

Uveitis and the menstrual cycle

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CLINICAL STUDY

Abstract

Purpose To establish whether there is a variation in the incidence of onset of acute anterior uveitis (AAU) in women during the phases of the menstrual cycle.

Methods Prospective open study in women attending the Acute Referral Centre with a first or recurrent attack of AAU.

Results There was a significant increase in the incidence of AAU during the late stages of the menstrual cycle.

Conclusions The onset of AAU is partially dependent on the levels of either oestrogen or progesterone, or both. The withdrawal of the proven anti-inflammatory effects of these hormones may provoke the onset of uveitis.

Eye (2004) 18, 451–454. doi:10.1038/sj.eye.6700713

Keywords: acute anterior uveitis; cyclical; menstrual cycle; sex hormone; oestrogen; progesterone

Introduction

Uveitis encompasses a broad spectrum of ocular inflammatory disorders influenced by systemic, genetic, immunological, environmental, infective, circulatory, and hormonal factors.¹ The initiating event remains unknown in a majority of patients, but many predisposing associations have been established. An influence of sex hormones on the course of uveitis has been suggested, and there are anecdotal reports of amelioration of uveitis² and Behçet's disease³ during pregnancy. This effect has now been demonstrated in an animal model.⁴ It has also been suggested⁵ that the occurrence of acute uveitis varies during the menstrual cycle.

Sex hormone levels are thought to affect some inflammatory diseases, and, for example, an increased incidence or severity of inflammation has been reported in the late phase of the menstrual cycle for women with asthma,⁶ rheumatoid arthritis,⁷ psoriatic arthritis,⁸ and

appendicitis.⁹ The purpose of this study is to test the hypothesis that hormonal variations in the menstrual cycle also contribute to the onset of attacks of acute anterior uveitis (AAU).

Patients and methods

Details were prospectively recorded by two of us (CS and KA) on women presenting to the Acute Referral Centre of the Manchester Royal Eye Hospital with an episode of AAU.

Information on patient age, side of inflammation, and number of attacks was included. The date of commencement of the last menstrual period (LMP) and the date on which symptoms commenced were recorded as were the normal length and regularity of the menstrual cycle, and information on the use of oral contraceptives. Women with irregular cycles or those unsure of the date of their LMP were excluded, as were postmenopausal or posthysterectomy, pregnant or lactating women.

The day of the cycle on which the attack of AAU commenced was calculated. For the purposes of data analysis, the menstrual cycle was firstly divided into the preovulatory phase (including the gradual rise in oestrogen secretion to a high preovulatory peak, days 1–13 from LMP), the ovulatory phase (days 14–16), and the postovulatory phase from day 17, including a large peak of progesterone secretion and a lesser oestrogen peak (Figure 1). Since the postovulatory phase is composed of two distinct phases each with different hormonal levels, we separately analysed the data by splitting the cycle into 4-day periods in order to gain a better idea of hormonal correlations.

Using the null hypothesis that there was no phasic variability in the onset of attacks of AAU, the data were analysed by χ^2 distribution using both the three-phase comparison and the 4-day block comparison.

Results

Data were collected on 113 adult women presenting with uveitis. After the exclusions

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Received: 2 April 2003
Accepted in revised form:
26 August 2003

The authors have no financial or proprietary interest in any drug, treatment or device mentioned in this article.

