Ankylosing Spondylitis — The Female Aspect

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ABSTRACT. Objective. To study reproductive performance and interaction between ankylosing spondylitis (AS) and pregnancy in a large population of female patients.

Methods. In collaboration with the Ankylosing Spondylitis International Federation, a questionnaire including clinical data and details on past and recent pregnancies was sent to the female members of national and regional AS societies in the USA, Canada, and 11 European countries.

Results. Nine hundred thirty-nine questionnaires were completed, showing the following clinical data. Mean age at onset of AS was 23 years. The onset was related to a pregnancy in 21%. The frequency of accompanying features of AS was as follows: peripheral arthritis 45%, acute anterior uveitis 48%, psoriasis 18%, and inflammatory bowel disease 16%. Six hundred forty-nine women with previous pregnancies had on average 2.4 pregnancies per woman, of which 1.4 pregnancies were during disease. Of pregnancies 15.1% ended with miscarriage. Disease activity during 616 previous and 366 recent pregnancies was unchanged in 33.2%, improved in 30.9%, and worsened in 32.5%. Improvement of disease activity during pregnancy was correlated with a history of peripheral arthritis. It was also observed more often among those having a female than a male child (p = 0.02). A postpartum flare within 6 months after delivery was experienced by 60%, most often patients with active disease at conception. Delivery occurred at term in 93.2% of cases. The rate of cesarean section was high and due to AS in 58% of cases. The majority of neonates were healthy and had a mean birthweight of 3339 g. AS had an adverse effect on being a mother and a caregiver.

Conclusion. AS did not adversely affect fertility, pregnancy outcome, or the neonate. Improvement during pregnancy was related to a history of peripheral arthritis and a female fetus. Active disease at conception was a predictor of a postpartum flare. (J Rheumatol 1998;25:120-4)

Key Indexing Terms: ANKYLOSING SPONDYLITIS FERTILITY PREGNANCY CHILD CARE

Ankylosing spondylitis (AS) is found worldwide and more often in Caucasians than in other races. The male-to-female ratio in adult patients is 3:1. Disease frequently starts during early adulthood, a life period when pregnancy is common among female patients with AS. Several studies have addressed the interaction between pregnancy and AS (for review see1). In contrast to what is observed among patients with rheumatoid arthritis (RA), pregnancy has been found to ameliorate the disease in only 20–25% of patients with AS, while in the majority disease activity remains unaltered or even aggravated.

There are no major studies on fertility, rate of spontaneous abortion, or pregnancy outcome in a large number of women with AS1. Details regarding problems associated with delivery have only infrequently been reported. As the inflammatory process of AS most often involves the sacroiliac joints, the question remains if this could interfere with normal delivery. There has also been lack of agreement on the frequency of postpartum flare. In a retrospective study2, 45% of patients had experienced aggravation of disease symptoms, whereas in a small prospective study 90% of patients had a relapse within 6 months after delivery3. Information about extraarticular manifestations during and after pregnancy is scanty. One study found anterior uveitis occurring more frequently post partum than during pregnancy4.

In previous investigations, the number of pregnant patients studied has been small. We found it therefore of interest to conduct an international study in a large group of patients to address questions of clinical relevance when counselling women with AS. The investigation was performed by means of a questionnaire among members of national AS societies in 13 countries. Data obtained by this approach indicated normal reproductive performance in women reporting AS. No marked influence of pregnancy on the activity of AS was found during pregnancy; however, first symptoms of AS and extraspinal manifestations occurred frequently in the postpartum period. The study confirmed that AS affects being a mother and caregiver.

MATERIALS AND METHODS

At the annual meeting of the Ankylosing Spondylitis International Federation (ASIF) in Portugal in 1994, the delegates asked one of the authors (MØ) to conduct a more detailed study on the interaction between pregnancy and AS. The main issues were agreed upon. An English questionnaire was constructed including the following sections: (1) Clinical data on AS (ascertainment of diagnosis, age at onset, onset related to pregnancy, extraarticular features, accompanying diseases); (2) outcome and disease activity of AS in previous pregnancies (to be answered only by

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women over the age of 40. We asked only for a global assessment of disease course and after pregnancy, omitting all details, as we supposed that recollection of distinct features of previous pregnancies and pregnancy outcome would be difficult and therefore unreliable.

