Menstrual arthritis

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Abstract

The menstrual cycle is characterised by variations in the absolute and relative concentrations of the hormones of the hypothalmic pituitary ovarian axis, which in turn affect cell function and cytokine and heat shock protein production. Menstruation involves the shedding of the secretory endometrium, which is part of the mucosal associated lymphoid tissue and hence is rich in immunologically competent cells such as CD8 T cells and macrophages. The case is reported here of a patient presenting with a recurrent but transient symmetrical inflammatory polyarthritis which only occurred at menstruation with no residual damage. The disease was suppressed by danazol. Endometrial degradation products are suggested as the trigger of this 'menstrual arthritis'.

(*Ann Rheum Dis* 1993; 52: 65–66)

There have been various reports of diseases associated with menstruation. We report here the case of a patient with a recurrent but transient symmetrical inflammatory polyarthritis which occurred only at menstruation with no residual damage. The disease was suppressed by danazol. Possible mechanisms including the role of the endometrium are discussed.

Case report

A 30 year old woman presented in 1988 with a nine month history of symmetrical polyarthritis occurring regularly within the first 48 hours of menstruation, affecting her wrist, shoulder, and knee joints, and lasting for four to five days. On examination there was tenderness and synovial thickening with a reduced range of movement at both wrist joints and pain at extremes of movement at both shoulders. There were bilateral knee effusions from which turbid yellow synovial fluid was aspirated. No crystals were seen on polarising microscopy and culture was negative. The white cell count of the synovial fluid was 88×10^9/l (99% neutrophils, 1% monocytes). Other investigations at this time were as follows: erythrocyte sedimentation rate (ESR) 10 mm/hour; white blood cell count $7{\cdot}9\times10^9$/l; platelets 439×10^9/l; haemoglobin 126 g/l; alkaline phosphatase 51 IU/l (normal range (NR) 25–95); IgM 0·91 g/l (NR 0·75–2·4); IgG 8·3 g/l (NR 6–16); and IgA 0·67 g/l (NR 0·65–3·0). Autoantibodies were negative. Radiographs of her knees were normal. Between menstrual periods she was asymptomatic and her menstrual cycle was regular with no significant dysmenorrhoea.

Treatment with oral contraceptives, coproxamol, and mefenamic acid was of no benefit. She had previously been well, was a mother of three children, and there was no family history of arthritis or autoimmune disease.

Treatment with danazol (200 mg every eight hours) was started in March 1988 and for seven months she had no acute episodes of arthritis and menstruation was completely suppressed. The danazol was then discontinued and menstruation returned but she remained asymptomatic until May 1991 when the arthritis recurred at the time of menses. She was reviewed in October 1991 when she required hospital admission for an acute polyarthritis affecting her ankles, knees, shoulders, and hips on day 2 of her menstrual cycle. On examination she was distressed with the pain. She was pyrexial (37·7°C) and the affected joints were tender, hot, and exquisitely painful with minimal movement. There was a mild effusion of her right knee from which turbid synovial fluid was subsequently aspirated. No crystals were seen on polarising microscopy and culture was negative. The white cell count of the synovial fluid was $63{\cdot}4\times10^9$/l (99% neutrophils, 1% monocytes, and no eosinophils). She settled with naproxen and was asymptomatic with a full range of movement in her joints by day 6 of her cycle. Other investigations at this time were as follows: white blood cell count 11×10^9/l; platelets 284×10^9/l; haemoglobin 125 g/l; ESR 38 mm/hour; bilirubin 8 μmol/l; alkaline phosphatase 70 IU/l; C reactive protein 48 mg/l; C3 and C4 normal; IgG 11·6 g/l; IgA 0·7 g/l (0·9–3·2); and IgM 0·8 g/l. Autoantibodies were negative.

Treatment with danazol was started again and one month later her indices had improved: ESR 5 mm/hour; white blood cell count $3{\cdot}9\times10^9$/l; platelets 333×10^9/l; haemoglobin 128 g/l; C reactive protein <4 mg/l; IgG 10·5 g/l; IgA 0·8 g/l; IgM 0·8 g/l; bilirubin 11 μmol/l; and alkaline phosphatase 66 IU/l.

Discussion

Menstruation is only one manifestation of the ovarian cycle, which is itself associated with many biological, psychological, and behavioural changes. There have been various reports of diseases associated with menstruation, for example, catamenial epilepsy and menstrual migraine, as well as exacerbations of established diseases such as diabetes, asthma, and rheumatoid arthritis. Latman found pain and morning stiffness to be considerably reduced during the

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Accepted for publication
2 September 1992

post-ovulatory phase of the menstrual cycle in a study of patients with rheumatoid arthritis and this was thought to be related to the higher levels of oestrogen and progesterone in this phase.[1] Rudge *et al* reported grip strength to peak at midcycle and finger joint size to peak at around menstruation.[2] Others, however, have found no effect of the menstrual cycle on disease symptoms in rheumatoid arthritis.[3]

The menstrual cycle is characterised by variations in the absolute and relative concentrations of the hormones of the hypothalmic, pituitary, ovarian axis and hence any interaction between gonadal steroids and the immune response will be complicated. Various parameters affecting the immune response have been reported to fluctuate in the normal ovulatory cycle—for example, lymphocytes reach a nadir midcycle, coinciding with the oestrogen peak.[4] Oestrogen has been reported to suppress the incidence and disease severity of the two T cell dependent arthritis models of collagen induced arthritis[5] and adjuvant induced arthritis.[6] The production of certain heat shock proteins has been shown to be dependent on sex hormones in a tissue specific manner and their concentrations are markedly increased by acute and chronic stimulation with oestrogen or progesterone, or both.[7] Sex hormones also appear to affect cell function—for example: macrophages[8] and cytokine production by such cells—for example, interleukin 1,[9] and tumour necrosis factor.[10] Immunoendocrinology, however, does not tell the whole story, as exemplified by the contentious role of oral contraceptives in the susceptibility of developing rheumatoid arthritis and the lack of evidence that hormone replacement therapy affects the incidence of rheumatoid arthritis in postmenopausal women.[11] Similarly, oral contraceptives did not ameloriate the arthritis of our patient. The arthritis described therefore appears solely related to the menses—a time when oestrogen, progesterone, and gonadotrophin levels are at near basal levels and not immediately related to peaks or nadirs.

Menstruation is the shedding of secretory endometrium with bleeding at the end of each ovarian cycle if conception has not taken place. The endometrium has been considered to be another component of the mucosal associated lymphoid tissue[12] and it has an important population of immunologically competent cells. The major populations are T cells (especially CD8) and macrophages, the latter increasing to form 20–25% of the stroma in the premenstrual phase.[13] The menstrual fluid therefore contains numerous endometrial proteins which, if not removed, may be recognised as foreign and trigger an autoimmune response. Retrograde menstruation occurs in normal women[14] and a population of intraperitoneal macrophages removes this in health.[15] It could therefore be suggested that if there was not complete removal for some reason an immune response could be triggered, as has been proposed in endometriosis.[15] In normal women there is limited maturation of peritoneal macrophages but in women with endometriosis there is a marked increase in their numbers, resulting in increased levels of interleukin 1.[16] Interleukin 6 is also produced by endometrial cells.[17] With this evidence we therefore suggest that due to retrograde menstruation or occult endometriosis, endometrial degradation products are phagocytosed by peritoneal macrophages which themselves release cytokines that affect the pathogenesis of the 'menstrual arthritis' experienced by our patient.

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