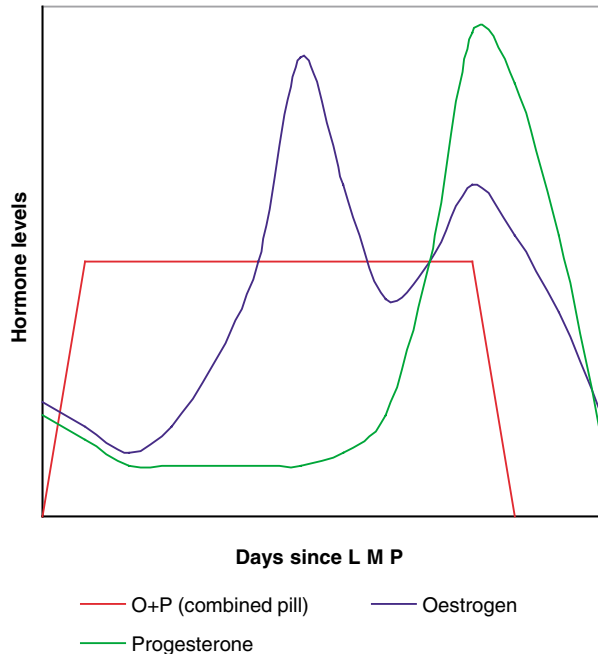


Figure 1 Hormonal changes during the normal female menstrual cycle, and for those women using a monophasic combined contraceptive pill. O + P = oestrogen and progesterone. LMP = last menstrual period

listed above, 76 regularly menstruating women were included in the study. The mean age was 31.5 years (range 16–48 years) and the mean cycle length was 28.1 days (SD 0.5). In 11 women (14.4%), the attack of AAU was their first. In all, 65 (85.5%) were suffering their second or subsequent attack. Of the 76 women, 13 (17.1%) were using a combined oral contraceptive. In total, 69 patients had unilateral uveitis (38 left eye, 31 right eye) and seven bilateral.

The day of onset of the AAU attack is shown in Figure 2. A total of 24 attacks commenced in the preovulatory period, six in the ovulatory period, and 46 postovulatory. Using three-phase analysis, there was a clear peak of attacks in the postovulatory phase ($P = 0.024$).

The data were also analysed in 4-day blocks by dividing the entire menstrual cycle into 4-day periods and analysing the frequency of uveitis in each of these. Thus seven 4-day periods were obtained into which the patients were distributed depending on the day of the cycle the attack commenced. One patient who had a cycle length of 29 days and whose attack started on the 29th day was included in the last group, but the analysis was appropriately adjusted to take this into consideration. The greatest numbers of uveitic attacks were seen to occur between days 25 and 29 (22) and the least between days 9 and 12 and 13 and 16 (six each). The P -value was

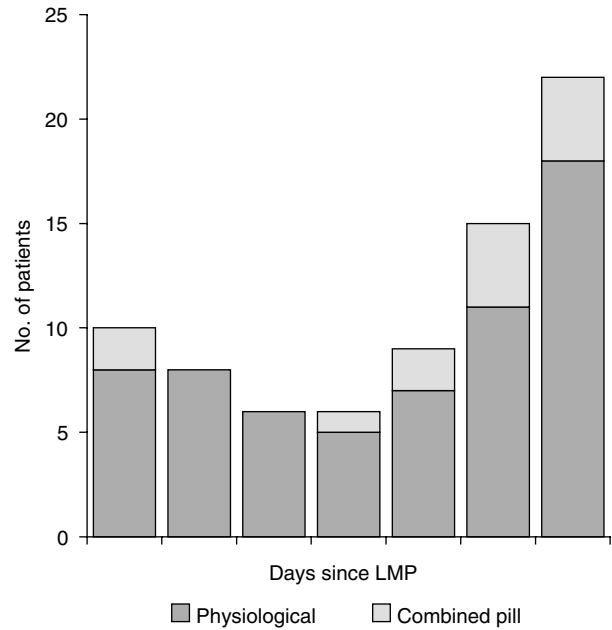


Figure 2 Day of onset of attacks of uveitis for 76 women in relation to LMP, including 13 women using a combined contraceptive pill.

found to be 0.055, that is, just approaching statistical significance but not achieving it.

Discussion

The menstrual cycle involves substantial changes in the levels of sex hormones (Figure 1). It consists of four phases. The first is menstruation, which lasts 4–5 days and in which both oestrogen and progesterone levels are low. In the second (follicular) phase, oestrogen levels increase to a high peak, provoking endometrial proliferation and culminating in ovulation. In the third (early luteal) phase, progesterone levels rise to a peak and oestrogen to a second, lower peak. In the late luteal phase, both oestrogen and progesterone levels drop rapidly, leading to menstruation in which the uterine lining is shed.

