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ORIGINAL REPORT

Estrogens and the risk of complex regional pain syndrome (CRPS)

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SUMMARY

Objective Since complex regional pain syndrome (CRPS) shows a clear female predominance, we investigated the association between the cumulative as well as current exposure to estrogens, and CRPS.

Methods A population-based case–control study was conducted in the Integrated Primary Care Information (IPCI) project in the Netherlands. Cases were identified from electronic records (1996–2005) and included if they were confirmed during a visit (using International Association for the Study of Pain Criteria), or had been diagnosed by a specialist. Controls were matched to cases on gender, age, calendar time, and injury. Measures of cumulative endogenous estrogen exposure were obtained by questionnaire and included age of menarche and menopause, menstrual life, and cumulative months of pregnancy and breast-feeding. Current estrogen exposure at CRPS onset was retrieved from the electronic medical records and determined by current pregnancy or by the use of oral contraceptive (OC) drugs or hormonal replacement therapy (HRT).

Results Hundred and forty-three female cases (1493 controls) were included in analyses on drug use and pregnancies, while cumulative endogenous estrogen exposure was studied in 53 cases (58 controls) for whom questionnaire data were available. There was no association between CRPS and either cumulative endogenous estrogen exposure, OC, or HRT use. CRPS onset was increased during the first 6 months after pregnancy (OR: 5.6, 95%CI: 1.0–32.4), although based on small numbers.

Discussion We did not find an association between CRPS onset and cumulative endogenous estrogen exposure or current OC or HRT use, but more powered studies are needed to exclude potential minor associations. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS — complex regional pain syndrome; hormones; estrogen

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INTRODUCTION

Rehabilitation from a physical trauma, such as a fracture or sprain, can be complicated by the complex regional pain syndrome (CRPS). CRPS is usually located in the distal part of the affected extremity and is marked by pain, vasomotor, sudomotor, and motor/trophic disturbances.[1] Its pathogenesis is subject to speculation, but nervous system involvement has since long been acknowledged. However, more recently the interest in inflammatory disease mechanisms underlying CRPS has increased.[2,3] Neurogenic inflammation is mediated by neuropeptides that are secreted by nociceptive nerve endings upon triggering by mechanical, chemical, or physical injury.[4] Neuropeptides, such as substance P (SP) and calcitonin gene-related protein (CGRP), induce plasma protein extravasation,[5] recruitment of immune cells,[6] and release of pro-inflammatory cytokines, for example, tumor necrosis factor α (TNFα), interleukin (IL)-1, and IL-6.[7,8] Moreover, reactive oxygen species (ROS) have been suggested to be involved in triggering or sustaining CRPS.[9,10]

CRPS has a clear female predominance with a female/male ratio between 3 and 4.[11,12] The peak incidence occurring between the fifth and seventh decade suggests an increasing risk after the menopause when endogenous estrogen levels drop. Furthermore, a previous study showed an association between CRPS and both menstrual cycle-related disorders and

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osteoporosis.[13] All these observations suggest that sex hormones, in particular estrogens, are of relevance in CRPS pathogenesis.

In women serum levels of 17β-estradiol (E2), the primary estrogen during pre-menopausal life, are influenced by menarche, menstrual cycle, menopause,[14] pregnancy, and postpartum period.[15] Estrogen levels may also be affected by synthetic estrogens or estrogen mimicking drugs such as oral contraceptive (OC) drugs[16] or as hormonal replacement therapy (HRT).[17] The latter is frequently prescribed to women during the peri- or post-menopausal life in order to attenuate the negative effects accompanying decreasing E2 levels, such as vasomotor symptoms, mood changes, and loss of bone mineral density. Beyond their role in sexual development and reproduction estrogens play an important role in the cardiovascular system[18] and in bone metabolism.[19] Additionally, estrogens are widely involved in mechanisms of inflammation[20] and may therefore interact with several presumed mediators in the pathogenesis of CRPS. For example, estrogens influence the metabolism of SP and bradykinin[21] and prevent the formation of ROS during ischemia or inflammation.[22] Moreover, NFκB, an important transcription factor in inflammation and probably also in CRPS,[23] is inhibited by interaction with estrogen receptors.[24] Overall, these estrogen effects may attenuate the disease mechanisms of CRPS, and we therefore hypothesized that high estrogen levels may prevent CRPS onset.

