Title

When stress happens matters: Effects of earthquake timing on stress responsivity in pregnancy

Journal

American Journal of Obstetrics and Gynecology, 184(4)

ISSN

0002-9378

Authors

Glynn, Laura M
Wadhwa, Pathik D
Dunkel-Schetter, Christine
et al.

Publication Date

2001-03-01

DOI

10.1067/mob.2001.111066

When stress happens matters: Effects of earthquake timing on stress responsivity in pregnancy

Laura M. Glynn, PhD,[a] Pathik D. Wadhwa, MD, PhD,[b] Christine Dunkel-Schetter, PhD,[c] Aleksandra Chicz-DeMet, PhD,[a] and Curt A. Sandman, PhD[a]

Irvine and Los Angeles, California, and Lexington, Kentucky

OBJECTIVE: The purpose of the study was to assess the effects of the timing of stress during pregnancy on emotional responses and birth outcome. We hypothesized that as pregnancy advanced women would become increasingly resistant to the adverse effects of stress, and so early stress would have more profound effects than later stress.

STUDY DESIGN: Forty pregnant women who had experienced an earthquake during pregnancy or shortly afterward were identified. Using regression analyses we determined whether the timing of the earthquake was related to an affective response to this event and to length of gestation.

RESULTS: The earthquake was rated as more stressful when it occurred early in pregnancy compared with late in pregnancy, and postpartum ratings were similar to first-trimester ratings (r_{quad} = .39; P < .05). Stress experienced early in pregnancy was associated with shorter gestational length (r = .35; P < .05).

CONCLUSIONS: As pregnancy advances, women become decreasingly sensitive to the effects of stress. This decrease in vulnerability may reflect increasing protection of the mother and fetus from adverse influences during pregnancy. (Am J Obstet Gynecol 2001;184:637-42.)

Key words: Pregnancy, timing of stress, length of gestation, emotion, corticotropin-releasing hormone, CRH

One result of pregnancy-induced changes in maternal physiologic characteristics[1, 2] is that as pregnancy advances women become less responsive, physiologically, to stress. The reactivity of both major components involved in the maternal stress response, the hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axes, is dampened during pregnancy.[3, 4] For example, it takes a significantly larger dose of exogenous corticotropin-releasing hormone (CRH) to elicit an adrenocorticotropic hormone (ACTH) response from pregnant women compared with their nonpregnant counterparts.[4, 5] Pregnancy is also associated with decreased vascular responses to norepinephrine and epinephrine infusion,[6] reduced heart rate and catecholamine responses to physical stressors,[6, 7] and smaller blood pressure responses to mental and physical challenges.[3]

Because prenatal stress is associated with a wide range of adverse birth outcomes in humans and other animals,[8-11] a reduction in maternal vulnerability during pregnancy may protect the mother and fetus from its harmful effects. If the progressive attenuation of the maternal physiologic stress response does serve a protective function, then the later in pregnancy the stress occurs, the less profound its effects ought to be. Here we present the results of our investigation of the importance of the timing of stress on two measures of vulnerability—maternal emotional responses to stress and gestational length. We expected that stress occurring early in pregnancy would have a greater emotional impact and would shorten gestation more than stress occurring late.

We examined the effects of an acute stressor—an earthquake of 6.8 magnitude that occurred in Northridge, Calif, in 1994. One major advantage of this stressor is its quasi-experimental nature: It allows study of the effects of a single major psychologic event that is randomly distributed across women at different stages of pregnancy. We examined whether psychologic responses to the stressor were dampened later in pregnancy and also whether gestational age at birth was affected differently, depending on when the earthquake occurred.

Methods

Participants. The participants included in our analyses were part of a larger sample of 281 pregnant women receiving prenatal care at a teaching hospital associated with the University of California, Irvine, and living in the Orange County, Calif, area (thus the participants lived,

From the Department of Psychiatry and Human Behavior, University of California, Irvine,[a] the Department of Behavioral Science, University of Kentucky,[b] and the Department of Psychology, University of California, Los Angeles.[c]

Supported by National Institutes of Health grant HD-28413 (to Curt A. Sandman).

Received for publication February 15, 2000; revised April 24, 2000; accepted August 22, 2000.

Reprint requests: Laura Glynn, Department of Psychiatry and Human Behavior, University of California, Irvine, 2501 Harbor Blvd, #7, Costa Mesa, CA 92626. E-mail: lglynn@uci.edu.

