Back pain in in-vitro fertilized and spontaneous pregnancies

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The influence of ovarian stimulation in in-vitro fertilization (IVF) on the prevalence of back pain with onset during pregnancy was studied in 31 women who became pregnant after IVF treatment and compared with that of 200 spontaneously pregnant women. A two times higher prevalence rate of sacral pain in late pregnancy was reported among IVF pregnant women (P < 0.0001), as well as a significantly higher prevalence rate of positive results of pelvic pain provocation tests performed in late pregnancy (0.0001 ≤ P ≤ 0.015), as compared with that of the spontaneously pregnant women. Among the IVF pregnant women, there was a significant positive correlation between relaxin concentrations in early pregnancy and the outcome of pelvic pain provocation tests (0.44 ≤ r ≤ 0.51, P < 0.05). In addition, the serum relaxin concentration was the factor that best explained differences in sacral pain prevalence. When the influence of serum relaxin concentration on back pain prevalence was taken into account, women carrying multiple pregnancies had no more pain than women carrying singletons, and IVF pregnant women had no more pain than spontaneously pregnant women. These results support the hypothesis that relaxin is involved in the generation of pelvic pain in pregnant women.

Key words: back pain/in-vitro fertilization/pregnancy/relaxin

Introduction

It is well known that the pelvis undergoes changes during pregnancy (Houghton, 1975; Putschar, 1976) and that pelvic pain is common among pregnant women (Östgaard et al., 1991; Kristiansson et al., 1996). MacLennan et al. (1986) were the first to show an association between reported severe incapacitating pain located in the symphysis in pregnant women and elevated concentrations of circulating relaxin.

Relaxin is a polypeptide hormone of ovarian origin of the insulin-like growth factor family. Relaxin is known to remodel pelvic connective tissue in several mammalian species during pregnancy (Sherwood, 1994). We recently observed that high mean serum relaxin concentrations were correlated to low back pain or symphyseal pain in late pregnancy (Kristiansson et al., 1996c). In another recent study, we found that the serum relaxin concentrations were about 10 times higher among women pregnant after IVF treatment than in spontaneously pregnant women (Kristiansson et al., 1996d). Moreover, in IVF pregnant women, the relaxin concentration during pregnancy was closely correlated to the number of follicles developed during ovarian stimulation as well as the number of oocytes recovered at oocyte retrieval in the treatment cycle, i.e. direct effects of the ovarian stimulation regimen.

If relaxin is essential for the development of pregnancy-related pelvic pain, including the sacral area, one would expect a higher incidence of back pain among IVF pregnant women than among spontaneously pregnant women. The present study was designed to evaluate back pain during IVF pregnancies prospectively and to compare it with that in spontaneous pregnancies, and we postulated that reported and provoked back pain would be more frequent in the IVF pregnant women.

Materials and methods

Study populations

The clinical material comprised IVF pregnant women who were compared with a reference group of spontaneously pregnant women. IVF pregnant women

Thirty-one consecutive women who became pregnant after IVF treatment during the period May 1992 to October 1993 agreed to participate in the study. At admission to the study the women were apparently healthy and 25–38 years old (mean 32.8 years). The gestational period ranged from 25 to 43 weeks (mean 36.8 weeks). Sixteen women gave birth to singletons (mean birth weight 3152 g, range 1322 to 4240 g), 14 women to twins (mean birthweight 2456 g, range 980 to 4075 g) and one woman had triplets (birthweights 1425 g, 1462 g and 1639 g). Seventeen women were pregnant for the first time, seven for the second time and six for the third time or more. Four women reported one previous delivery.

All patients followed a long gonadotrophin releasing hormone agonist (Suprefact, Svenska Hocchst AB, Stockholm, Sweden) and human menopausal gonadotrophin (Pergonal, Serono Nordic AB, Sollentuna, Sweden) protocol for ovarian hyperstimulation as described elsewhere (Czemiczyk et al., 1994). The day for ovum retrieval was determined when adequate stimulation was achieved, i.e. a continued rise of serum oestradiol and a leading follicle diameter of at least 17 mm. Then 5000 IU human chorionic gonadotrophin (HCG; Profasi, Serono Nordic AB) was given i.m. Approximately

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3233
35 h later, ovum retrieval was performed by transvaginal ultrasound-guided follicle aspiration. Gamete and pre-embryo handling as well as pre-embryo replacement have been described elsewhere (Palmstierna et al., 1997). Luteal-phase support was given as repeated HCG injections of 2500–5000 IU. The duration of pregnancy was expressed as completed weeks from the day of ovum retrieval plus 2 weeks.