In the present study, we investigated whether exposure to estrogens affects the risk for CRPS onset. We performed a population-based case–control study comparing measures of cumulative endogenous estrogen exposure during life, as well as current estrogen exposure at the moment of CRPS onset.

PATIENTS AND METHODS

Design and setting

The case–control study was nested within the integrated primary care information (IPCI) project, a general practitioners (GP) research database in the Netherlands. The database contains the electronic files of over one million patients and is representative of the Dutch population regarding age and gender.[25,26] All inhabitants of the Netherlands are registered with a GP who receives and stores all healthcare information of their patients.[27] Therefore, GPs can be considered to have complete medical information. GPs who participate in the IPCI project do not keep additional paper records. The electronic records store information on demographics, signs and symptoms (using the International Classification for Primary Care (ICPC)[28] and narratives), diagnoses (using ICPC and narratives), clinical findings, specialist referrals, laboratory findings, hospitalizations, and drug prescriptions. Summaries from medical correspondence with specialists are entered in a free text format and hard copies of original letters can be provided upon request. The IPCI project complies with the European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research.[29] The present study has been approved by the Scientific and Ethical Advisory Group of the Project and by the Medical Ethical Board of the Erasmus Medical Center (protocol number 2006-099).

Source population

The source population comprised all persons with at least 1 year of valid history in the IPCI database during the study period (January 1996 to June 2005) to ensure sufficient baseline information on all subjects. This meant that the practice had been contributing data for at least 1 year and that the patient had been registered with the GP for at least 1 year. Follow-up in the database started on the first of January 1996 or on the date that 1 year of valid history was available, whichever date was latest. Follow-up was ended upon transferring out of the practice, the date of last data supply by the GP, occurrence of CRPS, or at the end of the study period, whichever came first. Since GP co-operation was needed for additional data collection, the source population was restricted to practices that were still active in the IPCI database in 2006.

Cases

CRPS cases were retrieved from the electronic records using a string search algorithm on narrative journal text, including Dutch synonyms for CRPS, abbreviations, and obvious spelling errors. Initial case validation occurred with a brief questionnaire to the GP to confirm or reject the CRPS diagnosis as mentioned in the records.[11] Specialist correspondence was obtained if available. Subsequently, with mediation of the GP, confirmed cases were invited by mail for further study participation. Patients who provided informed consent were visited once by the primary investigator, a physician with clinical experience in diagnosing CRPS (M.M.). Prior to the visit participants had filled a questionnaire addressing present and past CRPS complaints, disease course, and treatment.

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During the visit, the investigator and the patient briefly went over the questionnaire together to ascertain completeness. Additionally, a physical examination of the affected limb and contralateral extremity was performed to assess signs of CRPS.

CRPS patients were included as cases in the study population if they could be confirmed by the investigator, applying the IASP criteria on the symptom and sign assessments during the visits, combined with information from the GP records and specialist letters. CRPS patients who could not be visited because they were untraceable or refused participation were included only if the CRPS diagnosis in the past had been confirmed by a medical specialist (instead of by GP only). The index date was chosen as the date on which the CRPS diagnosis was mentioned in the records for the first time. In this specific study, only female patients were included.

Controls

Per case, an unrestricted number of age (year of birth) and gender-matched controls were selected from the source population. Additionally, controls were required to have experienced an injury identical to the one that precipitated the CRPS in their matching case within a 2-year band of calendar time. This meant that cases with a fracture were matched to controls with a fracture, cases with a soft tissue injury were matched to controls with a soft tissue injury, etc. The index date in controls was chosen as the date of injury plus the delay time between injury and CRPS in the matching case. If a case had spontaneous CRPS (no precipitating injury), controls were not required to have had an injury either. A subset of the controls (1–3 per case) was invited to participate in assessments similar to the cases (self-administered questionnaire and physical examination).

Estrogen exposure

The role of estrogens was explored in various ways: (1) cumulative endogenous exposure, (2) current endogenous exposure, and (3) current exogenous exposure. Information on these determinants was obtained either from questionnaires or from the medical records.