Sections 3–6 included questions on pregnancies during the period 1989–94, comprising a global assessment of the activity of AS before, during and after pregnancy, treatment before, during and after pregnancy, extraarticular features, smoking, outcome of pregnancy, neonatal health, breastfeeding, and problems with caring for a baby or toddler. Activity of AS during pregnancy was addressed by the following questions: “Did AS get worse during pregnancy? Did AS get better during pregnancy? Did AS remain unchanged during pregnancy?” In addition, patients were asked about the occurrence of peripheral arthritis and anterior uveitis during and within 6 months after pregnancy. To evaluate a flare post partum they were asked: “Did AS become worse within 6 months after delivery?”

To test the comprehensibility of the questions, a pilot study was performed in a limited number of patients in the UK, Norway, and Denmark. Wording of the questions was adjusted according to results of the pilot study. Then the English version was translated into the languages of the participating countries. Back translation of the questions from native languages into English was done except for Slovenia (48 questionnaires) and the Czech Republic (18 questionnaires). The delegates of these two countries, however, vetted the completed questionnaires to ensure correct meaning. Distribution of the questionnaire was arranged by the national AS societies and done either by mail or, for the majority of countries, by publication in the society’s newsletter. Data from the spontaneously returned questionnaires were entered into a database and analyzed.

Statistics. Groups were compared by cross tabulation and bivariate comparison using the student t test and chi-squared test as appropriate. Statistical significance was set at the 0.05 level.

Definitions. AS subtypes were defined as follows: AS with pure spinal disease, AS with psoriasis, AS with inflammatory bowel disease (IBD), and AS with peripheral arthritis. Peripheral arthritis was defined as arthritis in joints of arms and legs, including hips and shoulders. A pregnancy related onset was defined as the first symptoms of AS occurring either during a pregnancy or within 6 months after a childbirth or a miscarriage. Preterm delivery was defined as termination of pregnancy before Week 36. Duration of labor was defined as regular uterine contractions each 5–10 min until the child was born. Birthweight was regarded as normal when reported to be 2500–4500 g at term. The postpartum period was defined as the first 6 months after delivery.

RESULTS
A total of 939 women from 13 countries completed the questionnaires. Less than 1% of all participants were of non-Caucasian origin. The participating countries are listed in alphabetical order and the number of completed questionnaires are given in parentheses: Austria (8), Belgium (29), Ontario, Canada (34), Czech Republic (18), Denmark (85), Germany (148), Ireland (12), Norway (60), Slovenia (48), Sweden (61), Switzerland (85), United Kingdom (286), and California, USA (65). The median age of the women at study entry was 43.0 years (range 21–78). Section 1 was completed by all women, Section 2 was answered by 649 women, and Sections 3–6 were answered by 366 women.

Clinical data of female patients with AS are presented in Table 1. Mean age at onset of AS was 23 years. Analyzing subgroups of AS separately revealed no differences in regard to age at disease onset (data not shown). Twenty-one percent of all patients reported a pregnancy related onset. This figure increased to 27.3% when women with disease onset at age 28 or more were analyzed separately. Subtypes of AS differed in regard to a pregnancy related onset (Table 2). When patients with a history of psoriasis and IBD were excluded from analysis, onset of AS occurred significantly more often (p = 0.02) within 6 months after delivery than during pregnancy (Table 2).

The second section was to be answered only by women aged 40 or more to estimate fertility and reproductive performance. We anticipated that women over the age of 40 had finished their reproductive years. The 649 respondents had a total of 1586 pregnancies, 2.4 pregnancies per woman; 1.4 of the pregnancies (total 616) had occurred during disease. Of pregnancies, 15.1% had ended in spontaneous abortion. Stillbirth had occurred in 1.7%. The number of live children at latest count was 1340, which means an average of 2 children per woman. Analysis of previous pregnancies showed that disease activity was unchanged in 35.3%, aggravated in 39.9% and improved in 24.8%. Analyzing only women with a radiologically confirmed diagnosis of AS did not change these results. In 84 women (20%) the course of AS had differed in subsequent pregnancies. Subtypes of AS responded differently to pregnancy (Table 3).

In all, 366 patients recorded a pregnancy during the years 1989–94. Active disease at conception was reported by 44.4%, requiring treatment with nonsteroidal antiinflammatory drugs (NSAID) in 24.8%. A physical training program or physiotherapy was performed by 48.6% of the pregnant patients. Similar percentages for alterations of disease activity during pregnancy were found: no change 31.1%, aggravation 32.2%, and improvement 37%. Pre-eclampsia was reported by 2.8% of patients with a recent pregnancy. A flare of AS during pregnancy was addressed by the following questions: “Did AS become worse within 6 months after delivery?”

Table 1. Characteristics of 939 women with AS.