Spontaneously pregnant women

All pregnant women living in two districts (population 23 350) of the city of Sundsvall (population 93 800), Sweden, in 1991 were identified through check-ups at the antenatal clinics in the city and its surroundings, at practising gynaecologists' surgeries and at the out-patient clinic at the local hospital. All women seen during early pregnancy in the year 1991 were sampled for this study. A total of 227 pregnant women fulfilled the sampling criterion, of which 222 women attended the antenatal clinic that served the two districts and five women attended other antenatal clinics. The 222 women were invited to participate in the study. Of these, 22 declined to participate, which left 200 (88.1%) women in the final study population. The 200 women were 18 to 42 years old (mean 27.9 years): 41% were pregnant for the first time, 37% for the second time and 22% for the third time or more. All women were apparently healthy, and none was taking continuous medication. During follow-up, 10 women left the study because of spontaneous abortion, two women declined further participation, and one woman moved from the area.

Methods

The women pregnant after IVF treatment completed a questionnaire at gestational weeks 12, 24 and 34. At the last visit, they also underwent a physical examination that included an assessment of back status and examination of the pelvis. Venous blood samples were drawn at gestational weeks 8, 16, 20, 28 and 34 with some minor variation. The blood samples were centrifuged immediately after sampling and the serum stored at −70°C until analysis.

The same schedule was used among the spontaneously pregnant women, as described in detail previously (Kristiansson and Svardudd, 1996b; Kristiansson et al., 1996), except that physical examination was also done at gestational weeks 12 and 24.

Questionnaire

The questionnaire included an instrument for measuring ongoing pain, its location and intensity. In addition, there were questions about earlier back pain problems (in connection with pregnancy or not), earlier obstetric history and smoking habits. The questionnaire was completed in privacy with no time limit.

The location of pain and pain modality were indicated by the woman on a pain drawing that consisted of a plain front-back drawing of a person. More than one location could be indicated. These locations were then coded as head, shoulder, arm, cervical spine, thoracic spine, lumbar spine, lumbar sacral area, sacral area, symphysis, anterior pelvis, chest, abdomen, trochanteric area, thigh and lower leg. Those who reported cervical, thoracic, lumbar, lumbar sacral or sacral pain were pooled into a group labelled ‘back pain’. In addition, leg. Those who reported cervical, thoracic, lumbar, lumbosacral or thoracic spine, lumbar spine, lumbosacral area, sacral area, symphysis, woman on a pain drawing that consisted of a plain front-back drawing completed in privacy with no time limit.

The intensity of pain was measured on two visual analogue scales (VAS) 100 mm long: 0 mm indicating no pain and 100 mm indicating intolerable pain. On the first VAS, the pain intensity at the moment was indicated and, on the second, the worst pain felt during the past week. The women were asked to indicate to which pain location the intensities referred.

Clinical examination of the back

The spine, including the pelvis, was examined by the same physician without knowledge of the previous case history or present questionnaire results. A standardized clinical examination programme which included tests of configuration, mobility and pain provocation was followed (Kristiansson and Svardudd, 1996b). The pain provocation tests were considered positive if they induced or increased pain in a location related to the test procedure. For this report, the results of the femoral compression test and the tender sacrospinous ligament test were used. The femoral compression test was performed in the supine position with the hip in 90 degrees flexion and pain was provoked by applying an axial femoral pressure force of approximately 50 to 150 Newton to the knee. The tender sacrospinous ligament test was performed during vaginal examination, where pain was provoked by applying direct pressure against the sacrospinous/sacrospinous ligaments. The responses to the tests were classified as negative, moderately positive or strongly positive.

Hormone assays

All serum samples were analysed blindly in duplicate in the same assay. Serum concentrations of relaxin were determined by a non-competitive double-antibody enzyme-linked immunosorbent assay (ELISA) based on purified antibodies raised against a recombinant human relaxin (RLX-2) as previously described (Lucas et al., 1989). The lowest detectable concentration was 20 ng/l. The intra- and inter-assay coefficients of variation were 5% and 12% respectively.

Statistical analyses

Data were analysed with the Statistical Analysis System program package. Possible relationships based on ordinal or nominal data were tested with the χ²-test or Student’s t-test. For multivariate analyses, the logistic regression technique was used. All significance tests were based on non-grouped data. Only two-tailed tests were used. P-values <5% were generally regarded as statistically significant. Very low P-values were indicated as < 0.0001.