Cumulative endogenous estrogen exposure until the index date was assessed using patient questionnaire data and included the following measures: age of menarche, age of menopause, menstrual life (in years), parity, cumulative months of pregnancy, and cumulative months of breast-feeding. Menstrual life was determined as the age of menopause minus the age of menarche (post-menopausal women) or as the index date minus the age of menarche (pre-menopausal women). Cumulative months of pregnancy were calculated by summing the reported months of all pregnancies experienced during life, including full-term, preterm, and aborted pregnancies. Similarly, the cumulative months of breast-feeding were calculated by summing the months of breast-feeding for each child. Since all these measures were derived from the patients' questionnaires, they could only be assessed in cases and controls that had participated in the additional data collection during visits.

Current endogenous estrogen exposure included pregnancy close to the index date. These pregnancies were identified in the IPCI database by a string and ICPC code search in free text and in the diagnosis table. Pregnancy start and duration were derived from the records. If this was not well recorded, we assumed 280 days for full-term deliveries, 245 days for preterm deliveries, 105 days for late miscarriages, 60 days for early miscarriages, and 70 days for intended abortions. The association between pregnancy and CRPS onset was studied in the three different time windows: current pregnancy: CRPS onset (index date) during a pregnancy; recent pregnancy: CRPS onset within 6 months after delivery; past/no pregnancy: CRPS onset more than 6 months after delivery.

Current exogenous estrogen exposure at the index date included the use of OC drugs (in pre-menopausal women) and the use of HRT (in post-menopausal women). Information about the drug prescriptions was retrieved from the IPCI database. The prescription records comprised the Anatomical Therapeutical Chemical (ATC) classification code, prescription start date, quantity, strength, indication, and prescribed daily dose. All estrogen-containing OCs were included (ATC codes G03AA and G03AB). For each 21 tablets we took into account a 28-day exposure period, including a pill free week. HRT included all (oral, vaginal, transdermal) estrogen-containing drugs intended for prevention or treatment of negative post-menopausal effects (G03C). For HRT we calculated the duration of a prescription as the quantity of prescribed units (mostly tablets) divided by the daily intake of units. Episodes of use were created by combining consecutive prescriptions and correcting for overlap. A person was classified as current user if the legend duration of the most recent prescription ended <30 days before the index date. Past users were subjects with the most recent prescription ending between 30 days and 1 year prior to the index date. Differentiation between pre- and post-menopausal status at the index date was done by imputing the

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reported average age of menopause in the visited patients into the unvisited patients.

Covariables

Determinants associated with either CRPS onset or with OC or HRT use were considered as potential confounders. Asthma, migraine, menstrual cycle-related disorders (dysmenorrhea, metro/menorragia, poly/oligomenorrhea), and osteoporosis were increased in CRPS patients during a previous study.[13] In addition to these, smoking, hypertension, cardiovascular disorders, climacterial complaints, breast cancer, and cancer of the female reproductive organs were tested since they might be associated with OC or HRT use. All information regarding potential confounders was derived from the electronic journal texts.

Statistical analyses

Standard comparative statistics were used to determine differences in means (paired *t*-test) and proportions (χ^2-test). Odds ratio (OR) and 95%confidence intervals (CI) for associations between cumulative or current estrogen exposure and CRPS onset were calculated using conditional logistic regression. Measures of cumulative endogenous estrogen exposure were tested both as continuous variables and as categorical variables. Covariables were included in the final model if they were univariately associated with the exposure or the outcome, or if they altered the odds ratio by more than 10%. All analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 12.0 for windows.

RESULTS

The selection of the study population is displayed in Figure 1. The response rate for participation concerning further data collection was 64% in CRPS cases and 28% in controls. Participants were not significantly different from non-participants regarding age and medical history. The final study population included 143 female CRPS patients: 81 visited by the investigator (at the moment of on average 5.7 years since CRPS onset) + 62 non-visited patients with a specialist diagnosis. These CRPS patients were matched with 1493 controls (median 12 per case, range 2–53). This study population was used to conduct analyses regarding OC and HRT use and actual pregnancies at the moment of CRPS. Since measures of cumulative estrogen exposure could not be retrieved from the IPCI database, but had to be derived from

