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Original article

Association between the serum levels of relaxin and responses to the active straight leg raise test in pregnancy

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ABSTRACT

There is a common belief that the laxity of pelvic joints increases in pregnancy. The hormone relaxin is suggested to be one of the most influential factors implementing this effect. Furthermore, increased laxity is assumed to induce pelvic girdle pain (PGP). The objectives were to examine the serum relaxin levels in pregnancy and to investigate whether relaxin levels relate to symptoms and clinical tests for PGP. Data from questionnaires, clinical tests and blood samples were collected once in pregnancy (gestation week 5–24) from 212 women. Serum from blood samples were analyzed by ELIZA to determine the concentration of relaxin. Self reported symptoms were assessed by Disability Rating Index (DRI) and pain intensity (VAS). Clinical examinations included Active Straight Leg Raise (ASLR) test and pain provocation tests. ANOVA was used to assess the effect of gestation age and multivariable statistics to examine the association between relaxin levels and the symptoms or responses to clinical tests.

The serum levels of relaxin varied widely between individuals and were only marginally influenced by the gestation age. There was no association between gestation age and responses to clinical tests or pain intensity, but DRI increased with gestation age. Serum concentration of relaxin showed a significant association to positive score on the ASLR test, but no significant associations to responses to pain provocation tests, pain intensity or DRI.

The results indicate that relaxin contributes to laxity of pelvic joints in pregnancy. Yet, no evidence of relaxin having an impact on symptoms or perceived disability was found.

1. Introduction

Relaxation of the pelvic girdle is a normal physiological response to pregnancy. However, in parallel with this adaptive response, a large number of women develop pelvic girdle pain (PGP) and disability (Albert et al., 2001; Olsson and Nilsson-Wikmar, 2004; Gutke et al., 2006; Robinson et al., 2006, 2010a, 2010b). The pain may be located to the low back area, the posterior pelvis, including sacroiliac joints and/or the pubic symphysis (Albert et al., 2002; Vleeming et al., 2008; Gutke et al., 2008). PGP influences weight bearing activities such as walking and standing and the women have problems moving around (Rost et al., 2006; Robinson et al., 2006, 2010a; Wu et al., 2008). Many of them are on sick leave and experience limitations in activities of daily life as well as lowered quality of life (Olsson and Nilsson-Wikmar, 2004).

The aetiology and pathophysiology of PGP are unclear, but biomechanical and hormonal factors are probably important (Vleeming et al., 2008). For many years, there has been a special interest in the possible effects of the hormone relaxin, which is released from the ovaries during pregnancy (Goldsmith and Weiss, 2009). This results in an elevated level of serum relaxin. Studies have shown that relaxin slows down the production and speeds up the degradation of collagen (Samuel, 2005). Furthermore, relaxin may induce a reorganization of collagen. Hence, relaxin can have a softening effect on many tissues, including ligaments with its large proportion of collagen.

Although the actions of relaxin in pregnant women are still poorly understood (Goldsmith and Weiss, 2009), it has been a common belief that this hormone contributes to the relaxation of the pelvic girdle and thus also to development of symptoms of PGP (Magee, 1997). More relaxed ligaments might induce increased joint laxity. Two studies have shown increased laxity in some, but not all, joints in fingers and knees during pregnancy (Calguneri et al., 1982; Schauberger et al., 1996). However, Schauberger et al. (1996) failed to show an association between the changes in laxity and relaxin level. These observations were based on peripheral joints, but the effects on the pelvis are unknown. More

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relaxed pelvic joints might be considered an adequate adaptation to child bearing, although the cost may be reduced functioning. If the laxity of the pelvic joints increases, one might need altered muscle activation as a compensatory mechanism to maintain proper function of the pelvis during weight transfer. Hence, an association between relaxin levels and difficulty in functional tasks is expected. Another possible effect is activation of nociceptors in or near the joints due to the increased mobility. Such an effect predicts an association between relaxin levels and positive response to pain provocation tests.

