Analysis of the Effect of the Oral Contraceptive Pill on Clinical Outcomes in Women with Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** There are unexplained sex-specific changes in the clinical expression of ankylosing spondylitis (AS). We sought to examine the potential effect of exogenous estrogen in the form of oral contraceptive pills (OCP) on AS initiation and severity.

Methods. This cross-sectional study consisted of women with AS from the membership of the Spondylitis Association of America. Measures of disease severity included use of biological agents and hip replacement surgery, while Bath AS Functional Index (BASFI) scores served as a surrogate marker of disability. Information was obtained using a patient questionnaire on patient demographics, OCP use, pregnancy history, AS duration, medication use, and hip replacement.

Results. There were 571 women with AS who participated in our study, consisting of 448 OCP ever-users and 123 non-OCP users. The mean age of OCP users was 42.7 yrs (± 11.5) and of non-OCP users, 48.4 yrs (± 12.1). No difference was noted in the age at initial onset of back pain. However, OCP users were significantly younger at the time of diagnosis of AS (36.5 yrs vs 39.1 yrs, p = 0.02). There were no significant differences between the 2 groups in tumor necrosis factor inhibitor or opioid use, BASFI scores, pregnancy complications, or hip surgery.

Conclusion. The use of exogenous estrogens in the form of OCP is not associated with a measurable effect on initiation or severity of AS. Biologic and social factors may contribute to earlier diagnosis of AS in OCP users. This is the largest study to date investigating the potential effect of exogenous estrogens in women with AS. (First Release June 15 2014; J Rheumatol 2014;41:1344–8; doi:10.3899/jrheum.130996)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS ORAL CONTRACEPTIVES EXOGENOUS ESTROGENS

The perception of ankylosing spondylitis (AS) in females, with respect to incidence and clinical features, has evolved significantly in recent decades. Once believed to be a male-dominated disease with male to female incidence ratios as high as 10:1, more recent studies have indicated that in fact females comprise a higher proportion of individuals with AS than originally believed[1,2,3,4,5,6,7,8]. The use of new magnetic resonance imaging has revealed a male to female incidence ratio of closer to 3:1[8,9]. Nevertheless, it has been demonstrated that females with AS differ from their male counterparts in several ways. Women with AS have been shown to have an older mean age at the time of disease onset and older age at diagnosis[1]. Additionally, women with AS more often experience cervical spine and peripheral manifestations as well as increased functional impairment in the setting of fewer radiographic changes when compared to men with AS[10,11]. Women with AS have also been shown to respond less effectively to tumor necrosis factor (TNF) inhibitors[1].

We examined the potential role of exogenous hormones in the form of oral contraceptive pills (OCP) on the onset and expression of AS in women. To our knowledge, this is the largest study to date examining the potential role of OCP in women with AS.

MATERIALS AND METHODS

The study population consisted of women with AS drawn from the membership of the Spondylitis Association of America (SAA). Women with a diagnosis of AS were categorized into 2 groups: OCP users (exposed group) and non-OCP users (unexposed group). Women with either past or present use of an OCP were assigned to the OCP user group. A study questionnaire was developed and distributed between April 2011 and July 2012 (Appendix 1). Women with any history of OCP use were identified using the question: "Have you used oral contraceptives in the past?" If they answered yes, they were asked to provide the names of the OCP used, as well as the start and stop dates of each OCP.

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The study questionnaire was developed by the authors, and obtained participant information on demographics, OCP use, duration and type of OCP used, pregnancy history, age at diagnosis of AS, and disease course. Surrogate markers of disease severity, including the use of TNF inhibitors, opioid therapy, and the history of hip replacement surgery were included. Ethics approval was obtained from the University Health Network Research Ethics Committee. The questionnaire was initially piloted at the Toronto Western Hospital Ankylosing Spondylitis clinic. It was later shared with SAA members through online survey distribution. Based on feedback, modifications were made to improve the clarity and comprehensibility of the survey. The modified survey was then uploaded to an online format (Survey Monkey) for distribution to SAA members. The survey was promoted to SAA members through e-mail newsletters, the SAA Website, a Facebook page, and a Twitter account. Confirmation of the diagnosis of AS in SAA members was demonstrated in a previous study[12]. Stone, *et al* performed a nested cohort, with physicians confirming the diagnosis of AS in SAA members.