These menstrual cyclic variations in hormonal levels also affect other body tissues; their influence on several ophthalmic variables has been investigated, and cyclical ocular changes in conjunctival maturation index,¹⁰ goblet cell count,¹¹ corneal topography,¹² thickness and sensitivity,¹³ and contact lens comfort¹⁴ have been documented. Oestrogens and progestogens have been found in aqueous humour,¹⁵ and sex steroid receptors are widespread in ophthalmic sites,¹⁶ including lacrimal gland, meibomian gland, lid, palpebral and bulbar conjunctiva, cornea, anterior and posterior uvea (including vascular endothelium), lens and retina, including retinal pigment epithelium. Both oestrogens

and progestogens have been shown to be metabolised by iris and ciliary body in the rabbit.^{17,18} A protective role for oestrogen has been postulated as a downregulator of interleukin-6 (IL-6) and E-selectin, a proinflammatory mediator,¹⁹ reducing cellular infiltration in endotoxin-induced uveitis (EIU) in an animal model.²⁰ In other tissues, several papers have reported modulation of proinflammatory cytokines including interleukin-1, IL-6, and tumour necrosis factor by oestrogens in monocytes and macrophages.^{21–23}

Evidence therefore suggests that mechanisms are in place, which would permit hormonal fluctuations to influence ocular physiology. This, together with evidence of cyclical variations in inflammation elsewhere in the body, appears to give a reasonable theoretical basis for hormonal influence on ocular inflammation, and in this study we sought to investigate this. Heaton⁵ studied 'ecologic' factors in uveitis patients some 40 years ago, and found a premenstrual increase in uveitis in a small group of women. A single case of cyclical premenstrual attacks of severe anterior uveitis responding to suppression of the pituitary–ovarian axis with danazol has been reported.²⁴ We have not located any other published reference to the subject. Our purpose was to find whether the onset of AAU has a predilection for any particular phase of the menstrual cycle and, if so, to postulate reasons for this.

Our results show that attacks of AAU commence more frequently in the postovulatory phase of the cycle ($P = 0.024$), especially in the premenstrual phase ($P = 0.055$). The luteal phase contains a high peak of progesterone and a subsidiary peak of oestrogen; the late luteal (premenstrual) phase is characterised by a substantial reduction in the levels of both these hormones. Which, if either, of these could be associated with this fluctuation in the incidence of uveitis?

There is substantial evidence that oestrogen is anti-inflammatory by inhibiting pro-inflammatory cytokines, at least in some tissues,^{21–23,25–27} including the eye, where EIU is inhibited.²⁰ However, progestogens have also been found to have anti-inflammatory properties, and have been used successfully to treat rheumatoid arthritis,²⁸ and premenstrual asthma.²⁹ We postulate that the rapid withdrawal of the protective effects of either oestrogen or progesterone or both in the late luteal phase may explain the higher frequency of AAU in this phase of the menstrual cycle. We have assumed that the temporal relationship between the two is short; the onset of AAU is abrupt, and we are confident that this correlated well with the date of onset of symptoms.

We have included 13 women who were using a standard-dose combined oral contraceptive at the time of their presentation (12 monophasic, one triphasic). All such contraceptives involve an abrupt withdrawal of

both oestrogen and progesterone at day 22. This is clearly nonphysiological, but we believe that the inclusion of these women is valid according to our hypothesis that the withdrawal of either or both of these hormones may provoke the onset of AAU. This seems to be borne out by the distribution of these patients throughout the menstrual cycle (Figure 2).

In summary, we have demonstrated a significant increase in the incidence of AAU arising late in the menstrual period. We postulate that the withdrawal of either or both oestrogen and progesterone provokes the onset of inflammation. The rise in incidence in the premenstrual period falls just short of statistical significance for this population; a further study using a larger cohort, possibly including the assessment of serum sex hormone levels on the day of presentation, would clarify this relationship.

Acknowledgements

We acknowledge the assistance of Mr Steve Roberts, statistician, Central Manchester and Manchester Children's University Hospitals NHS Trust.

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