There are conflicting results regarding the association between relaxin level in pregnancy and development of PGP (MacLennan et al., 1986b; Hansen et al., 1996; Albert et al., 1997; Kristiansson et al., 1999; Bjorklund et al., 2000). It has been discussed whether the differences could be due to different analytical methods for relaxin measurement (Bjorklund et al., 2000), but the disparity in results is seen even when applying the same method, e.g. the studies by Kristiansson et al. (1996) and Albert et al. (1997). Alternative explanations could be related to the design of the studies, including case definitions and sample size. Most often case definitions are based on self reported PGP, without additional criteria from clinical examinations. Also when PGP is categorized according to pain location the disparity in results remain (Kristiansson et al., 1996; Albert et al., 1997). These studies are quite large, and small sample size cannot cause the disparity.

One complicating aspect regarding definition of PGP in pregnancy, is the differentiation between the functional affliction of pregnancy itself and the additional complaints and symptoms due to PGP. Recent studies show that pregnant women without PGP may exhibit substantial disability (Robinson et al., 2010a, 2010c). This is particularly evident late in pregnancy, a time often used for collecting data on PGP in pregnancy. It might thus be beneficial to examine the relationship between relaxin and PGP at earlier gestation age before the effect of pregnancy itself has developed.

Previous studies have shown a huge variation in serum relaxin levels in pregnancy, with an increase in the very first weeks of gestation (MacLennan et al., 1986a; Petersen et al., 1995; Kristiansson et al., 1996; Bjorklund et al., 2000). In general, the individual level remains relatively constant throughout the pregnancy, although some studies indicate a weak peak around week 12 (Kristiansson et al., 1996; Bjorklund et al., 2000). Hence, any effects on the pelvic joints should be present already at early stages of pregnancy.

Case definitions can also be based on clinical tests of underlying mechanisms. It is expected that relaxin causes increased laxity of the joints through an effect on the ligaments. Two different tests with a high validity for PGP is expected to pick up such effects; the Posterior Pelvic Pain Provocation (P4) test and the Active Straight Leg Raise (ASLR) test. Through a mechanical loading to the posterior joints, the P4 test is supposed to provoke a positive pain response in afflicted joints (Östgaard et al., 1994). One previous study has shown an association between serum relaxin levels and responses to the P4 test (Kristiansson et al., 1996). The ASLR test is a functional test to assess load transfer through the pelvis (Mens et al., 2001). In an earlier study Mens et al. (1999) suggested an association between mobility of the pelvic joints and impairment assessed by ASLR. Other recent studies show an association between difficulty in this test and altered motor control patterns (de Groot et al., 2008; Beales et al., 2009), which might be indicative of increased laxity of the pelvic joints. If relaxin contributes to looser ligaments in pregnancy, an association between relaxin levels and scores on the ASLR test is expected.

To examine the relationships between serum relaxin levels and various aspects of PGP in pregnancy, we used data from a larger cohort of pregnant women (Robinson et al., 2010a, 2010c). Since the women were included at a wide range of gestation age, we were able to examine the patterns through the first two trimesters as well as studying them before the burden of pregnancy became too large.

The first aim of this study was to characterize the serum levels of relaxin at different stages of pregnancy and compare these with the levels seen in non-pregnant condition. A second aim was to examine whether serum relaxin is related to symptoms or results of clinical tests indicating pelvic girdle pain.

2. Methods

2.1. Design and study sample

The present study was part of a cohort study, following 326 pregnant women from their first visit to the maternity care unit (MCU) until about a year postpartum. Questionnaire data and data from clinical examinations were collected in early pregnancy (mean gestation week 15), at gestation week 30 and 12 weeks postpartum. Further details of the study design are presented elsewhere (Robinson et al., 2010b, 2010c). A blood sample was taken from 219 (67%) of the women. For the present study we included the 212 women that completed the questionnaires, clinical examinations and blood sample collection before 25 weeks of gestation. Characteristics of the participants are given in Table 1.

To compare the level of serum relaxin in pregnancy with the level in a non-pregnant condition, we asked the women (if they were not pregnant again) for a new sample at a follow up one year postpartum. A total of 96 women met to provide a new sample.

The Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services gave formal approval for the study.