The effects of age, multiple pregnancy, IVF pregnancy and mean relaxin concentrations on back pain were illustrated by odds ratios. Odds ratios indicate the odds of having back pain during the pregnancy among those who have certain characteristics in relation to those who have not. For the computations of odds ratios, the logistic regression technique was used. The variables singleton versus multiple pregnancy and spontaneous versus IVF pregnancy were treated as ordinal variables. The continuous variables mean relaxin value and age were ordinalized by grouping the variables arbitrarily into those who had the 15% lowest values, the 70% in the middle of the distribution, and those who had the 15% highest values.

Permission for this study was obtained from the Research Ethics Committee of Umeå University, Umeå and Karolinska Institute, Stockholm, Sweden. All women gave their informed consent to inclusion.

Results

Occurrence of back pain

The prevalence rate of back pain with onset during pregnancy among the 31 women pregnant after IVF treatment increased from 40.7 at the first visit to 66.7 and 76.0% at the second and third visit respectively, as shown in Table I. The corresponding rates for the spontaneously pregnant women were 19,
Table I. Prevalence of reported back pain starting during pregnancy according to location among in-vitro fertilization (IVF) pregnant and spontaneously pregnant women

<table>
<thead>
<tr>
<th>Location</th>
<th>First visit</th>
<th>Second visit</th>
<th>Third visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IVF</td>
<td>Spontaneously pregnant</td>
<td>P &lt;</td>
</tr>
<tr>
<td>n</td>
<td>27</td>
<td>195</td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>0</td>
<td>1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Thoracic</td>
<td>3.7</td>
<td>2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Lumbar</td>
<td>14.8</td>
<td>4.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Lumbosacral</td>
<td>14.8</td>
<td>6.7</td>
<td>NS</td>
</tr>
<tr>
<td>Sacral</td>
<td>22.2</td>
<td>9.7</td>
<td>NS</td>
</tr>
<tr>
<td>Back pain</td>
<td>40.7</td>
<td>19.0</td>
<td>0.01</td>
</tr>
</tbody>
</table>

P-values refer to the differences between the two groups.

Table II. Occurrence of a tender sacrospinous ligament test result and a painful femoral compression test result in late pregnancy among in-vitro fertilization (IVF) pregnant and spontaneously pregnant women

<table>
<thead>
<tr>
<th>Test</th>
<th>IVF pregnant</th>
<th></th>
<th>Spontaneously pregnant</th>
<th></th>
<th>P &lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Moderately positive</td>
<td>Strongly positive</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Tender sacrospinous ligament test</td>
<td>19</td>
<td>3</td>
<td>15.8</td>
<td>154</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>Painful femoral compression test</td>
<td>22</td>
<td>5</td>
<td>22.7</td>
<td>175</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>53</td>
</tr>
</tbody>
</table>

P-values refer to the differences between the two groups.

47.3 and 49.1% respectively. The difference in prevalence rate at the first and third visit was statistically significant (P = 0.01). The differences in back pain reporting were mainly confined to the lumbar, lumbosacral and sacral area. The prevalence rate of sacral pain among the IVF women at the third visit was 60%, which was 2.3 times higher than the rate among the spontaneously pregnant women (P = 0.0001).

There was no significant difference between the two groups in the proportion of earlier back pain problems, either in connection with pregnancy or not. Among the IVF pregnant women, 64.5% reported earlier back pain problems unrelated to pregnancy and 18.2% related to pregnancy. The corresponding proportions among the spontaneously pregnant women were 58.0 and 40.0% respectively.

The prevalence of positive pelvic pain provocation tests in late pregnancy among the IVF pregnant women and among the spontaneously pregnant women are shown in Table II. The IVF pregnant women had a significantly higher prevalence rate of a positive femoral compression test result, as well as a tender sacrospinous ligament test result, than the spontaneously pregnant women.

Pain intensity and sickness benefit

Among women who reported back pain, the pain intensity tended to increase during the pregnancy period (Figure 1). There were no significant differences between the two groups. However, IVF pregnant women had on average 100.2 days of sickness benefit during the pregnancy period and spontaneously pregnant women 39.1 days, a highly significant difference (P = 0.0001).

Back pain and number of fetuses

Of the 13 singleton pregnant IVF-treated women, nine (69%) reported back pain and seven (54%) sacral pain at the last visit. Among the 12 multiple pregnant IVF-treated women, 10 (83%) reported back pain and eight (67%) sacral pain at the last visit. There was thus a non-significant tendency towards
a higher prevalence of pain among multiple pregnant IVF-treated women than among singleton pregnant women. When the IVF-treated women and spontaneously pregnant women were analysed together, the 14 multiple pregnant women reported a significantly higher prevalence of back pain ($P = 0.01$), as well as sacral pain ($P = 0.02$), at the last visit, than singleton pregnant women.