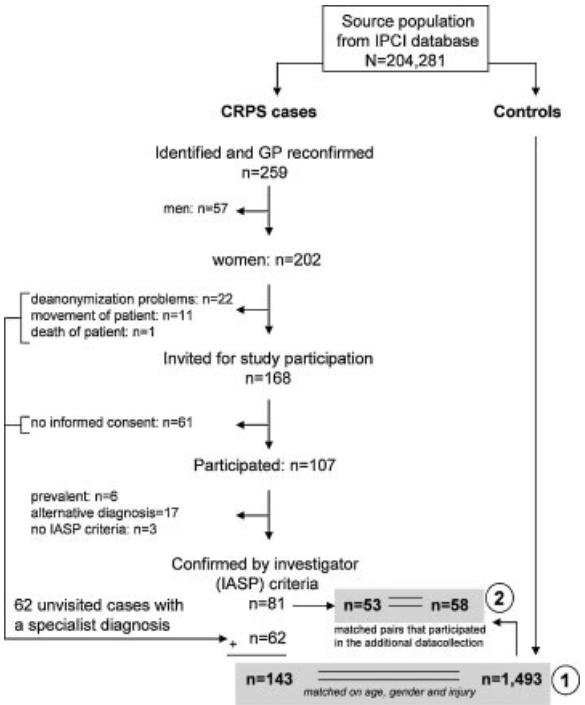

Figure 1. Selection of the study population. (1) This study population includes matched case–control pairs in the IPCI database. Cases ($n = 143$) were validated during a visit by the investigator ($n = 81$) or were confirmed by a specialist ($n = 62$). Controls ($n = 1493$) were selected from the database, matched to the cases on age, gender, and injury type. This study population was used in the analyses of determinants that were derived from the records in the IPCI database, namely OC and HRT use and pregnancies during follow-up time in the database. (2) This is a subset of the study population including only the matched case–control pairs whereby both the case and at least one control had participated in the additional data collection (visit and questionnaire). This subset was used in the analysis of determinants that were derived from the questionnaires, namely measures of cumulative estrogen exposure

patient questionnaires obtained during the visits, analyses regarding these determinants included only those individuals that had consented for participation in further data collection. For 53 of the participating cases, at least one participating matched control was found. Therefore, the analyses on cumulative estrogen exposure were conducted in 53 matched pairs (53 cases and 58 controls).

Characteristics of the study population are displayed in Table 1 and measures of cumulative estrogen exposure in Table 2. CRPS patients had more often a history of migraine and osteoporosis, as we have reported in a previous study, wherein we ascribed this association to the potential role of (neuro-)inflammatory peptides in CRPS.[13] Within the subset of visited participants (questionnaires available) the average age for onset of menopause was 46.6 (SD: 6.6) years for CRPS cases and 47.0 (SD: 6.9) for controls, which was statistically similar. The proportion of post-menopausal

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Table 1. Characteristics of the study population

	Cases ($n = 143$)	Controls ($n = 1493$)	OR* (95%CI)
Mean age at CRPS onset (SD)	51 (17)	Matched	
Female	100%	Matched	
Smoking	20.3% (29)	16.7% (249)	1.3 (0.9–2.1)
Migraine	7.7% (11)	3.6% (54)	**2.7 (1.3–5.2)**
Asthma	6.3% (9)	4.2% (62)	1.8 (0.8–3.8)
Osteoporosis	7.0% (10)	3.2% (48)	**2.5 (1.2–5.3)**
Hypertension	17.5% (25)	15.7% (231)	1.1 (0.6–1.7)
Cardiovascular disorders	8.4% (12)	7.8% (116)	1.2 (0.6–2.3)
Venous thrombosis	1.4% (2)	0.2% (3)	n.a.
Menstrual cycle-related disorders	7.7% (11)	5.9% (88)	1.8 (0.9–3.7)
Climacterial symptoms	9.1% (13)	6.4% (95)	1.6 (0.9–3.2)
Breast cancer	0.7% (1)	0.9% (13)	0.7 (0.1–5.7)
Cancer female reproductive organs	(0)	0.1% (1)	n.a.