2.2. Questionnaires

Socio-demographical data included age, parity, marital status, education, smoking and physical activity before pregnancy. Pre-pregnancy body mass index was calculated from self reported height and weight. They were also asked to report whether they had used hormone stimulation to become pregnant.

Disability was measured by the Disability Rating Index (DRI), consisting of twelve visual analogue scales (VAS) measuring the ability to perform activities of daily living (Salen et al., 1994). Pain

Table 1
Characteristics of the subjects ($N = 212$).

	Frequency n (%)	Mean (*SD*)
Age (years)		31 (4)
Gestation week		14 (4)
Pre-pregnancy BMI (kg/m^2)		23.7 (3.7)
Parity		
0	120 (56%)	
1	67 (32%)	
2–3	25 (12%)	
Education		
≤12 years school	32 (15%)	
≤4 years university	88 (42%)	
>4 years university	92 (43%)	
Smoking (yes)	11 (5%)	
Physical activity before pregnancy		
None	7 (3%)	
<2 h per week	65 (31%)	
2–4 h per week	115 (54%)	
>4 h per week	25 (12%)	
Self reported PGP (yes)	70 (33%)	
HSCL-25 (score≥1.75)	32 (15%)	
Hormone stimulation (yes)	12 (6%)	

intensity was measured by the response to the following two questions: "How strong is your worst evening pain before going to bed?" and "How strong is your worst morning pain after getting out of bed?". The responses to both were measured by a 0–100 mm VAS and the end points were "no pain" and "unbearable pain".

The Hopkins Symptom Check List (HCSL-25) was used to measure distress (self reported symptoms of anxiety, depression and somatisation) (Derogatis et al., 1974). The final score was dichotomized at 1.75 as established for women by Sandanger et al. (1998), and the cut-off reflected non-specific distress, rather than a psychiatric diagnosis.

2.3. Clinical examinations

The clinical examination included six pain provocation tests for the pelvic joints as well as the functional ASLR test and Beighton score for hypermobility. All the tests have been commonly used and have shown moderate to excellent inter-rater reliability (Östgaard et al., 1994; Laslett and Williams, 1994; Mens et al., 2001; Robinson et al., 2007). The examiner was blinded for all questionnaire data.

2.3.1. Functional test

The ASLR test was performed with the women supine, with straight legs and feet about 20 cm apart (Mens et al., 2001). The women lifted each leg separately about 20 cm above the couch. They were asked to score the difficulty on a six-point scale from 0 (not difficult to lift) to 5 (impossible to lift). The scores on both sides were added and the total score ranged from 0 to 10. We dichotomized the ASLR sum score (0, >0) (Mens et al., 2001).

2.3.2. Pain provocation tests

The six pain provocation tests were: P4 test (Östgaard et al., 1994), distraction test (Laslett and Williams, 1994), compression test (Robinson et al., 2007), Patrick–Faber test (Dreyfuss et al., 1996; Slipman et al., 1998), palpation of the pubic symphysis (Albert et al., 2000) and the long dorsal sacroiliac ligament (Vleeming et al., 2002). Details of how these tests were performed are published elsewhere (Robinson et al., 2010b).

The pain response for each test was recorded (yes, no). Bilateral tests were tested and scored separately. A sum score was calculated from the numbers of positive responses to pain of all the pain provocation tests apart from the P4 test. The sum score ranged from 0 (all negative) to 8 (all positive). We used the responses on the P4 test as a separate variable based on the relevance of the test for PGP reported in previous studies (Östgaard et al., 1994; Gutke et al., 2009).

2.3.3. Pain locations

Pain locations within the pelvic area were determined by a pain drawing filled in by the women before the clinical examination. After the examination, the women were asked to point out the pain sites on their body and, if necessary, the examiner corrected the pain drawing to reflect the areas pointed out. The pain locations in the pelvic area were subsequently coded: no pain, pain in symphysis only, only posterior pain (uni- or bilateral) and combined symphysis pain and uni- or bilateral posterior pain (Robinson et al., 2010b).