0002-9378/2001 $35.00 + 0 ***6/1/111066***

doi:10.1067/mob.2001.111066

on average, 50 miles from the epicenter of the earthquake). All participants gave written, informed consent, and the study was approved by the Institutional Review Board of the University of California, Irvine. From this larger study sample we identified women who had experienced the earthquake while pregnant or within 6 weeks of delivery. Our subsample did not differ from the larger sample in demographic characteristics (age, ethnicity, marital status, or parity), two of the key predictor variables (obstetric risk for preterm birth and CRH concentration), or the birth outcome variable under investigation (length of gestation; *t* tests were computed for the continuous variables, and χ^2 tests were conducted for the categoric variables; $P > .15$ for all). Four women who had experienced the earthquake during our study period were omitted from the analyses (3 because of elective cesarean section and 1 because the CRH concentration was >12 SD above the mean); thus 40 women remained under study.

Earthquake stress and psychologic response. We determined whether the point of gestation at which the earthquake occurred was related to the psychologic impact of this event by examining responses given on a life-events inventory.[8] Each woman rated how upsetting or aversive she found the earthquake on a 4-point Likert-type scale with the end points *not at all* and *extremely*. This life-events inventory was completed at 32 weeks' gestation (women reported events that had occurred since the beginning of pregnancy up to that study visit) and also at 6 weeks post partum (here the women reported on all events from the first visit up to the present).

We assessed the relation between psychologic response and stress by regressing timing of the earthquake on psychologic response to the earthquake with a quadratic function. (It is not until 6 to 12 weeks post partum that the hypothalamic-pituitary-adrenal response is fully restored, and thus a quadratic function is appropriate for this analysis.[12]) We anticipated a decline in affective response as pregnancy advanced and an increase in the response after parturition when the maternal physiologic characteristics were returning gradually to their nonpregnant state.

Earthquake stress and birth outcome. We next examined whether the timing of stress affected birth outcome. Specifically, we examined whether the offspring of those who experienced stress early in pregnancy would be born at a younger gestational age than the offspring of those who experienced stress later. The occurrence of the earthquake early in pregnancy, when the effects of stress are greatest, was expected to shorten gestation the most, whereas the occurrence of the earthquake late would have a smaller effect on gestation. (Of course, the occurrence of the earthquake during the postpartum period could not affect gestational length and therefore creates an excellent comparison group.) Gestational age at birth was determined by the best obstetric estimate on the basis of a combination of last menstrual period and early uterine size and was confirmed by ultrasonography. For cases in which a discrepancy between last menstrual period, clinical examination, and ultrasonography exceeded the margin of error of ultrasonographic biometric parameters for gestational age, the estimate of gestational age was revised according to the results of the ultrasonography.

We regressed timing of the earthquake on gestational age at birth to assess the effects of timing of stress on length of gestation. The latest delivery among those who experienced the earthquake post partum was at 41 weeks, and so for this analysis each participant who experienced the earthquake post partum was assigned a score of 41.5 weeks.

We also examined whether stress is associated with gestational length after we controlled for the effects of two other established predictors—obstetric risk and CRH concentrations. It has been shown that women who have a history of certain medical conditions or who experience certain medical conditions during pregnancy deliver earlier.[13] Further, maternal plasma concentrations of CRH, a neuropeptide produced by the placenta that plays a role in regulating maternal and fetal pituitary-adrenal function, are related to lower gestational age at birth.[14-16] An obstetric risk score was assigned by summing the number of medical conditions (historical and current)[17] related to low gestational age at birth for each participant. We entered the obstetric risk and CRH variables into a hierarchic regression model with timing of stress to determine their combined effects on length of gestation.