Statistical analyses were performed using the program SAS 9.1. Analytical methods included t-tests for continuous variables and chi-squared and Fisher's exact test for categorical variables. A p value of less than 0.05 was considered statistically significant.

RESULTS

Fifteen hundred SAA members opened e-mail invitations to participate in this study. A total of 571 female patients with AS participated, consisting of 448 women who had ever used OCP and 123 who had never used OCP. The ages of participants ranged from 18 to 77 years.

The OCP users were noted to be significantly younger than the non-OCP users (42.7 yrs vs 48.4 yrs, $p < 0.0001$). There was no difference between the groups with respect to age at menstruation (Table 1). There was no significant difference between the groups with respect to the age of onset of back pain, with mean age of 24.4 yrs in OCP users compared to 24.6 yrs in non-OCP users ($p = 0.90$). In terms of surrogate markers of disease activity, there was no appreciable difference in the use of TNF inhibitors between OCP and non-OCP users (65.4% vs 60.2%). This was consistent among different TNF inhibitors. Similarly, pain control, as reflected by the use of opioid analgesics, was similar between the OCP and non-OCP users (Table 1). There was no difference in the rates of hip surgery between the 2 groups (Table 1).

There was, however, a significantly earlier age at diagnosis of AS in the OCP user group, with a mean age at diagnosis of 36.5 years, compared to 39.1 years in the non-OCP user group ($p < 0.02$). There did not appear to be a difference between short-term and longterm OCP use on AS disease severity measures. A large number of women in the OCP user group were unable to recall any details of the timing of OCP use (119/448). Of the remaining 329 women, most were only able to provide rough estimations of OCP use duration; hence there was insufficient data available for further analysis.

Within the OCP user group, a variety of OCP had been used[1]. They all contained ethinyl estradiol, and each contained another ingredient such as levonorgestrel, drospirenone, norgestimate, desogestrel, or cyproterone. These OCP consisted of similar levels of estrogen and variations in the progesterone levels[13].

There was no difference between the groups in past pregnancies and pregnancy complications. Reported pregnancy complications included early losses, preterm deliveries, babies small for gestational age, preeclampsia, and premature rupture of membranes. Women in the OCP group reported a higher use of alternative contraception methods.

DISCUSSION

To our knowledge, this is the largest study to date investigating the potential role of exogenous hormones, in the form of OCP, in females with AS. We present the first evidence that the use of OCP does not alter disease initiation or severity of AS in women.

It is interesting to note that while there was no noted

Table 1. Comparisons of oral contraceptive pill (OCP) users and nonusers (n = 571) with ankylosing spondylitis (AS).

Variables	Frequencies (%) or Mean (SD)		p
	OCP Users, n = 448	Non-OCP Users, n = 123	
Age, yrs (SD)	42.7 (11.5)	48.4 (12.1)	< 0.0001
Age at menstruation, yrs (SD)	12.5 (1.7)	12.4 (1.9)	0.68
Age at start of back pain, yrs (SD)	24.4 (10.4)	24.6 (10.3)	0.90
Age at diagnosis of AS, yrs (SD)	36.5 (11.2)	39.1 (11.9)	0.02
Age at menopause, yrs (SD)	44.8 (9.2)	46.3 (7.4)	0.28
Race, white vs others	400 (91.7)	104 (86)	0.06
Menstrual cycle regular	319 (71.2)	91 (74)	0.54
Menopause reached	141 (31.5)	66 (53.7)	< 0.0001
Currently pregnant	6 (1.3)	0 (0)	0.35
Past pregnancies	300 (67)	87 (70.7)	0.45
Pregnancy complications	142 (47.5)	35 (40.7)	0.27
Other methods of contraception	281 (62.7)	62 (51.2)	0.02
Tumor necrosis factor inhibitor use	293 (65.4)	74 (60.2)	0.28
Opioid use	186 (41.5)	56 (45.5)	0.47
Past hip surgery	19 (4.2)	8 (6.5)	0.29

difference between the groups in the onset of back pain, the OCP users were diagnosed with AS at an earlier age. This prompts the question of whether there is truly a biologic effect of exogenous hormones on AS disease expression, in accelerating the pathogenesis and development of AS to the point at which clinical criteria manifestations are recognized. Alternatively, there could be social variables contributing to this interaction. We may be dealing with detection bias, in that women who use OCP likely attend physician assessments more frequently than do nonusers. Consequently, these women may be more conscious of their back pain and other AS-related symptoms and may seek medical advice earlier. This in turn may be what contributes to an earlier diagnosis of AS in those women who use OCP. It would be helpful to observe the number of physician assessments attended by the patient, both before and after the diagnosis of AS, in future studies.