**Serum relaxin and physical back examination**

The relaxin concentrations at the 16th gestational week in relation to the result of the tender sacrospinous ligament test and the femoral compression test performed in late pregnancy in the women pregnant after IVF treatment are shown in Figure 2. Women with a negative test result had the lowest relaxin concentrations (mean ± SEM), 5779 ± 1133 and 6550 ± 1150 ng/l respectively, those with a strongly positive test result had the highest, 11 428 ± 2329 and 9840 ± 1506 ng/l respectively, and those with a moderately positive test result had relaxin concentrations in between regarding the tender sacrospinous ligament test, 8833 ± 612 ng/l, but low regarding the femoral compression test, 4625 ± 1726 ng/l. However, for both tests there was a significant ($P < 0.05$) relationship between serum relaxin concentration and test result. The number of earlier pregnancies and the number of fetuses were not correlated to the relaxin concentrations nor with the results of the pelvic pain provocation tests.

**Relaxin and reported back pain**

Among the 31 IVF pregnant women, the average mean relaxin level was higher in women reporting sacral pain with onset during pregnancy at the third visit, 8921 ± 1546 ng/l, than in women with no such pain, 5406 ± 846 ng/l, but the difference did not reach statistical significance. However, when the IVF pregnant women and spontaneously pregnant women were analysed together as one group, the women reporting sacral pain with onset during pregnancy at the third visit had higher relaxin values at all five sampling visits, all differences being highly significant ($0.005 < P < 0.0001$). The mean relaxin value across all sampling visits for women reporting sacral pain was 2786 ± 597 ng/l as compared with 1016 ± 121 ng/l for those not reporting sacral pain. For other back pain locations, there were no similar consistent differences of relaxin values.

**Multivariate analysis**

The variables study population group (IVF pregnant or spontaneously pregnant), number of fetuses and serum relaxin concentration were thus all correlated to the prevalence of back pain during pregnancy. Since in addition these variables were intercorrelated (multiples were more common in IVF pregnancies, relaxin was higher in IVF pregnancies, etc.), an attempt was made to estimate the influence of each factor on pain prevalence with the influence of the other factors taken into account in a set of multivariate analyses. Age was not related to back pain prevalence but was included in the analyses to control for possible confounding. When all four variables were included no one reached significance, but after stepwise backward elimination of the least significant variables, relaxin concentration was the only one that remained significantly associated with pelvic pain prevalence ($P = 0.0008$).

**Size of effects**

The size of the effects of these variables on reported sacral pain at the third visit is summarized in Table III. In the univariate analyses, shown in the left hand part of Table III, women in the oldest age group had 1.36 times higher odds of reporting pain at the third visit than the youngest women. IVF pregnant women had 4.33 times higher odds than spontaneously pregnant women, women with multiple pregnancies had an odds ratio of 3.44 compared with that of women with singleton pregnancies, and women with the highest mean relaxin values had an odds ratio of 6.40 compared with those with the lowest values.

The effects adjusted in multivariate analyses are shown in the right hand part of Table III. Now the odds ratio declined somewhat with age, the odds ratios for IVF-induced pregnancy and multiple pregnancy were reduced to almost unity, whereas the odds ratios for the relaxin concentrations remained almost unchanged.
and multivariate logistic regression analyses back pain in women pregnant after IVF. Earlier studies in et al ELISA measuring human relaxin (RLX-2) was used (Lucas the results even more valid. Moreover, a sensitive and reliable pain or the pain provocation tests was found, which makes affect the association between relaxin concentrations and sacral was observed. In addition, no confounding factor that would between prevalence of sacral pain and relaxin concentrations was significant.

In conclusion, we found that hyperrelaxinaemia was closely related to a high prevalence of sacral pain in late pregnancy among IVF pregnant women. This is evidence supporting the theory that relaxin is involved in the generation of pelvic pain in pregnant women.