CRH concentrations were determined by radioimmunoassay (Peninsula Laboratories, Belmont, Calif). Maternal plasma samples were collected at 32.1 ± 0.8 weeks' gestation. These samples were acidified with an equal amount of 1% trifluoroacetic acid and centrifuged at 17,000*g* (20 minutes) at 4°C. Plasma-loaded C18 Spice-Pak (Analtech, Inc, Newark, Del) columns (preactivated with 60% acetonitrile and 1% trifluoroacetic acid; washed with 1% trifluoroacetic acid) were eluted slowly with 60% acetonitrile and 1% trifluoroacetic acid and lyophilized. Reconstituted samples in phosphate-buffered saline solution were incubated with anti-CRH serum (human) overnight at 4°C followed by a second overnight incubation with iodine 125–labeled CRH. Both labeled and unlabeled CRH were collected by immunoprecipitation with second antibody and normal rabbit serum after 90 minutes' incubation at room temperature. Samples were centrifuged at 1700*g* (20 minutes) at 4°C, and the pellets were quantified with a gamma scintillation counter. The CRH assay had less than 0.01% cross-reactivity with ovine and sauvagine CRH, 36% cross-reactivity with bovine CRH, and nondetectable reactivity with human ACTH. The coefficient of variation is approximately 5% at normal physiologic levels with 4 mL plasma or 8% with 2 mL with a minimum detectable dose (95% confidence) of 2.04 pg per sample. Tissue linearity has been evaluated up to 4.0 mL plasma with quantitative recovery.

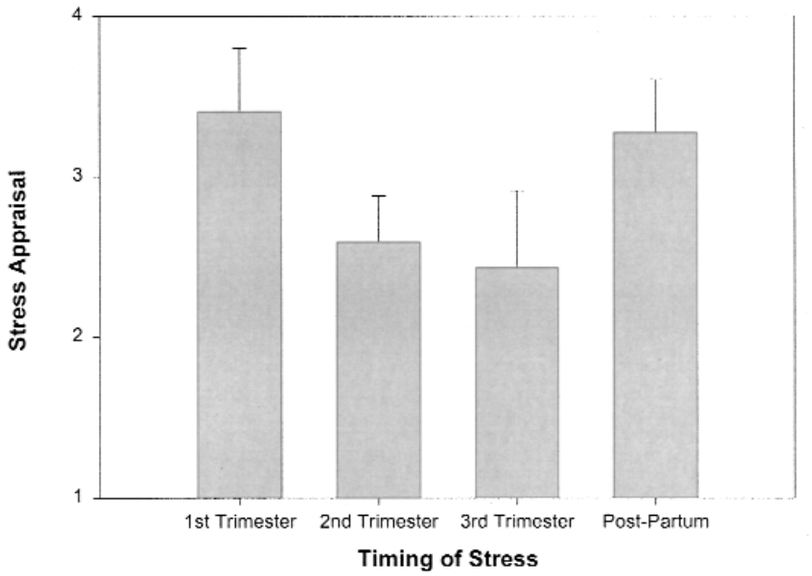

Fig 1. Effects of timing of earthquake during pregnancy on affective response. *Bars,* Mean and SE affective response to earthquake for each trimester and postpartum period.

Assessment of alternate explanations. We addressed possible alternative explanations for the results with 3 additional sets of analyses. We conducted Pearson correlations and *t* tests to assess whether timing of the earthquake was associated in any systematic way with medical or demographic factors. We also assessed whether any difference in affective responses might be caused by some sort of recall bias by examining the relation between timing of earthquake and length of time before recall. Last, we determined whether any differences in length of gestation as a result of timing of the earthquake might be an effect of the change in expected length of gestation as pregnancy progressed. For this analysis the gestational length of each woman who had experienced the earthquake during pregnancy (11 women had experienced the earthquake post partum, leaving 29 women) was compared with an adjusted comparison mean. This comparison value consisted of the mean gestational length for all women still in the larger sample (N = 281) at the time that the woman experienced the earthquake. For example, the woman in our sample who experienced the earthquake the earliest during pregnancy was at 5 days' gestation. Because no one had delivered before 5 days, her comparison value included everyone in the larger sample of 281 individuals. Thus her comparison value was the mean gestational length for this entire sample, 39.3 weeks. However, a woman who experienced the earthquake at 38 weeks was only compared with those women in the control sample who had not delivered before 38 weeks. Those women who had delivered after 38 weeks had an average gestational length of 39.8 weeks. We conducted a Wilcoxon signed rank test to compare the earthquake sample gestational lengths with the adjusted comparison values.

Results

The timing of the earthquake during pregnancy was associated with the magnitude of the ratings of stress (Fig 1; $r_{quad} = .39$; $P < .05$). The earthquake was rated as most stressful if it occurred during the first trimester and least stressful if it occurred during the third trimester (first-trimester mean, 3.40; second-trimester mean, 2.63; third-trimester mean, 2.38). The ratings for the postpartum period (mean, 3.27) were similar to those for the first trimester. This pattern of responses indicates that advancing pregnancy may attenuate the psychologic effects of acute stress.

