Oestrogen, Headache and Oral Contraceptives

W. H. UTIAN

SUMMARY

The possible relationship between headache and the oral contraceptive is considered. In the present study, no association has been demonstrated between oestrogen withdrawal (as produced by oöphorectomy, or cessation of exogenous oestrogen replacement therapy in oöphorectomised females) or by exogenous oestrogen therapy, and the symptom of headache. This would support current theories and evidence which appear to implicate the progestogenic component of the pill as the most likely aetiological factor.

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Headache is one of the most common side-effects among oral contraceptive users. Indeed, with some combinations of oestrogen and progestogen the incidence may be as high as 40%. This is a considerable price for women to pay towards the avoidance of an unplanned pregnancy; the fact that so many persevere with the pill despite unpleasant side-effects, is a strong indication of both the need for these agents and their effectiveness.

The use of hormonal steroids for oral contraception was first reported to the Laurentian Hormone Conference in 1956 by Gregory Pincus, John Rock and C. R. Garcia.[1] Pincus's personal research on hormonal steroids went back to the early 1930s. In 1936 came his discovery that temporary sterility could be induced in rabbits by the injection of oestrogens. The first field trial of the 'pill' was reported by Edris Rice-Wray in 1957, and in 1960 the pill was approved as a contraceptive for human use by the Food and Drug Administration.[1]

Despite 16 years of continuous research, resulting in what is surely one of the most intensively investigated groups of drugs in the history of medicine, there is still a considerable amount of missing information. The purpose of this article is to consider certain aspects relating to one symptom only, namely that of headache.

In considering the relationship between headache and the contraceptive pill, it must be appreciated that a great number of variables exist. For example, there are several different types of pill made up of varying combinations of oestrogen and progestogen. There are, moreover, numerous and different types of oestrogen and progestogen with different clinical and metabolic effects. Headache itself is merely a symptom resulting from a large number of possible causes; its presence in a contraceptive pill user could thus be coincidental, and exclusion of other possible causes is therefore mandatory. Any study into the incidence, aetiology, pathogenesis, or other aspects of the relationship between headache and the contraceptive pill is bound to be fraught with pitfalls. My own observations have been related to the oestrogenic component.

Groote Schuur Hospital, Cape Town
W. H. UTIAN, M.B. B.CH., PH.D., M.R.C.O.G., *Part-time Consultant Obstetrician and Gynaecologist*

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PRESENT STUDY

While planning a broad investigation into the clinical and metabolic effects of oestrogen, it was decided that the effect of such steroids on various symptoms should be clarified. Accordingly, the opportunity was taken at a special Hormone Replacement Clinic at Groote Schuur Hospital, Cape Town, to investigate the incidence of specific symptoms, headache included, in relation to ovarian status, and to test the response of such symptoms to various forms of oestrogen replacement therapy.

Patients were selected according to strict criteria. The only variable features related to the state of the ovaries and the uterus. These groups included normal premenopausal females and patients who had undergone hysterectomy with and without bilateral oöphorectomy (see Table IV).

The incidence and severity of headache was determined for patients in the above groups and then statistically compared. A further group of 50 oöphorectomised female volunteers were observed for a period of 1 year, during which time the control observations preceded single-blind crossover administration of two forms of oestrogen and a placebo. The post-oöphorectomy groups were selected for detailed study because it is virtually impossible to collect a study group of human material with known absence of the ovarian oestrogen component except in this way.

Treatment was prescribed or changed according to Table I.

TABLE I. TREATMENT SCHEDULE FOR OÖPHORECTOMY GROUP

Visit No.	Drug administered after investigation completed	Dose (mg/day)	Time lapsed since previous visit (mo.)
1	Oestradiol valerate (Progynova, Schering)	4	—
2	Oestradiol valerate	4	1
3	Oestradiol valerate	4	2
4	Oestradiol valerate	4	3
5	Placebo—single-blind	—	3
6	Conjugated equine oestrogen (Premarin, Ayerst)	5	3

TABLE II. THE INCIDENCE AND SEVERITY OF HEADACHE IN THE GROUPS OF PATIENTS INVESTIGATED

	Normal		Post-oöphorectomy											
			Premenopausal						Postmenopausal		Conserved ovaries post-hysterectomy			
	Premenopausal		Immediate		6 months		2 years		Immediate		6 months		2 years	
Headache	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Absent	7	77,8	11	78,6	11	84,6	13	72,2	4	80,0	7	87,5	9	50,0
Mild	2	22,2	2	14,3	0	0	2	11,1	1	20,0	1	12,5	6	33,3
Moderate	0	0	1	7,1	2	15,4	3	16,7	0	0	0	0	2	11,1
Severe	0	0	0	0	0	0	0	0	0	0	0	0	1	5,6
Total patients studied	9	100	14	100	13	100	18	100	5	100	8	100	18	100

