, and c) quitting versus no leave, controlling for covariates.

Analytic weights were used to adjust the sample back to the birth population by accounting for the over sampling of PTD and/or LBW infants and frequency matching of controls to cases. All weighted analyses were conducted using survey procedures in SAS version 9.1.2 [44] to calculate appropriate standard errors.

- We found that 52% of women took no leave, 32% took antenatal leave expecting to return to their job or employer sometime after giving birth, 9% quit their jobs, 5% cut back on their hours and 2% were fired during pregnancy. For leave-takers with paid leave (69%), the state was the main source of pay (74%). Medical problems (52%) rather than maternity leave benefits (25%) were the most common stated reasons for taking leave.
- After controlling for covariates the strongest predictors of leave-taking versus working through pregnancy were feeling both stressed and tired (OR=4.3, 95% CI [2.2-8.2]) and having young children (OR=2.1, 95% CI [1.2-3.7]), followed by occupational factors (night shift, unfulfilling and inflexible work, employment less than one year).
- Lack of employer-offered maternity leave benefits was associated with increased quitting relative to both leave-taking and working through pregnancy. Overall, 63% of women and 69% of antenatal leave takers were offered leave by their employer. Quitters were less likely than antenatal leave takers to have paid maternity leave (39% vs. 75%).
- The sources of pay for women with paid leave were similar for leave-takers and quitters, with the state covering 74% and 78%, and employers covering 21% and 23%, respectively.
- On average, antenatal leave takers stopped work one month later in pregnancy than quitters (33 weeks [95% CI=32.6-34.2] vs. 29 weeks gestation [95% CI=27.1-31.3]); 55% of leave takers exceeded the 4 weeks of antenatal leave allowed by the state.
- Lifetable analysis revealed that 50% of leave-takers, 51% of non-leave takers, and 15% of quitters returned to work by three months postpartum.

C. Assessing the Effects of Antenatal Leave Taking on Birth Outcomes

The purpose of this analysis was to identify women for whom antenatal leave would be beneficial. The outcome examined was gestational age. (We are in the preliminary stage of evaluating other outcomes, including birthweight and caesarian sections.) We restricted the analyses to women employed at least 35 hours/week since they are likely to have the least flexibility in re-arranging their schedules when they feel stressed or tired. To examine the relationship between antenatal leave and gestational age at birth we used life table models and were guided by the assumption that 39 completed weeks (i.e. 273 days) is the minimum gestational age recommended for delivery. Evidence suggests that delivery even a few days earlier is associated with higher respiratory distress for infants.[45-46] Caesarean delivery before the onset of labor is the main factor putting these babies at increased risk. [45] We

excluded post-term deliveries by truncating the outcome at 41 weeks in order to restrict estimates of average increases in gestational age to a desirable range. To examine the effects of antenatal leave on gestational age at birth, we used Cox proportional hazards models, treating leave as a time-varying covariate.[47] Failure to account for the timing of leave in relation to gestational age could lead to spurious results, as women delivering earlier have less opportunity to take leave and would thus appear to be non-leave takers. With leave as a time-varying covariate, the relative hazard of delivery associated with leave-taking is evaluated among those who have not yet delivered at each day of gestation. The hazards and odds ratios were further adjusted for other occupational, socio-demographic, lifestyle and health status covariates.. Further Cox modeling was performed in stratified analyses to investigate effect modification within subgroups of interest that were amenable to change through leave taking. All analyses were weighted by the inverse probability of sampling to account for the case-control design and frequency matching.

The first set of stratified analyses examined the relationship between antenatal leave taken prior to 36 weeks gestation (early leave) and of antenatal leave taken at or after 36 weeks gestation (late leave) on gestational age at birth. We used the 36 week cutoff based on policy relevance, given that women in California are eligible for paid leave four weeks prior to delivery. In addition, as expected, early leave was associated with medical complications during pregnancy and this association is likely attributable to reverse causality, i.e. medical complications contribute to leave taking.

- Late leave prolonged gestation, although the overall effect was not significant (HR=0.88; 95%CI=0.70-1.12). After adjusting for maternal age, parity, race/ethnicity, public or private prenatal insurance, occupation, chronic medical problems and infant sex, the benefit of leave in prolonging gestation remained about the same (HR= 0.89; 95%CI=0.69-1.14).
- We performed further stratified analyses to identify the sub-groups of women which appear most likely to benefit from leave taking. Three vulnerable groups stood out as benefiting from the effects of late leave: women whose efforts outstripped their rewards at work (HR=0.69; 95%CI=0.48-1.0); women reporting sleeping on average no more than 6 hours a night (HR=0.68; 95%CI=0.45-1.05) and women who often or always experienced anger (HR=0.43; 95%CI=0.18-1.04) Women with these characteristics comprised 62% of the population of full time- workers.
- Preliminary results from our analyses suggest a protective effect of leave for birthweight and caesarean section.

