Characterization of the Relationship Between Joint Laxity and Maternal Hormones in Pregnancy

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OBJECTIVE: To evaluate peripheral joint laxity during pregnancy and to correlate changes with serum cortisol, estradiol, progesterone, and relaxin.

METHODS: Forty-six women with first-trimester singleton gestations consented to participate in this longitudinal observational study. Bilateral wrist laxity measurements (flexion-extension and medial-lateral deviation) were made using a clinical goniometer, and serum levels of cortisol, estradiol, progesterone, and relaxin were determined during each trimester of pregnancy and postpartum. Patients were also screened for subjective joint complaints. Statistical analysis included Student *t* test, analysis of variance, and linear regression analysis.

RESULTS: Eleven women (24%) were excluded from the study after spontaneous first-trimester pregnancy loss. Fifty-four percent (19 of 35) demonstrated increased laxity (10% or higher) in either wrist from the first to the third trimester. Although serum levels of cortisol, estradiol, progesterone, and relaxin were significantly elevated during pregnancy, no significant differences in these levels were noted between those who became lax during gestation and those who did not. Linear regression analysis of wrist joint laxity and level of serum estradiol, progesterone, and relaxin demonstrated no significant correlation. Wrist flexion-extension laxity, however, did significantly correlate with level of maternal cortisol ($r = 0.18$, $P = .03$). Fifty-seven percent of women developed subjective joint pain during pregnancy, which was not associated with increased joint laxity, but was associated with significantly increased levels of estradiol and progesterone.

CONCLUSION: Peripheral joint laxity increases during pregnancy; however, these changes do not correlate well with maternal estradiol, progesterone, or relaxin levels. (Obstet Gynecol 2003;101:331–5. © 2003 by The American College of Obstetricians and Gynecologists.)

More than 50% of women complain of some degree of low back pain during pregnancy, and many describe pubic, pelvic, hip, knee, and various other joint discom-forts. Annually, over $50 billion is spent on the diagnosis and treatment of back pain in the United States.[1] Backache often persists after delivery and may last up to 1 year.[2]

Relaxation of joints appears to be a normal physiologic process associated with pregnancy. This phenomenon is essential in the pelvic joints as the woman's pelvis adapts to accommodate vaginal delivery. Ostgaard et al examined 855 women and found that primigravid women developed more laxity, and those primigravidas with increased laxity had less back pain than their nonlax counterparts.[3] Although we know that joint laxity increases in pregnancy, we are not certain of the implications that these joint changes have for women. Recent evidence suggests that the degree of joint laxity in women correlates well with another long-term sequelae of childbirth, namely genitourinary prolapse.[4]

Relaxin is a polypeptide hormone, similar to insulin, produced by the corpus luteum of pregnancy and decidua. In some studies, increased levels of serum relaxin during the third trimester have been associated with significant pelvic pain and pelvic joint laxity.[5–7] Other studies suggest that there is no definite evidence for a link between increased relaxin levels and pelvic girdle or peripheral joint relaxation.[8–10] It is well known that serum levels of cortisol, estrogen, and progesterone increase during pregnancy to maintain the fetus in utero. These hormones have also been suggested to be related to increases in joint laxity.[11,12] What we do not know is just which of these hormones influence joint laxity or ligament relaxation in pregnancy.

The goal of this study was to follow women through pregnancy and up to 6 weeks postpartum to establish if a correlation exists between increasing joint laxity, joint pain, and changing levels of four specific hormones (cortisol, estradiol, progesterone, and relaxin). No previously known study has combined the assessment of increasing laxity in pregnancy and its relationship to four of the major hormones of pregnancy (based on a MEDLINE search, 1966 to 2002, of the key words "pregnancy," "joint laxity," "estradiol," "cortisol," "progesterone," and "relaxin").

