Aqueous humour turnover and intraocular pressure during menstruation

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SUMMARY Both intraocular pressure and aqueous humour turnover rate were determined at intervals over three months in three females in order to investigate whether a correlation existed between these variables and the menstrual cycle. Not only was there a lack of correlation between intraocular pressure or aqueous humour flow rate and menses but intraocular pressure and aqueous humour flow rate were also not related to each other. If pharmacologically administered doses of progesterone or oestrogen influence intraocular pressure, the present data indicate that the effect is probably mediated through effects on the aqueous outflow pathways.

The cyclical changes in oestrogens and progesterones during the menstrual cycle are well documented.^{1,2} Despite several attempts, however, correlations between intraocular pressure (IOP), outflow facility (C), and the menstrual cycle have not been definitely proved.² An increased IOP has been reported to occur immediately before, or during menstruation,³⁻⁵ while an increased C during the progestational phase and a decreased C during the oestrogenic phase has also been reported.⁶ Paterson and Miller,⁷ however, found a bicyclic increase in C which occurred in both the mid-oestrogenic and the mid-oestrogenic-progesterone phases. An increased occurrence of glaucoma symptoms, especially in angle-closure versus open-angle glaucoma patients, has also been noted during the menses.⁸ Although pharmacological doses of progesterone⁹⁻¹⁰ and oestrogen^{11,12} have been shown to induce small decreases in IOP, it is not clear whether naturally produced progesterone plays a role in IOP regulation.¹³

We have measured IOP and aqueous humour turnover rate with fluorimetry at weekly intervals in three female volunteers through at least three consecutive menstrual cycles in order to determine whether correlations exist between these parameters and the menstrual cycle.

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Materials and methods

Three normal female volunteers, free from eye and systemic disease, aged 27, 31, and 35, and not taking oral contraceptives, were recruited from the nursing and administrative staff of the Princess Alexandra Eye Pavilion. After signed, informed consent had been obtained a schedule was arranged to permit weekly determinations of fluorescein decay kinetics in the eye and IOP.

Each volunteer was given a calendar on which to mark the dates of menstruation and the date upon which they were tested. On the test day fluorescein eye drops (Fluress, Barnes-Hind, California) were either self administered or administered by a friend at a rate of one drop every two minutes between 0800 and 0830 h. Readings were taken of corneal and mid anterior chamber fluorescein (over the pupil) every hour for 4 or 5 hours beginning at 1300 h. Normal activities continued between readings. Fluorescein was detected by a Gamma scientific apparatus attached to a Haag-Streit 900 slit-lamp.¹⁴ Aqueous humour flow rate was determined according to the method of Jones and Maurice,¹⁵ using the linear decay of corneal and anterior chamber fluorescein after the peak concentrations had been reached.¹⁶ IOP was taken with a Goldmann tonometer immediately preceding the 1500 h reading. Determinations were made on as close to a weekly schedule as was possible. Unfortunately, over the last week of

Table 1 Aqueous humour fluorescein decay kinetics for subject 1

Date	Eye	IOP (mmHg)	Slope (min ⁻¹)	Flow (μ l min ⁻¹)	K _{aca} (min ⁻¹)	Menses
8 Nov 1982	OD	12	-0.0021	1.00 $\pm$ 0.05	0.0010	
	OS	—	—	—	—	
15 Nov 1982	OD	10	-0.0012	0.56 $\pm$ 0.02	0.0005	18 Nov to
	OS	10	-0.0048	2.57 $\pm$ 0.12	0.0022	23 Nov
22 Nov 1982	OD	10	-0.0038	3.40 $\pm$ 0.30	0.0016	
	OS	10	-0.0034	2.17 $\pm$ 0.12	0.0015	
30 Nov 1982	OD	14	-0.0031	1.71 $\pm$ 0.04	0.0013	
	OS	12	-0.0028	1.71 $\pm$ 0.08	0.0012	
6 Dec 1982	OD	10	-0.0055	2.09 $\pm$ 0.14	0.0037	
	OS	10	-0.0063	3.05 $\pm$ 0.18	0.0031	
14 Dec 1982	OD	11	-0.0031	1.09 $\pm$ 0.05	0.0017	16 Dec to
	OS	10	-0.0047	3.67 $\pm$ 0.19	0.0019	20 Dec
21 Dec 1982	OD	11	-0.0047	1.45 $\pm$ 0.17	0.0026	
	OS	12	-0.0041	1.55 $\pm$ 0.17	0.0019	
18 Jan 1983	OD	13	-0.0038	2.31 $\pm$ 0.06	0.0016	13 Jan to
	OS	10	-0.0045	3.70 $\pm$ 0.13	0.0018	17 Jan
25 Jan 1983	OD	—	-0.0051	3.06 $\pm$ 0.22	0.0024	
	OS	—	-0.0070	3.67 $\pm$ 0.50	0.0036	
1 Feb 1983	OD	10	-0.0053	4.52 $\pm$ 0.34	0.0020	
	OS	10	-0.0063	4.63 $\pm$ 0.30	0.0025	
8 Feb 1983	OD	12	-0.0034	2.22 $\pm$ 0.27	0.0014	10 Feb to
	OS	12	-0.0011	0.50 $\pm$ 0.10	0.0005	14 Feb

For explanation of slope, flow, and K_{aca} see text.