The bold font highlights the significant association at p-value <0.05.
*Matched on gender, year of birth, calendar time (2-year band), and type of injury.

patients at the index date was similar between CRPS cases and controls. None of the measures of cumulative endogenous estrogen exposure was associated with CRPS onset, investigated either as continuous or as categorical variables.

When extrapolating the mean menopausal age from the questionnaires to the study population in the database, 44 cases (573 controls) were pre-menopausal at the index date and 99 cases (920 controls) were post-menopausal. In pre-menopausal patients neither current (OR: 1.0; 95%CI: 0.5–2.0) nor past (OR: 1.0; 95%CI: 0.3–3.2) use of OC was associated with CRPS onset (Table 3). In post-menopausal women current HRT use was less prevalent in CRPS patients

Table 2. Cumulative estrogen exposure in CRPS case patients and controls

	Cases ($n = 53$)	Controls ($n = 58$)	OR* (95%CI)
Post-menopausal at index date	60%	59%	1.3 (0.3–4.8)
Mean age of menarche (SD)	12.7 (2.4)	13.2 (1.7)	0.9 (0.7–1.1)
Category			
<12 yr	22%	14%	1.9 (0.6–5.8)
12–14 yr	40%	47%	Reference
≥14 yr	38%	40%	1.2 (0.5–2.7)
Mean age of menopause (SD)†	46.6 (6.6)	47.0 (6.9)	1.0 (0.9–1.1)
Category			
<40 yr	15%	14%	0.9 (0.2–3.8)
40–50 yr	47%	45%	Reference
≥50 yr	37%	41%	0.8 (0.3–2.3)
Mean cumulative years of menstrual life (SD)	30.8 (9.4)	30.1 (9.8)	1.0 (1.0–1.1)
Category			
<25 yr	23%	24%	0.7 (0.1–3.0)
25–35 yr	40%	35%	Reference
≥35 yr	37%	41%	0.7 (0.3–2.0)
Mean parity (SD)	1.8 (1.3)	1.9 (1.2)	0.9 (0.6–1.3)
Category			
0	23%	17%	1.8 (0.5–6.3)
1–2	56%	57%	Reference
>2	21%	26%	0.6 (0.2–1.6)
Mean cumulative months of pregnancy (SD)	17.6 (14.5)	17.7 (12.4)	(1.0–1.0)
Category			
<12 months	30%	33%	0.8 (0.3–2.0)
12–24 months	49%	38%	Reference
≥24 months	21%	29%	0.4 (0.1–1.2)
Mean cumulative months of breast-feeding (SD)	5.3 (7.8)	3.8 (5.4)	1.0 (0.9–1.1)
Category			
0 months	45%	43%	1.5 (0.6–3.3)
1–12 months	34%	45%	Reference
≥12 months	21%	12%	2.0 (0.4–8.1)

All data on determinants extracted from patient questionnaires, which were obtained only for a small subset of patients who were visited by the investigator.
*Matched on gender, year of birth, calendar time (2-year band), and type of injury.
†Calculated in post-menopausal women only (38 cases and 42 controls).

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Table 3. Estrogen therapy and the risk for CRPS

No use	54.5% (24)	57.6% (330)	Reference	Reference
Ever use (in prior year)	45.5% (20)	42.4% (243)	1.0 (0.5–1.9)	0.9 (0.5–1.8)
Current use	36.4% (16)	33.0% (189)	1.0 (0.5–2.0)	0.9 (0.4–1.8)
Past use	9.1% (4)	9.4% (54)	1.0 (0.3–3.2)	1.0 (0.3–3.2)
Hormonal replacement therapy (HRT) (in post-menopausal patients)	Cases ($n=99$)	Controls ($n=920$)	OR* (95%CI)	OR‡
No use	90.0% (90)	89.9% (827)	Reference	Reference
Ever use (in prior year)	9.1% (9)	10.1% (93)	0.9 (0.4–2.0)	0.9 (0.4–1.8)
Current use	3.0% (3)	6.1% (56)	0.5 (0.2–1.8)	0.5 (0.1–1.6)
Past use	6.1% (6)	4.0% (37)	1.6 (0.6–4.2)	1.4 (0.5–3.7)

*Matched on gender, year of birth, calendar time (2-year band), and type of injury.
†Adjusted for migraine, osteoporosis, smoking, and menstrual cycle-related disorders.
‡Adjusted for migraine, osteoporosis, and hypertension.

than in controls, but this was not statistically significant (OR: 0.5; 95%CI: 0.2–1.8; Table 3).