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MATERIALS AND METHODS

Forty-six healthy low-risk pregnant women presenting to the Mayo Medical Center prenatal clinic in the first trimester with a documented singleton intrauterine pregnancy were prospectively recruited for this Institutional Review Board-approved longitudinal observational study of peripheral joint laxity between April 1997 and April 1998. Women with a history of joint problems (systemic lupus erythematosus, rheumatoid arthritis, Ehlers-Danlos syndrome, wrist fracture, etc) or with subsequent spontaneous first-trimester pregnancy loss were excluded from the study. All women underwent an initial interview to document maternal demographic data and to screen for subjective joint complaints.

Bilateral wrist laxity measurements (flexion-extension and medial-lateral deviation) were made using a previously validated clinical goniometer (Laxitometer; Mayo Orthopedic Biomechanics Department, Mayo Clinic, Rochester, MN) during each trimester (first: 8–12 weeks, second: 16–22 weeks, third: 34–36 weeks) of pregnancy and 5–6 weeks postpartum.[13] All assessments of joint laxity were performed by a single skilled examiner (JSS) and laxity tracings reviewed by a single investigator (MLM). Wrist laxity measurements, using the dorsum of the forearm and the dorsal aspect of the hand (the third metacarpal region) as reference points, were measured according to the maximal angles of palmar flexion-dorsiflexion (flexion-extension) and radial/ulnar deviation (medial-lateral deviation) using gentle application of 2 lb of force. Laxity data were compiled and analyzed by computer software designed by the Mayo Engineering Department. Several practice trials were performed before actual laxity measurements were obtained. All measurements were made in triplicate and reported and averaged for the final measurement determination. None of the participants in this study were lost to follow-up.

Concurrent with joint laxity assessment, patients were screened for subjective joint complaints. Additionally, blood samples were obtained for determination of maternal serum levels of cortisol, estradiol, progesterone, and relaxin. Morning blood samples were obtained to provide consistency and to limit the effect of hormone diurnal variations. Spun serum samples were collected and stored at −70C until time of analysis. All assays were run in batch on the first freeze-thaw cycle after completion of the laxity measurements for all study participants. Cortisol and progesterone levels were determined using automated competitive binding immunoenzymatic assays (Access Automated Immunoassay System; Beckman Instruments, Chaska, MN). Estradiol levels were determined using a double antibody radioimmunoassay (Ultra-Sensitive Estradiol Assay; Diagnostic Systems Laboratories, Webster, TX). Serum relaxin levels were measured with an enzyme-linked immunosorbent assay using rabbit antihuman relaxin polyclonal antibody with streptavidin horseradish-peroxidase conjugate. Reagents for relaxin assay were graciously provided by Immunodiagnostic Labs, Bensheim, Germany. Inter- and intra-assay coefficients of variation for the assays used were less than 10%.

Table 1. Patient Demographics

Maternal age (y)	28 ± 0.8
Gravida	1.9 ± 0.2
Para	0.7 ± 0.1
Race (%)	
White	94 (33/35)
Black	0 (0/35)
Asian	6 (2/35)

Values represent mean ± standard error of the mean.

The sample size for the investigation was determined to detect a significant correlation coefficient of 0.46 between the joint laxity measurements and the hormone levels under study ($\alpha = 0.05$, $\beta = 0.20$). Statistical analysis for this investigation included the Student *t* test, analysis of variance, Fisher exact test, and linear regression analysis where appropriate.