1982 and the first week of 1983 it was impossible to schedule sessions.

Data analysis was performed only after the completion of the four-month study during which measurements were made without knowledge of the times of the menstrual cycle of the volunteers. The slope is the rate of decay of fluorescein in the anterior chamber expressed as the natural log of fluorescein concentrations. It has the dimension of min⁻¹, and

was obtained by linear least squares methods. K_{aca} is the transfer coefficient for fluorescein across the endothelium and has the dimension of min⁻¹. In order to calculate flow rate in μ l min⁻¹ we assumed an anterior chamber value of 200 μ l. Corneal volume was taken as 80 μ l. While these values are slight overestimates of previously used values,^{16,17} they do reflect recent estimates of anterior chamber and corneal volumes.^{18,19}

Table 2 Aqueous humour fluorescein decay kinetics for subject 2

Date	Eye	IOP (mmHg)	Slope (min ⁻¹)	Flow (μ l min ⁻¹)	K _{aca} (min ⁻¹)	Menses
8 Nov 1982	OD	15	-0.0048	2.49 $\pm$ 0.12	0.0023	
	OS	14	-0.0056	2.81 $\pm$ 0.39	0.0034	
16 Nov 1982	OD	16	-0.0054	2.59 $\pm$ 0.17	0.0029	14 Nov to
	OS	14	-0.0023	1.08 $\pm$ 0.03	0.0011	18 Nov
23 Nov 1982	OD	14	-0.0056	2.01 $\pm$ 0.14	0.0035	
	OS	13	-0.0040	1.29 $\pm$ 0.03	0.0030	
1 Dec 1982	OD	16	-0.0043	1.46 $\pm$ 0.11	0.0029	
	OS	16	-0.0041	1.73 $\pm$ 0.04	0.0022	
8 Dec 1982	OD	12	-0.0070	3.05 $\pm$ 0.32	0.0045	12 Dec to
	OS	12	-0.0070	3.24 $\pm$ 0.47	0.0054	15 Dec
22 Dec 1982	OD	14	-0.0059	2.90 $\pm$ 0.59	0.0079	7 Jan to
	OS	13	-0.0043	1.76 $\pm$ 0.13	0.0033	11 Jan
12 Jan 1983	OD	12	-0.0046	1.85 $\pm$ 0.29	0.0095	
	OS	13	-0.0041	1.57 $\pm$ 0.09	0.0029	
19 Jan 1983	OD	—	-0.0038	1.36 $\pm$ 0.07	0.0027	
	OS	—	-0.0046	1.85 $\pm$ 0.14	0.0032	
8 Feb 1983	OD	14	-0.0089	3.73 $\pm$ 0.73	0.0076	2 Feb to
	OS	14	-0.0047	1.10 $\pm$ 0.11	0.0049	8 Feb

For explanation of slope, flow, and K_{aca} see text.

Table 3 Aqueous humour fluorescein decay kinetics for subject 3

Date	Eye	IOP (mmHg)	Slope (min ⁻¹)	Flow (μl min ⁻¹)	K _{au} (min ⁻¹)	Menses
15 Nov 1982	OD	14	-0.0051	2.05±0.07	0.0029	21 Nov to 25 Nov
	OS	14	-0.0052	2.42±0.19	0.0026	
22 Nov 1982	OD	12	-0.0024	0.67±0.02	0.0032	
	OS	12	-0.0016	0.51±0.01	0.0011	
30 Nov 1982	OD	15	-0.0024	0.67±0.04	0.0017	20 Dec to 25 Dec
	OS	10	-0.0022	0.70±0.03	0.0013	
6 Dec 1982	OD	14	-0.0039	1.77±0.09	0.0018	
	OS	14	-0.0031	1.56±0.10	0.0013	
13 Dec 1982	OD	—	-0.0026	1.16±0.04	0.0012	18 Jan to 22 Jan
	OS	—	-0.0025	0.97±0.01	0.0014	
15 Dec 1982	OD	14	-0.0063	2.10±0.07	0.0051	
	OS	14	-0.0061	2.58±0.16	0.0039	
22 Dec 1982	OD	14	-0.0084	2.70±0.06	0.0074	17 Feb to 21 Feb
	OS	14	-0.0082	2.65±0.50	0.0050	
18 Jan 1983	OD	15	-0.0031	0.84±0.05	0.0030	
	OS	15	-0.0033	0.98±0.07	0.0022	
1 Feb 1983	OD	11	-0.0059	3.42±0.32	0.0021	
	OS	11	-0.0039	2.96±0.61	0.0014	
8 Feb 1983	OD	13	-0.0020	1.01±0.13	0.0008	
	OS	13	-0.0076	2.82±0.22	0.0050	

For explanation of slope, flow, and K_{au} see text.