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS diagnosed by a doctor</td>
<td>849 (90.4)</td>
</tr>
<tr>
<td>AS diagnosed by radiograph</td>
<td>746 (79.4)</td>
</tr>
<tr>
<td>History of peripheral arthritis</td>
<td>423 (45)</td>
</tr>
<tr>
<td>History of anterior uveitis</td>
<td>450 (47.9)</td>
</tr>
<tr>
<td>History of psoriasis</td>
<td>169 (18)</td>
</tr>
<tr>
<td>History of IBD</td>
<td>149 (15.9)</td>
</tr>
</tbody>
</table>

Table 2. Pregnancy related onset of disease in patients with subtypes of AS.

<table>
<thead>
<tr>
<th>Type of AS</th>
<th>No. of Patients</th>
<th>Onset During Pregnancy (%)</th>
<th>Onset Post Partum (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>939</td>
<td>9.5</td>
<td>11</td>
</tr>
<tr>
<td>With AS diagnosed by a doctor</td>
<td>531</td>
<td>8.0</td>
<td>12.2*</td>
</tr>
<tr>
<td>With peripheral arthritis</td>
<td>139</td>
<td>9.4</td>
<td>13.6</td>
</tr>
<tr>
<td>With psoriasis</td>
<td>169</td>
<td>11.8</td>
<td>10.7</td>
</tr>
<tr>
<td>With IBD</td>
<td>149</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

1Patients with psoriasis or IBD are excluded.

*Onset post partum significantly more frequent (p = 0.02) than during pregnancy.
Table 3: Disease activity in previous pregnancies of patients with subtypes of AS.

<table>
<thead>
<tr>
<th>Type of AS</th>
<th>No Change</th>
<th>Improvement</th>
<th>Aggravation</th>
</tr>
</thead>
<tbody>
<tr>
<td>With peripheral arthritis [n = 285] (%)</td>
<td>106 (37.2)</td>
<td>91 (31.9)</td>
<td>88 (30.9)</td>
</tr>
<tr>
<td>With psoriasis [n = 163] (%)</td>
<td>64 (38.8)</td>
<td>31 (18.8)</td>
<td>70 (42.4)</td>
</tr>
<tr>
<td>With IBD [n = 151] (%)</td>
<td>55 (36.4)</td>
<td>40 (26.5)</td>
<td>56 (37)</td>
</tr>
</tbody>
</table>

of AS within 6 months after delivery was experienced by 57.3% of patients and was significantly correlated to reporting active disease at conception (p = 0.02). Peripheral arthritis occurred significantly more often post partum in patients with a history of peripheral arthritis than in those without (p = 0.0001).

Compared extraspinal manifestations and treatment during and after pregnancy showed that peripheral arthritis and anterior uveitis occurred less frequently during pregnancy compared to the 6 months after delivery. Figures for treatment with NSAID were similar during pregnancy and lactation (Table 4).

We tested the hypothesis that the pattern of interaction between pregnancy and disease would depend on the subtype of AS. Analysis of previous pregnancies in women aged 40 years or more showed that patients with peripheral arthritis had reported improvement significantly more often than patients with psoriasis (Table 3). In patients who completed a pregnancy in the period 1989–94, improvement during pregnancy was recorded more often in patients with a history of peripheral arthritis, although differences between subtypes did not reach statistical significance (Table 5). In the other AS subgroups, amelioration, aggravation, or no change were nearly equally distributed. When we tested for any correlation between the sex of the child and the course of AS during pregnancy, we found that mothers of girls experienced improvement (40.9%) significantly more often than aggravation (27.5%) or no change (28.1%) (p = 0.02). This observation was not made in mothers of boys. Gestational improvement was unrelated to the birthweight of the neonate. When we tested the possible influence of AS subgroups or the pattern of disease activity during pregnancy on the occurrence of a flare within 6 months after delivery, no difference emerged.

Delivery occurred in 341 (93.2%) cases at term and in 251 (68.8%) by the vaginal route. The mean duration of labor was 6.1 hours (SD 3.6). Cesarean section was performed in 103 (28.1%) cases, with AS reported as the reason for it in 60 cases. Figures for cesarean section reported during the 1990s in the literature were as follows: US 24%, Canada 14.1%, Great Britain 12%, Sweden 11%, Denmark 12.5%, Norway 12.4%, and Southern Germany 17.7% (U. Hasbargen, personal communication). With the exception of 11, none specified malformations; children were in general healthy and had a mean birthweight of 3339 g (SD 689) (Table 6). Seventeen children weighed less than 2500 g, 11 of these were preterm, 3 others were born as a result of pre-eclampsia, and 3 were low birthweight as a result of twin birth. No difference in birthweight was found in children born to mothers who had smoked, were treated with NSAID, or had experienced aggravation during pregnancy. Immediate medical treatment for unknown reasons was given to 41 (11.2%) of the neonates (Table 6).