CRPS did not occur during pregnancy, therefore the association could not be calculated, but comparison with the controls suggests a protective effect. Two of the visited patients had reported in the questionnaire to have become pregnant after CRPS onset: one of them had experienced an improvement of CRPS during the pregnancy, while the other had noted no change whatsoever. The risk of CRPS was increased in the first 6 months after delivery (OR: 5.6; 95%CI: 1.0–32.4), but the actual numbers were very low (Table 4).

DISCUSSION

We studied the association between estrogen exposure and the risk of CRPS. Cumulative endogenous estrogen exposure was not associated with CRPS onset. In pre-menopausal patients OC use was not associated with CRPS, while in post-menopausal women we observed a non-significant protective effect during current HRT use. Although based on small numbers, the risk for CRPS seemed decreased during pregnancy and was increased during the first 6 months after delivery.

Measures of cumulative and actual estrogen exposure have to our knowledge not been studied before in relation to CRPS, which makes it impossible to discuss our results in view of previous findings. However, estrogen exposure has been studied in other inflammatory disorders, for example, in rheumatoid arthritis (RA) and multiple sclerosis (MS). In addition to the profound female predominance, these disorders share clinical features with CRPS, such as inflammatory signs, pain, and functional impairments. CRPS prevalence in a cohort of MS patients was high compared to estimated general population prevalences.[30]

Similar to our present findings for CRPS, studies in RA and MS patients commonly revealed no association with parity[31–34] and menstrual life,[31,33] although breast-feeding was protective for RA in one study.[33] The association between OC use and both RA[35] and MS[34,36,37] is still controversial and due to large heterogeneity between study populations meta-analyses could not provide a final answer.[35] Post-menopausal HRT use was only non-significantly protective for RA.[38] In line with the observations in RA and MS studies, we did not observe a strong association between OC or HRT use and the onset of CRPS either, although due to power limitations we cannot exclude a potential mild association. This is especially the case for HRT use, where the non-significant results point into the direction of a protective effect. Regarding OC use, the actual OR for current use is 0.9, which is suggestive of a non-association. It has been suggested before that OC affects endogenous estrogen serum levels only to a minor extent and therefore can, if any, only play a limited role in the mechanisms underlying immunological disorders.[20]

During pregnancy the risk for both RA[39,40] and MS[34] is known to decrease, while postpartum incidences are increased for both diseases. Hyperprolactinemia[41] and relative hypocortisolism[42] have been hypothesized to

Table 4. Pregnancy and the risk for CRPS

Time since last pregnancy (in pre-menopausal patients)	Cases ($n=44$)	Controls ($n=573$)	OR (95%CI)
>6 months or never pregnant	95.5% (42)	97.9% (561)	Reference
Current pregnancy	0% (0)	1.4% (8)	n.a.
0–6 months since partus	4.5% (2)	0.7% (4)	**5.6 (1.0–32.4)**

The bold font highlights the significant association at p-value <0.05.

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(partially) underlie this observation, since they both contribute to a pro-inflammatory immune status. Remarkably, we observed a similar pattern for CRPS, with a decreased risk of CRPS onset during pregnancy and an increased risk during the first months after pregnancy. However, it has to be noted that this was based on small numbers.

Estrogens interact with many modulators of the immune system, including immune cells, cytokines, growth factors, transcription factors, and more.[20] However, the precise role of estrogens is rather complex. Estrogens can induce predominantly anti- or pro-inflammatory responses, dependent of the cell type, kind of trigger, timing, estrogen receptor type, and other circumstances.[20] Although the relevance of estrogens in immunologic diseases is reflected in the demographic patterns (female predominance, age distribution), it has been difficult to demonstrate clear associations between such diseases and estrogen exposure parameters. Because of the biologic complexity, high powered prospective studies within homogeneous populations are needed to uncover potential associations. For RA this has already been proven complicated,[35] and for a rare disease with a heterogeneous clinical presentation as CRPS it will be an even bigger challenge.

