

# Sex hormonal factors and chronic widespread pain: a population study among women

T. V. Macfarlane, A. Blinkhorn, H. V. Worthington, R. M. Davies<sup>1</sup> and G. J. Macfarlane<sup>2,3</sup>

University Dental Hospital of Manchester, <sup>1</sup>Dental Health Unit, <sup>2</sup>Unit of Chronic Disease Epidemiology and <sup>3</sup>Arthritis Research Campaign Epidemiology Unit, University of Manchester, UK

## Abstract

*Objective.* The observation of higher rates of chronic widespread pain, the cardinal feature of fibromyalgia, in women has led to hypotheses about the role of sex hormonal factors in the aetiology of symptoms. There is little available evidence from epidemiological studies on their importance or role.

*Methods.* A population postal survey was carried out involving 1178 female participants living in south-east Cheshire in the north-west of England.

*Results.* Amongst pre- and peri-menopausal women, the risk of chronic widespread pain was unrelated either to the length of the menstrual cycle or the usual length of period reported by participants. Risk was similar in current users and non-users of the oral contraceptive pill, and amongst users there was no relationship with duration of use. However, the reporting of chronic widespread pain showed a relationship with total score on a premenstrual symptom questionnaire. However, this relationship was explained by pain symptoms. Amongst post-menopausal women, reporting chronic widespread pain was not related to age at menopause. An increased (but non-significant) risk of chronic widespread pain was associated with current hormone replacement therapy (HRT), which may be a consequence of HRT being prescribed for menopausal symptoms.

*Conclusion.* This study, conducted on a large unselected population, has not demonstrated an association between sex hormonal factors and chronic widespread pain.

KEY WORDS: Pain, Fibromyalgia, Sex Hormones, Epidemiology.

Chronic widespread pain is the cardinal symptom of fibromyalgia, one of the most common reasons for consultation at rheumatological clinics in western Europe and North America [1]. In the clinic, fibromyalgia is considerably more common in women than men, typically exhibiting a sex ratio of around 10 : 1. This excess cannot be explained completely by females with symptoms consulting more than males. Although the sex ratio is lower for studies of fibromyalgia and chronic widespread pain in the population, the excess amongst females is still evident. In Canada, a population telephone survey reported rates of chronic widespread pain among males and females of 4.7 and 9.0% respectively [2], while a questionnaire population survey in the UK reported rates of 9.4 and 15.6% respectively [3].

Submitted 8 March 2001; revised version accepted 2 November 2001.

Correspondence to: G. J. Macfarlane, Unit of Chronic Disease Epidemiology, University of Manchester, Medical School, Oxford Road, Manchester M13 9PT, UK.

Despite the observation of higher prevalence rates in females, a feature shared with several other regional pain syndromes, the role of sex hormones in the occurrence and severity of symptoms is largely unknown. One retrospective study of a small group of 26 women with fibromyalgia found that they reported a worsening of symptoms during pregnancy and a further worsening of symptoms in the post-partum period [4]. A further small study of 16 patients with fibromyalgia reported that there were significant changes in pain reporting throughout the menstrual cycle, with pain scores highest in the peri-menstrual phase in comparison with the ovulatory phases [5]. A further two case-control studies of a specific regional pain syndrome, temporomandibular pain disorder, using automated pharmacy and health-care records suggested a relationship between the use of exogenous sex hormones and pain reporting [6].

The aim of the present study was to determine whether endogenous or exogenous hormonal status was associated with reporting chronic widespread pain in an unselected population sample of females.

## Methods

### *Study population*

The sampling frame was the registered population of a general practice in Congleton, Cheshire. This is a market town in north-west England of mixed socio-demographic characteristics, similar to those of the whole county. The study sample, of 4000 subjects aged 18–65 yr, was selected by simple random sampling, and each received a questionnaire by post. Non-responders were followed up successively with a post-card reminder, a further mailed questionnaire and a short version of the questionnaire. Those who had still not returned a completed questionnaire and had not declined to participate were thereafter offered the option of a telephone interview.