Problems of caring for a baby or toddler (1989–94 pregnancies only) were addressed in the last section and were experienced by 65% of the patients. Difficult tasks were lifting (in 62%), carrying (in 67%), and bathing the baby (in 50%). Help from a third person was needed by 30% of the patients. Patients with a postpartum flare reported problems significantly more often than women without (p = 0.0001).

DISCUSSION

This large study in women with AS examined the female aspect of AS with an emphasis on reproductive events. The patients differ from population or hospital derived cases as the consist of patients who have defined themselves as sufferers and joined a patient group. Furthermore, they volunteered to respond to a questionnaire distributed by a regular newsletter or by mail to all members of their society. As no personal reminder was sent out, only those answering spontaneously were included in the study. Thus, the participating patients were self-selected and do not represent all female

Table 4. Manifestations and treatment during and after 366 pregnancies occurring during the years 1989–94.

<table>
<thead>
<tr>
<th>Manifestation or Treatment</th>
<th>During Pregnancy</th>
<th>After Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral arthritis (%)</td>
<td>69 (18.9)</td>
<td>97 (26.5)</td>
</tr>
<tr>
<td>Anterior uveitis (%)</td>
<td>25 (6.8)</td>
<td>39 (10.7)</td>
</tr>
<tr>
<td>Treatment with NSAID (%)</td>
<td>57 (15.6)</td>
<td>56 (15.3)</td>
</tr>
<tr>
<td>Physiotherapy (%)</td>
<td>178 (48.6)</td>
<td>Not studied</td>
</tr>
</tbody>
</table>

Table 5. Disease activity in pregnancies occurring during the years 1989 to 1994 in patients with subtypes of AS.

<table>
<thead>
<tr>
<th>Type of AS</th>
<th>No Change</th>
<th>Improvement</th>
<th>Aggravation</th>
</tr>
</thead>
<tbody>
<tr>
<td>With peripheral arthritis [n = 139] (%)</td>
<td>43 (31)</td>
<td>57 (41)</td>
<td>36 (25.8)</td>
</tr>
<tr>
<td>With psoriasis [n = 56] (%)</td>
<td>18 (32)</td>
<td>19 (33.9)</td>
<td>19 (33.9)</td>
</tr>
<tr>
<td>With IBD [n = 43] (%)</td>
<td>13 (30.2)</td>
<td>16 (37.2)</td>
<td>14 (32.6)</td>
</tr>
</tbody>
</table>

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members of the national AS societies. The percentage of responders is not known, as the open invitation to participate did not allow calculation of a response rate. As members of self-help groups do not necessarily have the disease they believe, confirmation of the diagnosis was asked for. The reliability of a diagnosis of AS was supported by the high frequency of a doctor and/or radiograph based diagnosis. Furthermore, the largest proportion of respondents were members of the British National Ankylosing Spondylitis Society in whom validation of a diagnosis of AS has been made. The results of our study were found consistent regardless of whether all patients or only those with a confirmed diagnosis were included in the analysis.

Age at onset and frequency of peripheral arthritis and anterior uveitis in this study were in agreement with figures reported by previous hospital based and epidemiological studies. In contrast to previous findings, subgroups of AS did not differ in regard to age at disease onset. The proportion of patients reporting psoriatic or enteropathic AS was higher than in previous studies. As figures for psoriatic and enteropathic AS varied markedly between participating countries, this may indicate true differences in prevalence. Indeed, variations in the prevalence of IBD are well known. Another possible explanation is over reporting due to self-reporting and lack of the confirmation of diagnosis by a dermatologist or gastroenterologist.

Our main purpose was to investigate the interaction between AS and pregnancy in a large population of patients. Use of a questionnaire was convenient, but clearly confers problems connected with the retrospective design and the possibility of variation in interpretation of the rather broadly formulated questions by the multinational patients. Pilot studies in different languages and back translations into English were therefore performed to ensure the comprehensibility and correct meaning of the questionnaires. Recall of the reproductive history has been shown to be good even with a period of 10 or 20 years of recall.