The difference in onset, clinical presentation, and severity of AS between males and females may be explained in part by the effect of both sex and gender. In current usage, sex specifically refers to the chromosomal-genetic phenotype of the individual, while gender incorporates societal factors such as environment, exercise, societal and social roles, and associated infection risk. Regarding possible mechanisms whereby the sex of the individual can influence disease expression, sex hormones, both endogenous and exogenous, can be considered important candidate mediators.

The effect of estrogen on inflammation and disease expression is complex. Paradoxical immunomodulatory roles of estrogen have been identified. On one hand, estrogen is associated with suppression of bone resorption and inflammation. On the other hand, estrogen metabolites have been associated with proinflammatory effects at the level of synovial tissue[14,15,16]. In systemic lupus erythematosus (SLE), estrogens impart immunomodulatory effects predominantly through B cell antibody production. This can enhance disease expression. There is evidence to support current use of combined OCP with increased SLE disease activity[17,18,19]. In rheumatoid arthritis (RA), increased levels of estrogen metabolites (including 16-α hydroxylesterone) have been found in synovial tissue, suggesting an association between estrogen and synovial inflammation[20,21]. However, studies on OCP and RA disease effect are limited. A systematic review conducted by Farr, *et al* failed to find a consistent trend between the use of OCP and RA disease activity[22].

The potential link of sex hormones and disease expression, as well as associated underlying mechanisms, remains incompletely understood in AS. There are very limited data examining the effect of exogenous hormones on AS. Jimenez-Balderas and colleagues conducted a small, uncontrolled study examining the role of exogenous hormones in the form of OCP and hormone replacement therapy (HRT) on AS severity[23]. A total of 17 women participated in the study, including 12 premenopausal women using OCP and 5 menopausal women taking HRT. The participants reported resolution of their peripheral arthritis, with improvement in their functional class and AS measurements, within 1 month of exogenous estrogen use. Interestingly, their symptoms returned once the exogenous estrogen was discontinued.

With respect to endogenous hormone levels in individuals with AS, Gooren, *et al* compared the level of serum testosterone and 17-β estradiol in women with and without AS[24]. Essentially, no differences were noted between the 2 groups. Similarly, serum testosterone levels were found to be similar among men with and without a diagnosis of AS. However, the question of potential effect of different hormones on AS manifestations was not addressed.

When considering the potential effect of hormonal shifts on AS development and disease expression, it is helpful to analyze alterations in AS associated with pregnancy. Lui, *et al*[25] conducted a retrospective study evaluating the effect of pregnancy in AS. Overall, no significant change in disease activity or severity of AS was noted postpregnancy. Ostensen and Ostensen similarly noted that AS did not adversely affect fertility, pregnancy outcome, or the neonate. Active disease at the time of conception was found to be predictive of postpartum flare[26]. Further, they hypothesized that clinical changes may in fact be secondary to cytokine milieu, specifically a decrease in serum TNF receptor, as opposed to hormonal shifts[27]. To that effect, it is interesting to note that there were no significant differences in pregnancy rates between OCP users and nonusers with AS in our study. The trend toward an increase in pregnancy complication rates among OCP users is unique and warrants further investigation.

It is noteworthy that despite differences in the time of diagnosis of AS between the 2 groups, no appreciable differences were noted with respect to severity of disease. Specifically, the surrogate markers for disease severity, which included TNF inhibitors, opioid analgesic use, hip replacement, and BASFI scores, were similar between groups. This suggests the possible early effect of exogenous estrogens in the initiating pathophysiology of AS, with less clinical effect during later stages of the disease. Our current understanding of the pathophysiology of exogenous estrogen on AS disease initiation and expression is limited. Proposed mechanisms have included the role of exogenous hormones on contributing to myopathic noninflammatory changes in early AS[28]. Further studies are warranted to better elucidate this issue.