Apart from power issues, other limitations may apply to our study, such as misclassification of the outcome (CRPS diagnosis), the determinants (estrogen exposure), and confounding. Outcome misclassification may have been caused by the retrospective assessment of the CRPS diagnosis. To minimize this as far as possible, we have used an extensive case validation strategy wherein we combined multiple sources to obtain diagnostic information, including electronic medical records, GP confirmation, specialist letters, and patient questionnaires if available. Moreover, we were strict in excluding patients for whom a possible alternative diagnosis was not sufficiently ruled out. However, final inclusion was based on the IASP criteria, which have been suggested to be low in specificity.[43] The more specific diagnostic criteria for research as proposed by Harden and Bruehl[44] would have been preferable, but require detailed information of objective signs at the moment of CRPS onset. Since this detailed information was lacking for many of the patients, we chose to apply the IASP criteria, realizing that some overdiagnosis may have been of relevance. Regarding exposure misclassification, the case/control status is known to potentially influence recall of past events. However, we have no reason to believe that CRPS affects the recall on measures of estrogen exposure as how they were addressed in the questionnaires. Therefore, causing only non-differential misclassification, recall problems will not likely have biased our results, although a potential minor association might have been diluted to such an extent that we have missed it. Recall was not an issue in the retrieval of OC and HRT use from the IPCI database, as this had been prospectively registered by the GP, who is the common prescriber for OC and HRT. Confounding may have been caused by factors that are associated with both CRPS and estrogen exposure. For the most common risk factors of CRPS, namely age, gender, and injury, we corrected through matching. Other potential confounders were included as covariables. However, in the analyses for OC use and HRT we were not able to correct for measures of cumulative estrogen exposure, because these were only available for the small subset of visited patients.

To our knowledge, we performed the first study addressing the association between estrogen exposure and CRPS. The strength of our study is that we were able to compare the findings in CRPS patients to a control group that was matched on injury, assuring an equal baseline CRPS risk for cases and controls. This detailed matching procedure was possible due to the large number of available controls in the IPCI database. Another strong point is that part of the data on determinants (OC, HRT, pregnancy) had been prospectively registered by the GP, making information bias unlikely. Moreover, our study was performed in a population-based setting, which means that the results are representative of CRPS patients in general, in contrast to hospital-based studies that usually represent a subset of severe patients.

In conclusion, we found no association between cumulative endogenous estrogen exposure and CRPS, and neither between OC or HRT use and CRPS. However, because of limited power minor associations cannot be excluded and larger, preferably prospective studies are needed to draw more solid conclusions. Based on the small numbers, a decreased risk of CRPS during pregnancy and an increased risk immediately after pregnancy was observed, which is in line with patterns observed in RA and MS.

CONFLICT OF INTEREST

M. de Mos and B.H.Ch. Stricker have no financial or other types of conflicts of interest.

M.C.J.M. Sturkenboom has been involved as project leader in analyses contracted by various pharmaceutical companies and received unconditional research grants from Pfizer, Merck, Johnson&Johnson, Amgen,

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KEY POINTS

- Because the age and gender distribution pattern of CRPS is suggestive for a role of female reproductive hormones in the pathogenesis, we studied the association between the onset of CRPS and cumulative and current estrogen exposure.
- We found no association between cumulative endogenous estrogen exposure and the risk of CRPS.
- We found no association between the use of oral contraceptive drugs and the risk of CRPS in pre-menopausal women.
- We found no association between the use of hormonal replacement therapy and the risk of CRPS in post-menopausal women.
- The risk of CRPS was increased within the first 6 months after pregnancy.
- The association between CRPS and estrogen exposure has not been described before, but our findings are generally in line with those for other inflammatory disorders with a female predominance, such as rheumatoid arthritis and multiple sclerosis.

Roche, and Altana; none of which are related to the subject of this study. She has been consultant to Pfizer, Servier, Celgene, Novartis, and Lundbeck on issues not related to this study.

J.P. Dieleman has been involved in analyses contracted by various pharmaceutical companies and received unconditional research grants from Pfizer, Merck, Johnson&Johnson, Amgen, Roche, and Altana; none of which are related to the subject of this study.

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