### *Information collected*

The questionnaire asked about any pain experienced during the past month which had lasted at least 24 h. Those responding positively were asked to indicate the site of pain on body manikins, which allowed us to determine whether subjects satisfied the American College of Rheumatology (ACR) definition of chronic widespread pain [7]. In brief, this requires at least pain in the axial skeleton and contralateral quadrant body pain (e.g. pain in the top left and bottom right body quadrants) which has lasted more than 3 months. Additional items of the questionnaire enquired about menstrual history and symptoms, use of the oral contraceptive pill and hormone replacement therapy (HRT). A 12-item questionnaire (the premenstrual symptom questionnaire) was included, enquiring about 'how you usually feel in the week before a period' [8]. The items relate to gain in weight, tension, headache, stomach pains, anxiety/worry, backache, tiredness, feeling sick or vomiting, irritability, feeling swollen or bloated, depression, and tender breasts. Each is recorded as none/slight/moderate/severe, corresponding to scores of 0–3 and providing a total score between 0 and 36. In addition, for the purpose of the present study, a modified nine-item scale, excluding the three pain items (backache, stomach-ache, headache), was constructed, providing a score between 0 and 27.

In order to determine the repeatability of some of the exposure information reported, a small group of 50 subjects stratified by pain status were randomly selected from amongst the participants and asked to complete an identical questionnaire 2 months after their original response. In addition, eight subjects voluntarily completed the questionnaire twice after they had inadvertently been sent a reminder questionnaire.

### *Analysis*

Analysis of the relationship between sociodemographic factors, reproductive factors and chronic widespread pain included all female subjects. Analysis of other hormonal factors and chronic widespread pain was conducted separately for pre-/peri-menopausal and

post-menopausal women. Post-menopausal women were defined as those who reported that their periods had stopped completely. Analysis used Breslow's extension of the Cox regression model [9] and the relationships were expressed as relative risks (RR) with 95% confidence intervals (CI). This is a more meaningful effect measure for cross-sectional studies than the odds ratio [10]. Risk measures are shown crude and adjusted for age. Repeatability of categorical exposure reporting was assessed using  $\kappa$ , a measure of agreement above that expected by chance. Values range from 0 (agreement at the level expected by chance) to 1 (perfect agreement) and values in the range 0.6–0.8 and  $>0.8$  are considered as indicating good and very good agreement respectively [11]. The 95% CIs were also calculated for this measure of agreement. A reliability coefficient [12] was used to assess the reliability of continuous variables, such as the score derived from the premenstrual symptom questionnaire data.

## Results

From 4000 persons selected randomly, a total of 2504 completed questionnaires were returned. Of the persons who did not return a questionnaire, 620 were assumed not to have received the questionnaire because they were no longer registered at that address on the electoral roll ( $n = 469$ ), because notification had been received from the occupant or post office that the subject had moved ( $n = 132$ ) or because we had been notified that the person was severely disabled or terminally ill ( $n = 13$ ) or had died ( $n = 6$ ). This resulted in an adjusted participation rate of 74%, which was higher in women (79%) than men (69%). For the present analysis, only female subjects who completed a full study questionnaire ( $n = 1245$ ) with no missing information on pain status ( $n = 1178$ ) were included. The prevalence of chronic widespread pain, using the ACR definition, amongst the female subjects was 11.2%.

Amongst pre- or peri-menopausal women (66% of the study participants), the risk of chronic widespread pain was unrelated either to the length of the menstrual cycle or to the usual reported length of a period. Risk was similar in current users and non-users of the oral contraceptive pill, and amongst users there was no relationship with duration of use (Table 1). The reporting of chronic widespread pain did, however, show a relationship with the total score on the premenstrual symptom questionnaire. Relative to those with scores in the lowest tertile, those in the middle tertile had a risk (RR) of 1.29 (95% CI 0.66–2.53) and those in the highest tertile a risk of 2.02 (95% CI 1.10–3.70). When the modified premenstrual symptom scale score was considered (excluding items relating to regional pain sites), the relationship between scale score and chronic widespread pain was attenuated and no longer significant (RR 1.25, 95% CI 0.72–2.16).