RESULTS

Forty-six women were initially enrolled for this prospective investigation of joint laxity. Of the initial women, 11 (24%) women were excluded from the longitudinal investigation after first-trimester pregnancy loss. Table 1 depicts the patient demographics for the study cohort. Mean delivery gestational age for the study cohort was 39.7 ± 0.2 weeks. Mean wrist flexion-extension (Figure 1, top) and medial-lateral deviation (Figure 1, bottom) joint laxity increased as gestation progressed, with greatest increase noted during the third trimester. Interestingly, the increased joint laxity noted during pregnancy did not resolve by 6 weeks postpartum. Fifty-four percent (19 of 35) of the study cohort demonstrated clinically significant increased laxity (10% or higher) in either wrist flexion-extension or medial-lateral deviation from the first to the third trimester. No significant differences were noted between those women who developed joint laxity in the third trimester and those who did not with regard to maternal age, parity, delivery gestational age, or birth weight (Table 2). No significant differences were noted between the women who developed joint laxity (10% or higher) with regard to the reporting of subjective joint complaints (Table 2). In addition, no significant differences were noted between the women who developed laxity and those who did not with respect to third-trimester serum cortisol, estradiol, progesterone, or relaxin levels (Table 2).

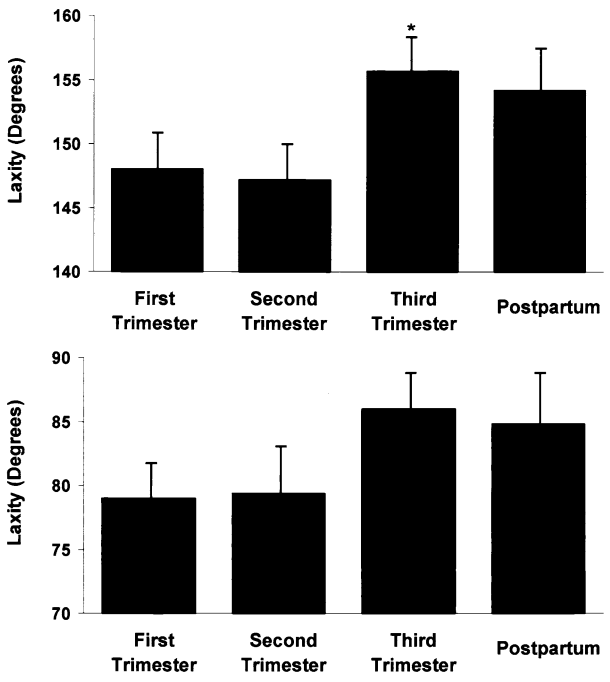

Figure 1. Changes in peripheral joint laxity throughout gestation and postpartum period. Peripheral joint laxity at the wrist increased throughout gestation, persisting into the postpartum period. Mean (±standard error of the mean) flexion-extension laxity of the wrist *(top)* was maximal in the third trimester and was significantly greater than in the first trimester. Similarly, mean medial-lateral wrist deviation *(bottom)* increased as gestation progressed. *Statistically significant, $P < .05$.

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Subjective joint pain complaints (wrist, back, hip, lower extremity) developed as gestation progressed in 57% (20 of 35) of the study cohort. Low back pain was the most common complaint noted during pregnancy. Low back pain significantly increased from the first to third trimesters (relative risk [RR] 1.5; 95% confidence interval [CI] 1.1, 2.0; $P = .004$): first trimester 9% (three of 35), second trimester 26% (nine of 35), and third trimester 40% (14 of 35). Hip joint pain also significantly increased from the first to the third trimesters (RR 1.3; 95% CI 1.1, 1.5; $P = .01$): first trimester 0% (zero of 35), second trimester 3% (one of 35), and third trimester 20% (seven of 35). Comparison of wrist flexion-extension and medial-lateral laxity measurements across gestation revealed no significant differences between those patients who developed joint complaints and those who did not. Interestingly, third-trimester maternal serum estradiol and progesterone levels were significantly higher in those patients who developed joint complaints during pregnancy (Table 3). Conversely, third-trimester serum relaxin levels were significantly lower in those patients who developed subjective joint complaints (Table 3). No significant difference was noted between the women who developed joint complaints and those who did not with regard to third-trimester serum cortisol level (Table 3).