The results also indicate that timing of the earthquake was related to gestational age at birth: Stress experienced early in pregnancy was associated with shorter gestation (Fig 2; first-trimester mean, 38.06 weeks; second-trimester mean, 38.69 weeks; third-trimester mean, 38.99 weeks). Women who did not experience the earthquake during pregnancy had the longest mean gestational length (39.50 weeks). The regression analysis confirms the importance of the timing of stress in determining length of gestation ($r = .35$; $P < .05$).

Obstetric risk and CRH concentration accounted for 24% of the variance in gestational age at birth. Adding our timing of stress variable into the equation significantly increased the amount of variance the model accounted for to 41% ($\Delta R^2 = .17$; $P < .01$; obstetric risk β [standardized coefficient] = –.44, $P < .01$; CRH β = –.34, $P < .05$; timing of earthquake $\beta = .44$, $P < .01$). The timing of stress predicted

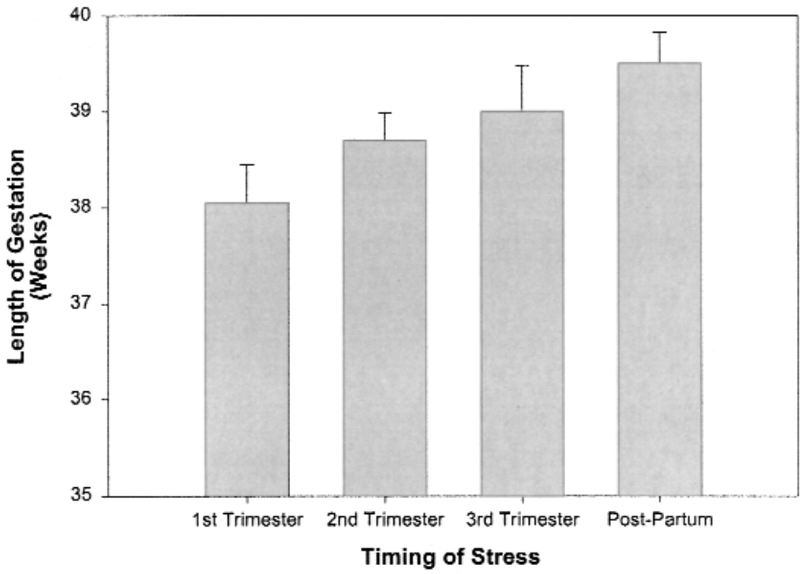

Fig 2. Effects of timing of earthquake on length of gestation. *Bars,* Mean and SE of gestational length for each trimester and postpartum period.

Table I. Mean gestational lengths for earthquake group and adjusted comparison mean expectancies (collapsed over trimester)

	Mean gestational length (wk)		
Group	*First trimester*	*Second trimester*	*Third trimester*
Earthquake	38.06	38.69	38.99
Expected	39.29	39.29	39.45

gestational age at birth after we adjusted for the effects of obstetric risk and CRH concentrations.

Assessment of alternative explanations. It is not likely that the relation between the timing of earthquake and the psychologic response or length of gestation is caused by demographic or medical factors. There was no relation between timing of earthquake and maternal age, ethnicity, marital status, or parity (Pearson correlations were computed for the continuous variables, and t tests were conducted for the categoric variables; $P > .11$ for all).

It is also unlikely that the affective response findings are the result of some sort of recall bias associated with the length of time between the earthquake and the self-report. Participants were divided into 4 groups determined by the stage of pregnancy at which the earthquake occurred (each of the trimesters and post partum). Whereas the groups did differ systematically in the length of time before recall, the pattern of means was not consistent with a recall bias explanation (first trimester, 164 days; second trimester, 100 days; third trimester, 36 days; post partum, 32 days).

As pregnancy progresses, the probability that a woman will deliver at term increases. However, the small effect associated with this change in expected length of gestation across pregnancy did not account for the earthquake timing and gestational length finding (and could not account for the earthquake timing and affective response finding). To illustrate the potential ramifications of this change in expectancy on our finding, consider that a pregnancy at 6 weeks has a lower probability of continuing to term than a pregnancy that has already reached 39 weeks. On the basis of this "expectancy factor" alone, the later that the earthquake occurs during pregnancy, the longer the gestational length should be. Thus both this "expectancy factor" and the putative changes in "vulnerability" to stress predict that stress early in pregnancy will be related to shorter gestations. We can eliminate the effects of "expectancy" by comparing the gestational lengths in our earthquake sample with appropriately adjusted expected lengths of gestation. For each woman who experienced the earthquake during pregnancy (n = 29), we calculated a comparison gestational length by taking the average length of gestation for individuals still in the larger sample (N = 281) at the same time point.