V. Discussion and Interpretation of Findings

Consistent with recent evidence [14-15,27-28] we found that after adjusting for other covariates, elevated CRH levels measured between 15 and 20 weeks gestation, significantly increased the risk of delivery prior to 35 weeks gestation, near term

delivery at 36-37 weeks gestation and of term low birthweight. Additionally, similar to recent studies [13,23, 48-49] we found an increase in the odds of both early preterm and near-term delivery with increasing levels of perceived prenatal stress, suggesting a dose-response effect and an association between perceived stress and term low birthweight at high levels of stress. Nevertheless, we found no evidence that CRH mediates the maternal stress-preterm relationship, as indicated by the lack of positive bi-variate association between perceived prenatal stress and CRH in the second trimester of pregnancy. We also found no marked change in the CRH effect on each of the PTD outcomes when adding stress into the adjusted models, suggesting the CRH effect is independent of perceived stress. Maternal stress, which may be more closely associated with stressors external to the pregnancy, and CRH, which has been strongly associated with fetal distress in the literature, [8,28] may have significant, yet different pathways to PTD.

Furthermore, we found no evidence of effect modification of CRH on the stress-birth outcomes relationships. Further research is needed to examine the factors associated with CRH and maternal perceived stress and to assess the mechanisms by which stress and CRH affect birth outcomes.

From a policy perspective, antenatal leave-taking during pregnancy may be one strategy that could potentially ameliorate stress and fatigue in working women, providing beneficial effects in prolonging gestation and buffering against other adverse pregnancy outcomes.

Our findings show that the majority of women (52%) work through their pregnancy and only one out of three women take antenatal leave with the expectation of returning to their job after delivery, with an additional 9% quitting employment. A recent Census Bureau report showed that between 1991-95, 35% of US pregnant working women took antenatal leave and 23% quit their jobs.[48] Our findings suggest that paid state disability benefits offered in California are not contributing to excess antenatal leave-taking or quitting among working women.

Among antenatal leave-takers in our study, the majority stated that they stopped work due to health reasons or physical discomfort that prevented them from carrying out their work activities. Women were far less likely to use time off to take advantage of the antenatal leave cash benefits, to prepare for the birth, or to give themselves rest and relaxation. Moreover, as our multivariate models indicated, the strongest predictors of leave-taking compared to working through pregnancy were feeling stressed and tired during the second trimester and having children under the age of five. These findings suggest that rather than being used predominantly as a health promoting behavior, antenatal leave constitutes a coping response to stress and tiredness and the need to mother young children, in itself a potentially stressful and tiring activity.

Women who are stressed and tired in the second trimester also tend to have more medical problems. This association may help to explain why among full-time workers, women who took early leave (prior to 36 weeks gestation) had a higher probability (hazard ratio) of delivering earlier than women who continued working through pregnancy. In contrast, women who took later leave at 36 weeks or later

experienced benefits of leave in prolonging gestation. The beneficial effects of late leave versus no leave were not statistically significant overall, but were much stronger for women who during pregnancy reported that they lacked sufficient sleep, felt angry and experienced an effort/reward imbalance at work. These findings are from the first study to examine the health effects of pregnancy leave among US working women and need to be corroborated by further research. Studies done abroad support our findings that antenatal leave may protect against obstetric interventions and poor pregnancy outcomes.[30-33]

We also found that most non-leave takers are offered leave by their employers and are eligible for state-funded benefits. Non-leave takers are more likely to be affluent and to have a post-graduate education compared to women who take antenatal leave or quit work. Non-leave takers are also more likely than leave-takers to feel fulfilled with their work and to feel less stressed and tired. These findings corroborate the Census Bureau report on national maternity leave and employment patterns.[50] The results further suggest that a strong work attachment and fear of sacrificing career advancement opportunities deter such women from taking leave, rather than immediate financial need. However, our findings suggest that by not taking time off during pregnancy, vulnerable women who work straight up to the point of delivery and who feel highly stressed (i.e. do not get enough sleep, feel angry, experience an effort/reward imbalance at work) may be incurring the risk of delivering earlier. Since deliveries before term are associated with increased infant feeding and maturation problems, heightened maternal anxiety and bonding difficulties, prolonging gestation to 39-40 weeks can give mother and child a healthier start.

The findings from this study require cautious interpretation. The *Juggling Life and Work During Pregnancy* study used a retrospective study design and relied on self-appraised measures of stress. These measures are vulnerable to recall bias since reporting of stress could have been influenced by the outcome of birth. We did not observe evidence of recall bias related to duration of recall or exaggerated stress responses to specific stressors among cases compared to controls. However, differential misclassification cannot be ruled out. Because we could not ascertain the timing of obstetric risks in relation to the second trimester, we were unable to evaluate whether early pregnancy medical problems may have confounded our perceived stress measure. Furthermore, we only measured CRH at one point in pregnancy and we did not assay its binding protein which may limit the biological activity of circulating placental CRH.