**Discussion**

In this study, a high prevalence rate of back pain among women pregnant after IVF, as compared with that of spontaneously pregnant women, was found. The two times higher chance of reporting sacral pain might be due to the supraphysiological concentrations of relaxin among women pregnant after IVF. In fact, the serum relaxin level was the factor that best explained differences in sacral pain prevalence. When the influence of serum relaxin concentration on back pain prevalence was taken into account, women carrying multiple pregnancies had no more pain than women carrying singletons, and IVF pregnant women had no more pain than spontaneously pregnant women. Thus, the ovarian stimulation would affect the prevalence rate of low back pain, since the number of follicles developed was significantly correlated to relaxin concentrations during subsequent pregnancy (Kristiansson et al., 1996d). Furthermore, the data suggest that milder ovarian stimulation might lower the pain prevalence rate. The IVF pregnant women had many days of sickness benefit, to which back pain may have contributed. This fact would have lowered the difference in prevalence of reported pain between spontaneously and IVF pregnant women. Interestingly, in a multivariate logistic regression analysis, the influence of multiple pregnancy did not remain significant but the serum relaxin was significant.

Data were collected prospectively and in a standardized way in the two groups of women. In the cohort of spontaneously pregnant women, our observations were certainly representative of pregnant women in the area and, in the cohort of IVF pregnant women, they were sampled consecutively. The IVF group was relatively small. Still, a highly significant correlation between prevalence of sacral pain and relaxin concentrations was observed. In addition, no confounding factor that would affect the association between relaxin concentrations and sacral pain or the pain provocation tests was found, which makes the results even more valid. Moreover, a sensitive and reliable ELISA measuring human relaxin (RLX-2) was used (Lucas et al., 1989).

This is, to our knowledge, the first study presenting data on back pain in women pregnant after IVF. Earlier studies in spontaneously pregnant women have reported a relationship between relaxin concentrations and pain in the pelvis, including the sacral region (MacLennan et al., 1986; Kristiansson et al., 1996c). Petersen et al. (1994) could not present data supporting this effect of relaxin. However, the present study gave further evidence for the hypothesis that relaxin may be related to back pain with onset during pregnancy.

A proposed effect of relaxin in women is remodelling of the connective tissue of the pelvis in preparation for parturition. A side-effect of this remodelling might be a predisposition to pain in the pelvic area. Results from several studies indicate that pregnancy affects ligaments and bones in the pelvic region. For example, in anatomical studies, variably deep, coalesced bony pits and craters have been observed at the attachments of the ligaments of the pelvis in women who had been pregnant, but not in women who had never been pregnant or in men (Houghton, 1975). It has been proposed that the pain is triggered from the insertions of the ligaments of the pelvis (Kristiansson and Svarðsudd, 1996b). One of the possible locations for pain release is the sacrospinous ligament, where the loading power of the back is concentrated (Irvin, 1997). Provoked pain in this region was also related to elevated relaxin concentrations in the present study. This view is also supported by the finding that pain in the lower back could only be induced occasionally from the internal genital organs (Konincx and Rener, 1997).

The effect of human relaxin on the pelvis remains speculative. Human relaxin decreased synthesis and secretion of collagen in normal human skin fibroblasts (Unemori and Amento, 1990) and reduced collagen accumulation in rodents (Unemori et al., 1993). In addition, human relaxin reduced the total collagen content in non-pregnant rat pubic symphyses (Samuel et al., 1996). The reduced soft-tissue collagen synthesis may predispose developing pain when loading the pelvis.

In conclusion, we found that hyperrelaxinaemia was closely correlated to a high prevalence of sacral pain in late pregnancy among IVF pregnant women. This is evidence supporting the theory that relaxin is involved in the generation of pelvic pain in pregnant women.

**Table III.** Effects of age, number of fetuses, conception status and mean serum relaxin concentration on reported sacral pain in late pregnancy after univariate and multivariate logistic regression analyses

<table>
<thead>
<tr>
<th>Reported sacral pain</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Age, 18–23 years</td>
<td>27</td>
<td>8</td>
</tr>
<tr>
<td>Age, 24–34 years</td>
<td>151</td>
<td>44</td>
</tr>
<tr>
<td>Age, 35–42 years</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Spontaneous pregnancy</td>
<td>175</td>
<td>45</td>
</tr>
<tr>
<td>IVF-induced pregnancy</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Singleton pregnancy</td>
<td>186</td>
<td>52</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Mean relaxin 186–382</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>Mean relaxin 383–1665</td>
<td>144</td>
<td>38</td>
</tr>
<tr>
<td>Mean relaxin 1666–16 800</td>
<td>26</td>
<td>16</td>
</tr>
</tbody>
</table>

OR = odds ratio; CI = 95% confidence interval for OR; IVF = in-vitro fertilization.
P.Kristiansson et al.

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