The gestational lengths in the earthquake group were shorter than those in the comparison group (Table I; Wilcoxon signed rank test; n = 29; T = 121; $P < .05$). These data indicate that the observed effect that stress early in pregnancy has a greater impact on gestational length cannot be attributed only to the change in expected length of gestation. Instead, it seems that a

change in vulnerability to stress accounts for the effect on gestational length.

Comment

These data are the first to suggest that psychologic responses to stress are progressively attenuated throughout pregnancy. Our data are also the first to indicate that the timing of stress during pregnancy may be an important factor in determining gestational age at birth: The effects of stress early in pregnancy are more pronounced than those later in pregnancy.

It is plausible that the dampened response of the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal-medullary system during pregnancy plays a role in the effects of timing of stress on appraisals and gestational length. A diminished hypothalamic-pituitary-adrenal response is observed when the administration of exogenous CRH does not produce a normal ACTH response.[3] During pregnancy, elevated levels of hormones such as CRH, ACTH, β-endorphin, and cortisol (among others) may down-regulate the corticotropic system and account for this decreased response.[4] Similarly, the reduced activity of the sympathetic-adrenal-medullary axis is reflected by decreased catecholamine and blood pressure responses to stress.[6, 7] It is possible that this is caused by exposure of the locus ceruleus and norepinephrine system to elevated free cortisol[18] and to pregnancy-induced vascular changes such as diminution of the baroreceptor reflex and increased plasma volume.[19] The blunting of the psychologic response to stress as pregnancy advances may be associated with a decreasing capacity for the physiologic stress response and is consistent with theories proposing that emotions are inferred from internal states.[20, 21]

The precise mechanism through which stress affects length of gestation is not known. Several factors have been implicated, ranging from behavior to immune function.[22] One possibility is that stress activates a placental clock that controls the length of gestation. Recent evidence suggests that increases in the stress-related placental peptide CRH may be associated with advancement of the placental clock and initiation of early labor and delivery.[14-16] Unlike hypothalamic CRH, release of placental CRH is stimulated by cortisol.[23] Environmental stress activates the hypothalamic-pituitary-adrenal axis and increases cortisol levels[24] and thus has the potential to stimulate placental CRH and advance the placental clock. If stress occurs early in pregnancy, before the hypothalamic-pituitary-adrenal response is dampened, this mechanism may result in a precocious rise in CRH and earlier parturition.

Our findings reinforce the evidence of a relation between stress and pregnancy outcome. Moreover, they are the first to demonstrate that the timing of stress in human pregnancy is important in determining its impact on appraisals and length of gestation. A failure to take into account when the stress happens may result in an underestimation of the relation between stress and pregnancy outcome. A simplistic analysis of the effects of the earthquake on length of gestation, comparing those who experienced the earthquake during pregnancy with those who did not, produced quite different results. The effect of this dichotomous, stress–no stress variable was not statistically significant ($T = 1.55$; $P = .13$).

It is well established that there are critical periods in the development of the human fetus during which insults and teratogens have particularly devastating consequences. It now appears that there may be a critical period that is related not to fetal but to maternal vulnerability; the earlier the stress during pregnancy, the more profound its effect on the pregnant woman. As pregnancy advances, women become decreasingly sensitive to the effects of stress. This decrease in vulnerability may reflect increasing protection of the mother and fetus from adverse influences during pregnancy.

We thank N. Christenfeld for useful discussion and editorial advice.