Results

The data obtained in this study are shown in Tables 1 to 3. While variations exist in all parameters as a function of time, none of the variations appear to be correlated with any part of the menstrual cycle.

IOP variations for the subjects varied between 10 and 16 mmHg, and, although the values differed at various times of the cycle, they did not correlate with it over the course of several cycles. The mean IOP and aqueous humour flow rate values for both eyes of each subject are shown in Figs. 1 and 2 respectively.

These graphs illustrate the lack of correlation between these values and the occurrence of the menses.

Subject 1 tended to show a reduced IOP at or before the menstrual period for two of the four cycles, but her IOP was increased at other menses (Fig. 1). Subject 2 tended to have a slightly lower IOP after menses, although an exception occurred with the second menses in the testing series. No pattern existed for subject 3, whose IOP could not be even vaguely correlated with menses (Fig. 1). Similarly, in Fig. 2 it is evident that no relationship exists between aqueous humour flow rate and the menstrual cycle.

Fig. 1 Plot of intraocular pressure versus time. Each set of symbols corresponds to the identification shown in the upper block where the menses are indicated for each subject.

Fig. 2 Plot of aqueous humour flow (turnover) rate versus time. Each set of symbols corresponds to the identification shown in the upper block where the menses are indicated for each subject.

Comparison of Figs. 1 and 2 also illustrates that IOP can vary independently of aqueous humour flow rate.

Discussion

Fluorophotometry has proved valuable in assessing not only drug effects on aqueous humour dynamics^{16, 20-22} but also in determining the changes in aqueous flow rate in a variety of clinical conditions.^{17, 23-25} The validity of the technique has therefore been well proved. In the present study we assumed that the subjects had the same anterior chamber and corneal volumes, and, while this is probably not true, we were comparing changes which occurred with time in the same subjects, thus making the absolute value of the volumes of little importance. Nevertheless, the average values obtained for the slope, K_{aeh} , and aqueous flow rate are very similar to those published in other studies.^{16, 17, 20-25} Although the final number of subjects in the current study is small, the subjects were followed up for over three months, thus providing a longitudinal study of considerable duration, which is perhaps of more value than a shorter term study with more subjects. The subject drop-out rate was over 50% for several reasons.

Several studies have indicated an association between IOP or C and the menstrual cycle,³⁻⁷ although a variety of changes have been noted in relation to the phases of the menstrual cycle. Certainly the administration of pharmacological doses of progesterones and oestrogens (alone or in combination) has been recorded to induce a small fall in intraocular pressure

in both experimental animals²⁶ and man^{7-10, 27, 28} despite some findings to the contrary.²⁹⁻³¹

The present study indicates that the assumed normal, physiological hormonal changes associated with the menstrual cycle in our subjects had no influence on either IOP or aqueous flow, confirming at least one earlier study.² If progesterone or oestrogen has an effect at pharmacological dose levels the mode of action cannot be deduced from our studies, though the lack of effect on aqueous inflow in our study would suggest that the steroid effect would be directed primarily towards the outflow pathways. Evidence exists that outflow facility is affected both in normal females and in those subjects treated with progesterone-oestrogens^{6-8, 12} as well as in experimental animals.³²

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References

- 1 Mountcastle VB. *Medical physiology*. Vol. 1. St. Louis: Mosby, 1968.
- 2 Feldman F, Bain J, Matuk AR. Daily assessment of ocular and hormonal variables throughout the menstrual cycle. *Arch Ophthalmol* 1978; **96**: 1835-8.
- 3 Larsen V. Studien über die Beziehungen des einfachen Glaukoma zur inneren Sekretion. *Bibl Laeger* 1934; **126**: 318-22.