Amongst post-menopausal women, reporting chronic widespread pain was not related to age at menopause

TABLE 1. Association of hormonal and menstrual factors with chronic widespread pain: premenopausal and peri-menopausal women ( $n = 773$ )

Factor	Total number <sup>a</sup>	RR (95% CI)	
		Crude	Adjusted for age <sup>b</sup>
Oral contraceptive use			
No	568	1.00	1.00
Yes	194	0.98 (0.58–1.65)	0.97 (0.53–1.75)
Duration of oral contraceptive use (months)			
Not current user	568	1.00	1.00
1–90	91	1.35 (0.73–2.48)	1.43 (0.69–2.98)
91–420	97	0.69 (0.30–1.56)	0.68 (0.28–1.60)
Duration of menstrual cycle (days)			
$\leq 27$	294	1.00	1.00
28	336	1.23 (0.73–2.08)	1.23 (0.71–2.13)
$\geq 29$	140	1.04 (0.53–2.07)	1.03 (0.50–2.11)
Duration of menstrual period (days)			
$\leq 4$	240	1.00	1.00
5	280	0.70 (0.42–1.17)	0.70 (0.41–1.20)
$\geq 6$	183	0.68 (0.38–1.24)	0.68 (0.36–1.27)
Premenstrual symptom questionnaire (total score)			
0–9	240	1.00	1.00
10–14	248	1.29 (0.68–2.46)	1.29 (0.66–2.53)
15–36	278	2.01 (1.13–3.60)	2.02 (1.10–3.70)
Premenstrual symptom questionnaire (modified scale) <sup>c</sup>			
0–7	260	1.00	1.00
8–11	235	0.82 (0.45–2.79)	0.82 (0.77–1.53)
12–27	271	1.25 (0.75–2.10)	1.25 (0.72–2.16)
Ever had painful periods			
No	443	1.00	1.00
Yes	325	1.11 (0.71–1.75)	1.11 (0.69–1.78)

<sup>a</sup>Numbers do not always total 773 because of missing information; <sup>b</sup>age groups: 18–30, 31–40,  $\geq 41$  yr; <sup>c</sup>excluding pain-related items.

(Table 2). There was an increased but non-significant risk associated with reporting current HRT.

#### Repeatability of exposure information

Forty-one women completed the questionnaire a second time approximately 2 months after completing the original questionnaire. The information on menstrual status showed perfect agreement ( $\kappa = 1.0$ ). Agreement for all other factors [ever had painful periods,  $\kappa = 0.6$ , 95% CI 0.4–0.9; use of oral contraceptive,  $\kappa = 0.7$ , 95% CI 0.4–1.0; HRT use,  $\kappa = 0.9$ , 95% CI 0.6–1.0) was within the range which is considered to represent good or very good agreement. The reliability coefficient for the premenstrual symptom questionnaire was 0.91, which, given a maximum possible coefficient of 1.0, is considered to be high.

## Discussion

This study has not provided any strong evidence that sex hormonal factors are related to chronic widespread pain. Pain was not related to any of the hormonal/menopausal factors examined in pre-/peri- or post-menopausal women. Amongst post-menopausal women, risk increased modestly (and not significantly) with duration of hormone replacement therapy, although this may have reflected the prescription of HRT because of menopausal symptoms.

TABLE 2. Association of hormonal and menstrual factors with chronic widespread pain: post-menopausal women only ( $n = 403$ )

Factor	Total number <sup>a</sup>	RR (95% CI)	
		Crude	Adjusted for age <sup>b</sup>
Hormone replacement therapy use (current)			
No	259	1.00	1.00
Yes	143	1.31 (0.82–2.07)	1.34 (0.80–2.27)
Duration of HRT use (months)			
Not currently used	259	1.00	1.00
$\leq 48$	76	1.14 (0.62–2.07)	1.21 (0.61–2.38)
$> 48$	63	1.48 (0.84–2.63)	1.46 (0.77–2.79)
Age periods stopped (yr)			
$\leq 45$	109	1.00	1.00
46–50	99	0.81 (0.43–1.53)	0.74 (0.36–1.55)
$\geq 51$	82	0.91 (0.48–1.73)	0.79 (0.36–1.75)
Ever had painful periods			
No	205	1.00	1.00
Yes	192	1.48 (0.93–2.35)	1.53 (0.92–2.55)

<sup>a</sup>Numbers do not always total 403 because of missing information; <sup>b</sup>age groups: 19–52, 53–58,  $\geq 59$  yr.