Serum levels of cortisol, estradiol, and progesterone significantly increased as gestation progressed. In contrast, serum relaxin levels did not significantly change during gestation but fell to significantly lower levels postpartum (Table 4). Comparison of serum hormone levels between the patients who became lax during gestation and those who did not revealed no significant differences in the serum cortisol, estradiol, progesterone, or relaxin at each trimester and postpartum. Similarly, linear regression analysis of wrist joint laxity and level of serum estradiol, progesterone, and relaxin demonstrated no significant correlation (Table 5). Interestingly, wrist flexion-extension laxity, one component of peripheral joint laxity measured, did positively correlate with level of maternal cortisol ($r = .18$, $P = .03$).

Table 2. Comparison of Patient Demographics and Hormone Measurements Between Women Who Developed Increased Mediolateral or Flexion/Extension Wrist Joint Laxity (≥10%) and Those Who Did Not

	No increased joint laxity ($n = 16$)	Increased joint laxity (≥10%) ($n = 19$)	P
Maternal age (y)	28.6 ± 1.3	28.9 ± 1.1	.86
Parity	0.7 ± 0.3	0.7 ± 0.2	>.99
Gestational age at delivery (wk)	39.7 ± 1.3	39.7 ± 1.1	>.99
Birth weight (g)	3474 ± 109	3479 ± 79	.97
Subjective joint complaint (%)	56.3 (9/16)	57.9 (11/19)	>.999
Third-trimester hormone levels			
Cortisol (μg/dL)	26.5 ± 1.4	31.0 ± 2.2	.11
Estradiol (ng/mL)	8856 ± 1083	10,115 ± 895	.37
Progesterone (ng/mL)	79.5 ± 12.9	69.6 ± 12.0	.58
Relaxin (pg/mL)	133.2 ± 8.6	121.2 ± 11.3	.42

Values represent mean ± standard error of the mean.

Table 3. Comparison of Demographics and Hormone Measurements Between Women Who Developed Subjective Joint Complaints During Pregnancy and Those Who Did Not

	No joint complaints (n = 15)	Joint complaints (n = 20)	P
Maternal age (y)	30.6 ± 5.0	27.0 ± 4.4	.03*
Parity	0.9 ± 0.9	0.5 ± 0.8	.18
Gestational age at delivery (wk)	40.0 ± 1.0	39.4 ± 1.2	.13
Birth weight (g)	3463 ± 327	3487 ± 430	.86
Increased wrist joint laxity ≥10% (%)	46.7 (7/15)	55.0 (11/20)	.74
Third-trimester hormone levels			
Cortisol (μg/dL)	26.1 ± 8.2	31.2 ± 8.0	.07
Estradiol (ng/mL)	7085 ± 3159	11,225 ± 3812	.002*
Progesterone (ng/mL)	59.7 ± 23.8	103.9 ± 58.0	.009*
Relaxin (pg/mL)	145.6 ± 43.7	112.2 ± 38.4	.02*

Values represent mean ± standard error of the mean.
* Statistically significant, $P < .05$.

DISCUSSION

This study, along with several previous investigations,[12,14,15] confirms that peripheral joint laxity generally increases over the course of pregnancy and in the postpartum period. We did not confirm a significant association between increasing laxity and parity, maternal age, gestational age at birth, or race. Unique to this study is the use of a laxitometer designed and tested by the Mayo Orthopedics Biomechanics Department. This device is accurate in detecting minimal changes in wrist laxity and thus provides an objective and quantitative measure of these changes. The laxitometer has previously been shown to correlate significantly with a commonly used clinical test for joint hypermobility (General Joint Laxity Assessment).[13] A correlation between increasing laxity and joint pain or injuries has not been well established. As Schauberger et al[12] hypothesize, potentially the increased joint laxity is not of a significant magnitude to commonly cause joint injury. It is possible, however, that the increased laxity is of a degree that joint discomforts become more evident. We were unable to find a definite relationship between joint laxity and the development of joint complaints. As the most common complaints usually involve the larger joints (low back, hips, knees), these symptoms more likely may be related in large part to the weight of the fetus on these areas. There are also changes in body mechanics with progression of pregnancy, as the center of gravity in women shifts more anteriorly. Possibly the changes in posture, weight, and decreased ambulation are more responsible for the discomfort rather than increasing laxity. Most likely, these complaints stem from a combination of the two.