- 4 Marx E. L'influence de la menstruation et de la grossesse sur la tension oculaire. *Ann Oculist (Paris)* 1923; **160**: 873-82.
- 5 Dalton K. Influence of menstruation on glaucoma. *Br J Ophthalmol* 1967; **51**: 692-5.
- 6 Becker B, Friedenwald JS. Clinical aqueous outflow. *Arch Ophthalmol* 1953; **50**: 557-71.
- 7 Paterson GD, Miller SJH. Hormonal influence in simple glaucoma. *Br J Ophthalmol* 1963; **47**: 129-37.
- 8 Avasthi P, Luthra MC. Effect of sex hormones on intraocular pressure. *Int Surg* 1967; **48**: 350-5.
- 9 Obal A. Gelbkörperhormon-Anwendung zur Glaukomtherapie. *Klin Monatsbl Augenheilkd* 1950; **117**: 201-3.
- 10 Posthumus RG. The use and the possibilities of progesterone in the treatment of glaucoma. *Ophthalmologica* 1952; **124**: 17-25.
- 11 Medgyaszar A. Intraocular pressure and hormonal therapy. *Ophthalmologica* 1963; **145**: 243-8.
- 12 Treister G, Mannor S. Intraocular pressure and outflow facility. Effect of estrogen and combined estrogen-progestin treatment in normal human eyes. *Arch Ophthalmol* 1970; **83**: 311-8.
- 13 Kass MA, Sears ML. Hormonal regulation of intraocular pressure. *Surv Ophthalmol* 1977; **22**: 153-76.
- 14 Waltman SR, Kaufman HE. A new objective slit lamp fluorophotometer. *Invest Ophthalmol Visual Sci* 1970; **9**: 247-9.
- 15 Jones RF, Maurice DM. New methods of measuring the rate of aqueous flow in man with fluorescein. *Exp Eye Res* 1966; **5**: 208-20.
- 16 Yablonski ME, Zimmerman TJ, Waltman SR, Becker B. A fluorophotometric study of the effect of topical timolol on aqueous humor dynamics. *Exp Eye Res* 1978; **27**: 135-42.
- 17 Nagataki S, Mishima S. Aqueous humor dynamics in glaucoma-cyclitic crisis. *Invest Ophthalmol Visual Sci* 1976; **15**: 365-70.
- 18 Fontana ST, Brubaker RF. Volume and depth of the anterior chamber in the normal aging human eye. *Arch Ophthalmol* 1980; **98**: 1803-8.
- 19 Johnson SB, Coakes RL, Brubaker RF. A simple photogrammetric method of measuring anterior chamber volume. *Am J Ophthalmol* 1978; **18**: 469-74.
- 20 Nagataki S, Brubaker RF. Effect of pilocarpine on aqueous humor formation in human beings. *Arch Ophthalmol* 1982; **100**: 818-21.
- 21 Dailey RA, Brubaker RF, Bourne WM. The effects of timolol maleate and acetazolamide on the rate of aqueous formation in normal human subjects. *Am J Ophthalmol* 1982; **93**: 232-7.
- 22 Nagataki S, Brubaker RF. Early effect of epinephrine on aqueous formation in the normal human eye. *Ophthalmology* 1982; **88**: 278-82.
- 23 Brubaker RF, Nagataki S, Townsend DJ, Burns RR, Higgins RG, Wentworth W. The effect of age on aqueous humor formation in man. *Ophthalmology* 1981; **88**: 283-7.
- 24 Johnson DH, Brubaker RF. Dynamics of aqueous humor in the syndrome of exfoliation with glaucoma. *Am J Ophthalmol* 1982; **93**: 629-34.
- 25 Wentworth WO, Brubaker RF. Aqueous humor dynamics in a series of patients with third neuron Horner's syndrome. *Am J Ophthalmol* 1981; **92**: 407-15.
- 26 Lamble JS, Lamble AP. Some effects of progestogens, oestrogens and androgens on the ocular tension of rabbits and owl monkeys. *Exp Eye Res* 1978; **26**: 599-610.
- 27 Meyer EJ, Leibowitz H, Christman EH, Niffenegger JA. Influence of norethynodrel with mestranol on intraocular pressure in glaucoma. *Arch Ophthalmol* 1966; **75**: 157-61.
- 28 Meyer EJ, Roberts CR, Leibowitz HM, McGowan B, Houle RE. Influence of norethynodrel with mestranol on intraocular pressure in glaucoma. II. A controlled double-blind study. *Arch Ophthalmol* 1966; **75**: 771-3.
- 29 Lee PF, Donovan RH, Mukai N. Effect of norethynodrel with mestranol on the rabbit eye. *Arch Ophthalmol* 1969; **81**: 89-98.
- 30 Siebenbiedel H. The treatment of glaucoma with proluton. *Dtsch Gesundh-Wes* 1952; **7**: 374-5.
- 31 Treumer K. The treatment of glaucoma with progesterone. *Klin Monatsbl Augenheilkd* 1952; **120**: 523-34.
- 32 Gieriek A, Sosnierz M, Bialas B, Szaflik J. Influence of estrogens on intraocular tension in the eyeballs of rabbits. *Ophthalmology* 1976; **172**: 400-10.