We acknowledge limitations to our study. To obtain a sizable cohort, a retrospective trial design was used. Additionally, the questionnaire relied upon accurate patient recall of initial disease presentation, pregnancy history, and medication use. We were not able to reliably obtain information on cumulative dose of OCP as well as age at initial

use of OCP. Because of poor patient recall regarding timing of OCP use, we were unable to accurately report the proportion of women who were using OCP at the time they were diagnosed with AS. Further patient stratification with respect to OCP use would be ideal. Specifically, comparison of "ever" OCP users to current and past users would help to delineate the potential influence of OCP on disease. Categorizing OCP use, duration, and dose before and after the diagnosis of AS would help to clarify any proportional effect of OCP use on disease initiation and progression. Owing to poor patient recall regarding duration and timing of OCP use, we were unable to study whether a potential relationship existed between duration of OCP use and measures of disease severity. This is an important question, which we hope to clarify in future studies.

Additionally, we acknowledge that age-matched controls between our OCP user and nonuser groups would have been ideal. The earlier age of OCP users at the time of diagnosis of AS may be in part due to the overall younger age of OCP users compared to nonusers. Further, it is assumed that all respondents from the SAA have been formally diagnosed with AS. While we were constrained by our study design, these are important considerations for future studies in this area.

In terms of future studies of hormonal modulation of AS, it would be worthwhile to analyze other markers of disease severity. It would be ideal to assess BASFI and Bath AS Disease Activity Index before and after initiation of OCP treatment. Additionally, measures of radiographic severity and spinal mobility would provide further insight into disease severity. It would be helpful to differentiate women who use OCP by the type of oral contraceptive used. Specifically, the stratification of this group based on the actual estrogen/progesterone content may elucidate stronger relationships between exogenous estrogen use and disease onset and markers of disease severity. Because most of our study participants were unable to accurately recall the specific OCP used, we were unable to explore this concept.

Our study demonstrates that the use of exogenous estrogens in the form of OCP does not have a measurable effect on AS symptom onset or severity. However, the use of OCP was associated with an earlier age of diagnosis of AS. There may be hormonal implications with respect to early expression of disease, contributing to an earlier diagnosis. The potential effect of estrogen on AS disease activity warrants further investigation.

APPENDIX 1. Ankylosing spondylitis and oral contraceptive pills (OCP) use questionnaire.

1. Are you a woman with a confirmed diagnosis of Ankylosing Spondylitis (AS)?
2. How old were you when your back pain started?
3. How old were you at the time of diagnosis of AS?
4. Have you used anti-TNF agents (Enbrel, Remicade, Humira or Simponi) for AS?
5. Please specify which anti-TNF agent you have used by indicating the START DATE and END DATE for the medications you have used. When possible, please provide dates in this format: Month/Year to Month/Year (E.g. 06/04 to 09/08).
6. Have you used opioids (such as Codeine, Oxycodone, Morphine, etc) for pain management of AS?
7. Please specify which opioid you have used by indicating the START DATE and END DATE for the medications you have used. When possible, please provide dates in this format: Month/Year to Month/Year (E.g. 06/04 to 09/08).
8. Please list any other medical conditions that you are being treated for
9. Have you had previous hip surgery? If so, when?
10. Have you used oral contraceptives (birth control pills) in the past? *IF YES, Please provide Name/s of all Oral Contraceptive/s used, and list the Start Date and End Date for each to the best of your ability - (E.g. used from 06/04 to 09/08).
11. Have you used other methods of contraception, other than oral contraceptives?
12. How old were you when you had your first menstrual period?
13. Has your menstrual cycle generally been regular?
14. Have you reached menopause? If so, at what age did your periods end?
15. Are you currently pregnant?
16. Have you been pregnant in the past?
17. Have you experienced any pregnancy losses or complications (such as pre-term labour, pre-mature rupture of membranes, small for gestational age fetus)?
18. Please list the delivery dates of successful pregnancies below. (E.g. 08/15/1999)
19. What is your age?
20. What is your ethnicity?

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