The progressive laxity that occurs over the course of pregnancy and into the postpartum period seems to follow the steady, dramatic increases in estradiol and progesterone that occur as well; however, this correlation was not significant. It has long been suspected that the increasing laxity of pregnancy is related to the hormonal changes that occur during this time. However, it remains unclear as to which hormone, or set of hormones, is most responsible for these changes. It has been suggested as well that serum levels of relaxin are highest during the first trimester, and there is no antenatal surge of the hormone at the end of pregnancy in humans.[16] Hart et al[17] with their work in pregnant rabbits conclude that the knee medial collateral ligament may be susceptible to sex-related hormones because it is known that estrogen can influence relaxin receptor expression. Guinea pig research by Sutro and Sutro[18] and Wahl et al[19] has also led to the idea that estrogen, with likely influence by progesterone and/or relaxin, works on some type of receptor mechanism in the pubic symphysis

Table 4. Changes in Serum Hormone Levels Throughout Gestation and Postpartum Period

	First trimester	Second trimester	Third trimester	Postpartum
Cortisol (μg/dL)	11.2 ± 0.7	18.4 ± 1.1*†	29.1 ± 1.5*†	9.8 ± 0.8
Estradiol (ng/mL)	487.1 ± 85.5†	3627.4 ± 341.2*†	9569.4 ± 743.0*†	66.9 ± 5.5*
Progesterone (ng/mL)	22.0 ± 1.4†	29.2 ± 1.4*†	85.4 ± 9.2*†	0.2 ± 0.0*
Relaxin (pg/mL)	129.7 ± 5.8†	122.6 ± 6.6†	126.2 ± 7.7†	19.0 ± 9.1*

Values represent mean ± standard error of the mean.
* Statistically significant compared with first trimester value, $P < .001$.
† Statistically significant compared with postpartum value, $P < .001$.

Table 5. Correlation of Serum Hormone Levels With Peripheral Joint Laxity

	F/E laxity (r)	P	M/L laxity (r)	P
Cortisol	0.18*	.03	0.06	.53
Estradiol	0.13	.13	0.07	.44
Progesterone	0.16	.08	0.09	.30
Relaxin	−0.02	.74	−0.14	.12

F/E = maximal wrist flexion/extension; M/L = maximal wrist medial/lateral deviation.

Statistical analysis using liner regression: r = correlation coefficient.

* Statistically significant, $P < .05$.

to cause loosening of this area in pregnancy. MacLennan et al[6] measured serum relaxin by radioimmunoassay in 35 patients with severe pelvic pain and pelvic joint instability during late pregnancy. Results were compared with a control group of 368 samples obtained throughout pregnancy from normal singleton pregnancies. Most of the relaxin concentrations in the study group were above the 95% confidence limits of the median for the corresponding gestational age in the control group. Progesterone, estradiol, and relaxin did not correlate with increased laxity when measured objectively in this study.

Curiously, in this current study, maternal serum levels of estradiol and progesterone are higher in those patients with subjective joint complaints compared with those without new complaints. The controversy that exists in the literature regarding each of these four serum hormones and the development of joint laxity and/or pelvic pain potentially can be explained by possible differences in the expression or presence of various receptors for these individual hormones. The expression of different estrogen isoforms in the vagina and pelvic connective tissues may explain the development of these complaints in pregnancy and subsequent problems with urogenital atrophy and ultimately pelvic prolapse and incontinence. Future studies should focus on evaluation of the status of the various receptors for each of these four hormones in both pregnancy and the immediate postpartum period and their relationship to joint laxity and the development of joint pain.

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