There are few other epidemiological studies of musculoskeletal pain and sex hormones with which to compare these results. This may be because it has not been studied previously or that studies, failing to find an association, have not been published (i.e. publication bias). Two studies of healthy subjects reported no correlation between the hormonal phase of the menstrual cycle and pain threshold measurements or the elicitation of tender points [13, 14], while in a study of 40 pregnant patients with fibromyalgia, although severity changed during pregnancy, severity was not related to hormonal changes associated with abortion, the use of hormonal contraceptives or breast-feeding [4].

If the difference in prevalence of chronic widespread pain between men and women is not explained by sex hormones, what other explanations could there be for the difference? There is little evidence that genetic factors are important. A study comparing monozygotic with dizygotic twins showed similar rates of concordance for pain threshold [15]. A possible explanation for the difference in prevalence rate is that women have a lower threshold for reporting these symptoms. This may be due to differences in pain processing mechanisms, differences in coping strategies or social factors. For example, in the case of social factors, it may be considered more acceptable for women to report such symptoms than men. An alternative hypothesis is that women are more commonly exposed to risk factors for the development of chronic widespread pain. There is some evidence for all these hypotheses from studies of regional and chronic widespread pain [16–18], and future studies may usefully clarify the role of each.

#### Conclusion

This study, the first to examine the relationship between chronic widespread pain and sex hormonal factors, both endogenous and exogenous, in a large unselected

population, failed to demonstrate consistent associations. It seems unlikely that such factors can account for the gender differences observed.

### Acknowledgements

The authors thank the patients and staff at Lawton House Surgery, Congleton, Cheshire, UK.

### References

1. White KP, Speechley M, Harth M, Ostbye T. Fibromyalgia in rheumatology practice: a survey of Canadian rheumatologists. *J Rheumatol* 1995;22:151–6.
2. White KP, Speechley M, Harth M, Ostbye T. The London Fibromyalgia Epidemiology Study: The prevalence of fibromyalgia syndrome in London, Ontario. *J Rheumatol* 1999;26:1570–6.
3. Croft P, Rigby AS, Boswell R, Schollum J, Silman AJ. The prevalence of chronic widespread pain in the general population. *J Rheumatol* 1993;20:710–3.
4. Ostensen M, Rugelsjoen A, Wigers SH. The effect of reproductive events and alterations of sex hormone levels on the symptoms of fibromyalgia. *Scand J Rheumatol* 1997;26:355–60.
5. Anderberg UM. The role of sex hormones in pain response. *Pain* 2000;87:109–11.
6. LeResche L, Saunders K, von Korff MR, Barlow W, Dworkin SF. Use of exogenous hormones and risk of temporomandibular disorder pain. *Pain* 1997;69:153–60.
7. Wolfe F, Smythe HA, Yunus MB *et al*. The American College of Rheumatology 1990. Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990;33:160–72.
8. Crowther DL. Is there a link between the consulting patterns of premenstrual women and the menstrual cycle? *Fam Pract* 1994;11:402–7.
9. Breslow NE. Covariance analysis of survival data. *Biometrics* 1974;30:89–99.
10. Lee J. Odds ratio or relative risk for cross-sectional data? *Int J Epidemiol* 1994;23:201–3.
11. Silman AJ. *Epidemiological studies: a practical guide*. Cambridge University Press, 1995.
12. Dunn G, Everitt B. *Clinical biostatistics. An introduction to evidence-based medicine*. London: Edward Arnold, 1995.
13. Johns KR, Littlejohn GO. The role of sex hormones in pain response. *Pain* 1999;83:112–3.
14. Hapidou EG, Rollman GB. Menstrual cycle modulation of tender points. *Pain* 1998;77:151–61.
15. MacGregor AJ, Griffiths GO, Baker J, Spector TD. Determinants of pressure pain threshold in adult twins: evidence that shared environmental influences predominate. *Pain* 1997;73:253–7.
16. Unruh AM. Gender variations in clinical pain experience. *Pain* 1996;65:123–67.
17. McBeth J, Morris S, Benjamin S, Silman AJ, Macfarlane GJ. Associations between adverse events in childhood and chronic widespread pain in adulthood: are they explained by differential recall? *J Rheumatol* 2001;28:2305–9.
18. Papageorgiou AC, Macfarlane GJ, Thomas E, Croft PR, Jayson MIV, Silman AJ. Psychosocial factors in the workplace—Do they predict new episodes of low back pain? *Spine* 1997;22:1137–42.