Our study was limited to women working at least 20 hours a week for two consecutive trimesters, and for some analyses it was restricted to those who worked for at least 35 hours/week. Since women who work during pregnancy are likely to represent a healthy population, results may not apply to other populations. Because working status was determined after sampling and initial consent, it is not possible to determine how representative the final sample is of working women. In addition, we were unable to confirm the reported employment and leave patterns, the employment

benefits, or demographics of our study population, yet these measures are objective and presumably less subject to recall bias. Moreover, we employed seasoned telephone interviewers and provided training and continuous feedback.

We were also limited in our ability to study the effects of voluntary antenatal leave taking on adverse birth outcomes due to most women's desire or need to work as long as possible during pregnancy and a lack of paid benefits to cover leave much before 36 weeks gestation. Furthermore, we could only study the relationship of leave taking with outcomes starting at 36 weeks because of medical confounding and reverse causality. It is not possible for leave after 36 weeks gestation to have an impact on early preterm deliveries. If leave were taken for rest and relaxation prior to 36 weeks it would be unusual in our workplace culture and, as presently designed in California, unlikely to be covered by maternity insurance. Non-leave takers could have been subject to misclassification as we were unable to identify women who used sick and vacation days off in lieu of formal leave. Furthermore, non-leave takers may have had less opportunity to take leave due to preterm delivery. However, we estimate that only 0.3% of non-leave takers would have taken leave had they not delivered early. Furthermore, because younger women were underrepresented in our study, the proportion of quitters may be underestimated.

Despite these limitations, we conclude that working pregnant women in California appear to be cautious in their leave-taking behaviors utilizing antenatal leave more to cope with health problems and fatigue rather than for health promotion. Maternal perceived stress and elevated CRH levels during the second trimester are significant independent determinants of adverse birth outcomes among working women. Maternal stress may be amenable to intervention through pregnancy leave, particularly among the subgroups of women who are sleep deprived, feel angry and experience effort-reward imbalances at work during pregnancy. Healthcare providers can facilitate access to antenatal leave for working women for whom leave is beneficial by fostering an environment that promotes antenatal leave as a viable option. We recommend that organizations offering clinical practice guidelines consider a more definitive stand using research-based evidence to support this issue. Job-protected, paid antenatal leave can strengthen work stability and economic security, while potentially promoting women's health. Since California leads the nation in its efforts to provide paid maternity leave, findings from our study may help to increase awareness of the benefits that maternity leave policies can provide to pregnant working women in California and other states.

Further research is needed to determine how antenatal leave versus working through pregnancy affects the pregnancy outcomes explored in this study as well as other outcomes such as breastfeeding and postpartum adjustment, Given that the biological mechanisms through which stress may contribute to preterm birth, term low birth-weight and C-sections are not well understood, future research needs to examine the pathways through which maternal perceived stress and CRH affect various health outcomes. Further research should also distinguish between spontaneous and medically-indicated deliveries and should examine the role of duration and timing of stress to assess critical periods and cumulative exposure in the

relationship between stress and birth outcomes with multiple points of exposure assessment.

VI. Products

a. Peer reviewed articles:

Guendelman S, Pearl M, Graham S, Angulo V, and Kharrazi M. Utilization of pay-in antenatal leave among working women in Southern California. *Maternal and Child Health Journal* 2006; 10:63-73.

Guendelman S, Pearl M, Graham S, Holzman C, Hubbard A, Kharrazi M. Psychosocial stress, corticotropin releasing hormone, preterm delivery and term low birthweight among working women. *Under review.*

Guendelman S, Pearl M, Graham S, Hubbard A, Kharrazi M. The relationship between pregnancy leave and perinatal outcomes among working women in Southern California. *In preparation*.

b. Masters theses:

Stachel L. Psychosocial job strain during pregnancy and preterm birth: Does Full time employment make a difference? May, 2006.

Ertel K. Testing a clustering technique to measure prenatal stress. May, 2004

c. Conference presentations: (Co-authored by Guendelman S, Pearl M, Graham S, Hubbard A, Kharrazi M)

"Maternity Leave Arrangements Prior to Delivery Among Working Women." Presented at Rockefeller Institute, Bellagio, Italy, March 31, 2004. (Also co-authored by V.Angulo)

"Antenatal Leave and its Impact on Birth Outcomes among Working Pregnant Women in California". Poster presentation in two sessions at APHA, Washington DC November 8 and 9, 2004.

"Psychosocial Stress, Corticotropin-releasing Hormone and Preterm Delivery among Working Women". Presented at Plenary Session 1: Stress, Biomarkers and Preterm Birth. Society for Pediatric and Perinatal Epidemiologic Research. Toronto-Canada June 26, 2005. (Also co-authored by C. Holzman)

"Psychosocial Stress, Corticotropin-releasing Hormone and Advrse Birth Outcomes among Working Women. Poster presented at SER:Epidemiology Without Borders, Toronto-Canada June 29, 2005.(Also-co-authored by C. Holzman)

d. Press conferences:

Various local Radio Programs;National Public Radio;Oakland Tribune; and a live interview on the Dean Edell TV show, a popular show in the San Francisco Bay Area..

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