2.4. Blood sample analysis

Serum was separated and frozen immediately after blood sample collection, and thereafter stored at −20 °C until analysis. Relaxin was determined by use of a commercial ELISA kit (Immundiagnostik, Bensheim, Germany). The polyclonal antibody was raised in rabbits. The kit had an analytical detection limit of 4.0 pg/ml that was calculated from the mean optical density of the zero standard (measured in duplicate) plus two standard deviations. The intra-assay coefficient of variation is 10% at 16 pg/ml and the interassay coefficient of variation is 10% at 100 pg/ml. The kit is highly selective for human relaxin, with cross-reactivity measuring 100% for the H1 form and 100% for the H2 form. Cross-reactivity against insulin, insulin-like growth factors, LH, FSH, and prolactin is less than 0.01%. The samples were assayed after dilution 1:10 in the kit dilution buffer. Levels below detection level were set to 4 pg/ml in the analysis.

2.5. Data analysis and statistics

Data are presented as mean (*SD*), median (range) or frequency. The effects of gestation age were analyzed by univariate analysis of variance (ANOVA) or Chi square. Multivariable linear regression analysis (GLM) was used to examine the association between relaxin and symptoms or results of clinical tests. Pain location, gestation age and hypermobility were entered as covariates in these analyses. We also tested for the impact of hormone stimulation. Data exhibiting skewed distributions were transformed (log 10) before analyses.

For a few women, the time for blood sampling and clinical examination differed by more than 5 weeks. These data were omitted from analysis of associations between relaxin levels and clinical findings.

3. Results

3.1. Relaxin concentration in serum

The mean serum concentration of relaxin showed large variations at all stages of gestation without any significant effect of gestation age (ANOVA, $p = 0.72$; Table 2). The mean values varied between 689 and 920 pg/ml for the different gestation age bands, with *SD*s from 260 to 1973 pg/ml. By omitting the outlier of 11,380 pg/ml, the mean (*SD*) was 594 (618) pg/ml for gestation age 20–24 weeks. For the samples taken one year postpartum about 50% were below the detection limit and 66% displayed values below 100 pg/ml. The level postpartum was significantly lower than during pregnancy ($p < 0.001$).

3.2. Self reported symptoms and results of clinical examination

The intensity of morning and evening pain as well as disability (DRI) displayed large variations at all stages of gestation (see Table 3). Most of the distributions were skewed, as illustrated by the differences in mean and median values. There were no significant effects of gestation age on morning pain or evening pain

Table 2
Serum concentration of relaxin in pregnant women at different gestation age ($N = 212$) and one year postpartum ($N = 95$).

Gestation age[a]	*n*	Relaxin concentration (pg/ml)	
		Mean (*SD*)	Median (range)
5–9 weeks	43	689 (260)	656 (272–1619)
10–14 weeks	66	788 (609)	675 (156–4509)
15–19 weeks	70	737 (559)	606 (206–4093)
20–24 weeks	33	920 (1973)	476 (53–11,380)
Non-pregnant			
1 year postpartum	95	–	4 (4–2600)[b]

[a] Gestation age at the time of blood collection.
[b] Results below detection limit set to four.

Table 3
Self reported pain, disability and fear avoidance beliefs in pregnant women at different gestation age ($N = 212$).

Gestation age[c]	*n*	Morning pain intensity[a]		Evening pain intensity[a]		DRI[b]	
		Mean (*SD*)	Median (range)	Mean (*SD*)	Median (range)	Mean (*SD*)	Median (range)
5–9 weeks	29	3.9 (13.8)	0 (0–71)	2.7 (7.7)	0 (0–34)	10.0 (12.7)	4.5 (0–45.4)
10–14 weeks	81	7.5 (16.8)	0 (0–79)	10.9 (20.1)	0 (0–74)	18.3 (18.4)	13.3 (0–93.3)
15–19 weeks	77	7.0 (14.1)	0 (0–80)	13.6 (22.9)	0 (0–78)	20.4 (17.8)	13.7 (0–65.7)
20–24 weeks	25	6.1 (10.2)	0 (0–32)	10.0 (18.1)	0 (0–74)	22.2 (15.0)	21.5 (1.8–75.9)

[a] Worst pain intensity (VAS 0–100).
[b] Disability Rating index (score range 0–100).
[c] Gestation age at the time of clinical examination.