The fertility rate found in our study was identical to the figure for women with AS reported by us and similar to figures reported for healthy women in other affluent Western societies. Pregnancy related onset was reported by 21% of the patients, confirming previous findings. As pregnancy is a frequent event in the age group studied, the occurrence of AS closely related to pregnancy may be merely coincidental, and if so, first symptoms of AS should occur with equal frequency during pregnancy and post partum. In our study this was the case only in patients with psoriasis or IBD. In patients without accompanying disease, the first symptoms of AS occurred significantly more often after a pregnancy, similarly to RA, which manifests preferentially in the postpartum period in young women. Additional findings arguing against mere coincidence were the increase of a pregnancy related onset in women with disease onset at age 28 or more.

The present large international study by and large confirms retrospective and prospective results on the interaction between AS and pregnancy. As no change, aggravation, or improvement were recorded with nearly equal frequency, one can assume that pregnancy has no major effect on AS. Pregnancy did, however, influence extraspinal manifestations of AS. Both peripheral arthritis and anterior uveitis were reported more often post partum. The latter confirms our finding of an increased risk of anterior uveitis after delivery. Previous investigations have shown that rheumatic diseases with polyarticular involvement are more prone to remit in the pregnant state. The factors responsible for pregnancy induced improvement may affect arthritis in peripheral joints, but not in the spine.

The percentage of women, including those with pure, spinal AS, who reported improvement during a recent pregnancy was higher than found in a prospective study. Our study did not detail symptoms of AS during pregnancy and allowed only a global assessment of disease activity for the entire pregnancy. By contrast, the previous prospective study was based on a prospective clinical and laboratory followup. Another explanation may be a selection of patients with less severe disease compared to the present study as indicated by the moderate proportion of women with active disease at conception and need for treatment with NSAID.

We tested whether type of AS would influence the interaction between disease and pregnancy. When patients aged 40 or older recalled their previous pregnancies, improvement was significantly more frequent in women with a history of peripheral arthritis versus those with a history of psoriasis. This correlation was also found in patients with a recent pregnancy; however, in such patients the association did not reach statistical significance. In earlier studies, we found an association between gestational improvement and accompanying peripheral arthritis, psoriasis, and IBD. It may be that the patients who had reported psoriasis or IBD in our previous studies were those who had a history of peripheral arthritis. The observation of a significant correlation between improvement and carrying a female fetus is new. It may be that maternal biochemical and hormonal changes during pregnancy differ according to fetal sex.

Overall, pregnancy outcome was uneventful, with the rate of spontaneous abortion, stillbirth, frequency of assisted delivery, and duration of labor within the limits for healthy women. Cesarean section was performed more frequently in our study than figures reported for healthy women in North America and Europe. However, the decision for surgical delivery is influenced by factors not always related to medical problems, and there has been an increase in the rate of cesarean section during the last decades all over the world. AS was reported as the reason for cesarean section for about 58% of the cases. Severity of AS could be one possible explanation, or, more likely,
inclusion of the obstetrician to do a primary surgical delivery in a woman with inflammatory joint disease. Inflammation of the sacroiliac joints, though painful, is not a mechanical hindrance for the progress of parturition. Therefore, the majority of women with AS will be able to deliver by the normal, vaginal route.

AS is a disease with few systemic features. Not unexpectedly therefore, the children born were as a rule delivered at term, had normal birthweight, and were healthy. In our study, treatment with NSAID or smoking during pregnancy did not influence birthweight.

The frequency of reporting aggravation of AS within 6 months after delivery in our study was unrelated to the subgroup of AS and comparable to that found in a previous retrospective study. It cannot be excluded that this flare merely reflected the normal fluctuations of disease activity that would occur also in non-pregnant patients with AS in a comparable period of time. Interestingly, the frequency of a postpartum aggravation was significantly increased in women with active AS at conception, an observation not made before.

Difficulties in caring for a baby or toddler were reported by 65% of the patients, most often in women experiencing a flare within 6 months after delivery. As these were the same who had active disease at conception, this reinforces the practice to caution against becoming pregnant in an active state of disease. Activities stressing the lower back like lifting and carrying were reported to be the most cumbersome. Similar findings were reported by us in an earlier study of mothers with inflammatory rheumatic diseases, including AS. It confirms the notion that activities demanding bending or endurance of the back create greater problems in AS than tasks related to the mobility of peripheral joints.

Our study confirmed that AS does not negatively interfere with reproductive performance or pregnancy outcome. Pregnancy had no major effect on AS, but did suppress peripheral arthritis and anterior uveitis. Preconditions for improvement during pregnancy were a history of peripheral arthritis and female sex of the fetus. Active disease at conception was a predictor of a flare post partum. AS did have an effect on caring for small children.

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