REFERENCES

1. Challis JR, Matthews SG, Van Meir C, Ramirez MM. Current topic: the placental corticotropin-releasing hormone axis. Placenta 1995;16:481-502.
2. Petraglia FP, Florio P, Nappi C, Genazzi AR. Peptide signaling in human placenta and membranes: autocrine, paracrine and endocrine mechanisms. Endocr Rev 1996;17:156-86.
3. Matthews KA, Rodin J. Pregnancy alters blood pressure responses to psychological and physical challenge. Psychophysiology 1992;29:232-40.
4. Schulte HM, Weisner D, Allolio B. The corticotropin releasing hormone test in late pregnancy: lack of adrenocorticotropin and cortisol response. Clin Endocrinol 1990;33:99-106.
5. Suda T, Iwashita M, Ushiyama T, Tozawa F, Sumitomo T, Nakagami Y, et al. Response to corticotropin-releasing hormone and its bound and free forms in pregnant and nonpregnant women. J Clin Endocrinol Metab 1989;69:38-42.
6. Nisell H, Hjemdahl P, Linde B, Lunell NO. Sypmpatho-adrenal and cardiovascular reactivity in pregnancy-induced hypertension. I. Responses to isometric exercise and a cold pressor test. BJOG 1985;92:722-31.
7. Barron WM, Mujais SK, Zinaman M, Bravo EL, Lindheimer MD. Plasma catecholamine responses to physiologic stimuli in normal human pregnancy. Am J Obstet Gynecol 1986;154:80-4.
8. Lobel M, Dunkel-Schetter C, Scrimshaw SCM. Prenatal maternal stress and prematurity: a prospective study of socioeconomically disadvantaged women. Health Psychol 1992;11:32-40.
9. Wadhwa PD, Sandman CA, Porto M, Dunkel-Schetter C, Garite TJ. The association between prenatal stress and infant birth weight and gestational age at birth: a prospective investigation. Am J Obstet Gynecol 1993;169:858-65.
10. Kay G, Tarcic N, Poltyrev T, Weinstock M. Prenatal stress depresses immune function in rats. Physiol Behav 1998;63:397-402.
11. Schneider ML, Roughton EC, Koehler AJ, Lubach GR. Growth and development following prenatal stress exposure in primates: an examination of ontogenetic vulnerability. Child Dev 1999;70:263-74.
12. Magiakou MA, Mastorakos G, Rabin D, Gold PW, Chrousos GP. Hypothalamic corticotropin-releasing hormone suppression during the postpartum period: implications for the increase in psychiatric manifestations at this time. J Clin Endocrinol Metab 1996;81:1912-7.
13. Shiono PH, Klebanoff MA. A review of risk scoring for preterm birth. Clin Perinatol 1993;20:107-25.

14. McLean M, Bisits A, Davies J, Woods R, Lowry P, Smith R. A placental clock controlling the length of human pregnancy. Nat Med 1995;1:460-3.
15. Wadhwa PD, Porto M, Garite TJ, Chicz-DeMet A, Sandman C. Maternal corticotropin-releasing hormone levels in the early third trimester predict length of gestation in human pregnancy. Am J Obstet Gynecol 1998;179:1079-85.
16. McLean M, Bisits A, Davies J, Walters W, Hackshaw A, De Voss K, et al. Predicting risk of preterm delivery by second-trimester measurement of maternal plasma corticotropin-releasing hormone and α-fetoprotein concentrations. Am J Obstet Gynecol 1999;181:207-15.
17. Hobel CJ. Identifying the patient at risk. In: Bolognese RJ, Schwarz RH, Schneider J, editors. Perinatal medicine: management of the high risk fetus and neonate. Baltimore: Williams & Wilkins; 1982. p. 3-28.
18. Chrousos GP, Torpy MB, Gold PW. Interactions between the hypothalamic-pituitary-adrenal axis and the female reproductive system: clinical implications. Ann Intern Med 1998;129:229-40.
19. Monga M, Creasy RK. Cardiovascular and renal adaptation to pregnancy. In: Creasy RK, Resnick R, editors. Maternal-fetal medicine: principles and practice. Philadelphia: WB Saunders; 1994. p. 758-67.
20. James W. Principles of psychology. New York: Holt; 1890/1950.
21. Schachter S, Singer JE. Cognitive, social, and physiological determinants of emotional states. Psychol Rev 1962;69:379-99.
22. Paarlberg KM, Vingerhoets AJ, Passchier J, Dekker GA, Van Geijn HP. Psychosocial factors and pregnancy outcome: a review with emphasis on methodological issues. J Psychosom Res 1995;39:563-95.
23. Robinson BG, Emanuel RL, Frim DM, Majzoub JA. Glucocorticoid stimulates expression of corticotropin-releasing hormone gene in human placenta. Proc Natl Acad Sci U S A 1988;85:5244-8.
24. Axelrod J, Reisine TD. Stress hormones: their interaction and regulation. Science 1984;224:452-9.