(ANOVA of transformed data, $p = 0.12–0.34$), but a significant effect was seen for DRI (ANOVA of transformed data, $p < 0.001$).

About 50% of the women reported that they had pain localized to the pelvis and most of these had posterior pain only (Table 4). There was no significant effect of gestation age on pain localization (Chi square test, $p = 0.17$).

Between 28 and 56% had positive responses to the different clinical tests (Table 5). There were no significant effects of gestation age on responses to clinical tests (Chi square test, $p > 0.24$). The Beigthon score for hypermobility was in general low and showed no significant association with gestation age (ANOVA, $p = 0.56$).

3.3. Associations between serum relaxin and clinical variables

When performing bivariate correlation analyses, the only significant association was seen between serum relaxin concentration and ASLR ($r = 0.14$, $p = 0.042$). Hypermobility, the P4 test and the Sum of positive pain provocation tests all failed to show significant association to serum relaxin ($p = 0.43–0.97$).

When the associations were examined by multivariable statistics, including pain location in the pelvis, hypermobility, parity and gestation age in the model, the significant association to ASLR was strengthened ($p = 0.025$), while associations to P4 or Sum of positive pain provocation tests were still far from statistical significance ($p = 0.53–0.86$) (Table 6). The adjusted mean values (and 95% CI) for serum relaxin concentration were 601 (453, 748) pg/ml and 780 (626, 933) pg/ml for negative and positive response to the ASLR test in the multivariable analyses.

Including hormone stimulation as a variable in the multivariable analysis, showed no significant association to relaxin ($p = 0.55$) and had negligible effects on the estimates.

4. Discussion

The main finding of this cross-sectional study was that serum concentration of relaxin in pregnancy is associated to the results of the functional ASLR test, but unrelated to the responses to pain provocation tests. Moreover, there were no associations between the level of relaxin and self reported disability, pain intensity or pain location in the pelvis.

Table 4
Self reported pain localization for pregnant women at different gestation age ($N = 212$).

Gestation age[a]	*n*	No pain *n* (%)	Symphysis pain only *n* (%)	Posterior pain only *n* (%)	Combined symphysis and posterior pain *n* (%)
5–9 weeks	29	17 (59%)	1 (3%)	11 (38%)	0 (0%)
10–14 weeks	81	44 (54%)	2 (3%)	32 (40%)	3 (4%)
15–19 weeks	77	36 (47%)	4 (5%)	28 (36%)	9 (12%)
20–24 weeks	25	10 (40%)	2 (8%)	13 (52%)	0 (0%)

[a] Gestation age at the time of clinical examination.

The observation that higher relaxin level is related to increased effort in performing the ASLR test indicates that relaxin has an impact on the functional properties of the pelvis. de Groot et al (2008) showed that pregnant women with PGP reported higher ASLR scores and had a higher muscle activation level during the test compared with asymptomatic pregnant women. Other studies of patients with chronic PGP or sacroiliac joint pain have also shown altered motor control strategies during the ASLR test (O'Sullivan et al., 2002; Beales et al., 2009) in keeping with a need for compensation for increased laxity or mobility of the pelvic joints. Hence, the association between relaxin and the ASLR score shown in the present study supports the belief that high levels of relaxin is an important contributor to increased laxity of the pelvic girdle in pregnancy.

A previous study came to the opposite conclusion, as no association between relaxin levels and joint laxity of peripheral joints was observed (Schauberger et al., 1996). This was a study following a cohort of 21 pregnant women during and after pregnancy and they measured the serum relaxin levels and the laxity of seven joints in the extremities. They reported a gradual increase in laxity of the knees, with only initial or no increase in laxity of other joints in pregnancy. Serum levels of relaxin increased from pre-pregnancy to first trimester, but declined the next two trimesters. The disparity in the temporal changes of relaxin and joint laxity of the knees led them to conclude that the cause of the increased laxity was still obscure. However, since all joints examined had increased their laxity in the first trimester, one might still hypothesize that relaxin has an impact on this initial increase.

A small decline in relaxin level from first to third trimester is also shown by Björklund et al. (2000) together with an increased width of the symphysis. They concluded that the altered ligament properties of the joint were unrelated to relaxin levels. This finding was based on the changes from 12 to 35 weeks of gestation, and hence do not preclude a possible role of relaxin in the early phase of pregnancy, as indicated by the present data.

The Beighton score for general hypermobility used in the present study should to a certain degree reflect the same

Table 5
Results of clinical examination in pregnant women at different gestation age ($N = 212$).

Gestation age[e]	*n*	P4 test positive[a] *n* (%)	ASLR test positive[b] *n* (%)	Sum provocation tests positive[c] *n* (%)	Beighton score[d] Mean (*SD*)
5–9 weeks	29	9 (31%)	8 (28%)	13 (45%)	2.2 (1.7)
10–14 weeks	81	28 (35%)	36 (44%)	38 (47%)	1.7 (1.6)
15–19 weeks	77	37 (48%)	32 (42%)	43 (56%)	1.7 (1.6)
20–24 weeks	25	9 (36%)	9 (36%)	11 (44%)	1.9 (2.0)

[a] Posterior Pelvic Pain Provocation test score >0.
[b] Active Straight Leg Raise test >0 (the two sides added).
[c] Sum of eight tests >0.
[d] Beighton hypermobility score (range 0–9).
[e] Gestation age at the time of clinical examination.

Table 6
The associations between serum relaxin concentration (measured as pg/ml) and the results of clinical tests and self reported disability or evening pain intensity ($N = 201$).

Independent variable	β (95% CI)	*P*-value
ASLR score (score 0 vs >0)	178 (23, 334)	0.025
P4 (score 0 vs >0)	53 (−113, 219)	0.53
Sum of eight provocation tests (0 vs >0)	−14 (−177, 148)	0.86
DRI score (0–100)	0.9 (−3.8, 5.5)	0.71
Evening pain intensity (VAS 0–100)	0.5 (−3.8, 4.9)	0.82

Separate multivariable analysis for each independent variable with adjustment for pain location, gestation age, parity and hypermobiity.

underlying phenomena of joint laxity as assessed by Calguneri et al. (1982) and Schauberger et al. (1996). In keeping with their conclusions, our data showed far from significant associations between relaxin levels and general hypermobility. However, the present results showed a relationship between relaxin and scores of the ASLR test, and one might hypothesize that relaxin has a larger impact on the pelvic joints than joints of the extremities. From a functional point of view, a specific action directed to the pelvic joints seems reasonable. However, further research is needed to investigate this hypothesis and to examine the possible mechanisms for it.

Increased laxity or mobility of the pelvis in pregnancy might be expected to cause difficulty in moving around and in other weight bearing activities. Yet, we found no relationship between relaxin and self-reported disability, in spite of the association between relaxin and ASLR score. These somewhat contradictory observations suggest that the possible impact of relaxin on pelvic function in early pregnancy is compensated for in our daily activities. The most obvious explanation is enhanced muscle activation, as shown during the ASLR test for several muscles (de Groot et al., 2008). Through this enhanced activation a “bracing” effect is obtained causing an improved force closure and stability of the pelvis (O'Sullivan et al., 2002; Beales et al., 2009).

Although we found a relationship between relaxin levels and ASLR, no associations were found to self reported pain intensity or to responses to pain provocation tests. Hence, it seems that relaxin has little or no impact on the nociceptors or the nociceptive pathways from the pelvis of pregnant women. One might have anticipated that looser ligaments could trigger nociceptive activation due to increased shear forces in the joints (Macefield, 2005). The lack of this effect might be caused by compensatory mechanisms to improve force closure and thus reduce the mechanical instability and friction in the joints.

5. Conclusion

Although the present study confirms that the hormone relaxin contributes to the laxity of the pelvic joints in pregnancy, no evidence of relaxin having an effect on symptoms or perceived disability was found. These observations suggest that the increased mobility of the joints is compensated for in daily living.

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