TABLE III. THE INCIDENCE OF HEADACHE IN AN OÖPHORECTOMISED POPULATION AND THE EFFECT OF OESTROGEN AND PLACEBO THERAPY

	Control		3 months' oestradiol valerate		6 months' oestradiol valerate		3 months' placebo		3 months' conjugated oestrogens	
Headache	No.	%	No.	%	No.	%	No.	%	No.	%
Absent	39	78,0	38	76,0	36	72,0	34	68,0	42	85,7
Mild	5	10,0	9	18,0	11	22,0	13	26,0	5	10,2
Moderate	6	12,0	3	6,0	3	6,0	2	4,0	1	4,1
Severe	0	0	0	0	0	0	1	2,0	0	0
Total patients treated	50	100	50	100	50	100	50	100	49	100

RESULTS

The numbers and percentages of patients complaining of headache are shown in Tables II and III. The response of oöphorectomised females in terms of relief of headache following oestrogen and placebo therapy is summarised in Table III. The statistical comparison for any significant difference in the incidence of headache of all degrees of severity between the various groups of patients investigated, is outlined in Table IV.

No significant relationship was demonstrated between the incidence of headache and menopause or removal of ovaries. Thus the percentage of patients complaining of headache was similar in the premenopausal group (22,2%) and in the group of patients who had undergone oöphorectomy (22,0%).

The results in the groups investigated after hysterectomy with conservation of both ovaries are somewhat incongruous (12,5% at 6 months and 50% at 2 years). The higher incidence in the 2-year group is of possible statistical significance ($P<0,05$).

Oestradiol valerate administration (Table III) did not decrease the incidence of the symptom and there was no placebo effect. Administration of conjugated oestrogen after placebo reduced the incidence of headache from 32,0% to 14,3%, but this was of possible significance only ($P<0,05$). In this respect, therefore, the effect of conjugated equine oestrogen was possibly superior to that of oestradiol valerate ($P<0,05$).

Headache is thus shown to be a symptom unrelated to oöphorectomy but possibly relieved by conjugated oestrogen therapy.

DISCUSSION

The present results thus indicate, in what is admittedly a small study, that at worst oestrogen therapy is not associated with an increased incidence of headache; and that at best the use of certain types of oestrogen might even result in a decreased incidence of this symptom.

Incidence of Headache

The incidence of this problem is difficult to define. Vascular reactions appear to be the most frequent and troublesome side-effects of oral contraceptives, the most common clinical manifestations of these being headache. The incidence in different studies varies tremendously, depending on factors such as type of pill, dose, duration of therapy and so on. For example, Grant[2] reported the incidence of headache in women before joining her trial to be 17%, and to vary in the same women from 8% to 60% during treatment with different oral contraceptive formulations. Tyler[3] found an incidence of 10% in 675 patients on a graduated sequential type of contraceptive. The scatter has been equally wide in numerous reports from other authors.[4]

One short 'before and after' comparison[5] reported a decrease in the incidence of headache in a group of patients treated with a low-dose combined type of pill. Another large study of over 3 000 women[6] reported no general accentuation to be produced by the oral medication. Still, there was a small number of women in whom the contraceptive pill either accentuated the discomfort or produced it for the first time: they improved, moreover, on discontinuing medication. Adverse publicity was found

TABLE IV. STATISTICAL COMPARISON BETWEEN THE GROUPS OF PATIENTS INVESTIGATED AND THE OVER-ALL INCIDENCE (ALL DEGREES OF SEVERITY) OF HEADACHE FOR SIGNIFICANT DIFFERENCES

Groups compared				
Group No.	Over-all incidence of headache	Group No.	Over-all incidence of headache	Statistical significance $P<$
1	22,2	2	21,4	NS
1	22,2	3	15,4	NS
1	22,2	4	27,8	NS
1	22,2	5	20,0	NS
1	22,2	6	12,5	NS
1	22,2	7	50,0	0,05
2	21,4	3	15,4	NS
2	21,4	4	27,8	NS
2	21,4	5	20,0	NS
2	21,4	6	12,5	NS
2	21,4	7	50,0	0,05
3	15,4	4	27,8	NS
3	15,4	5	20,0	NS
3	15,4	6	12,5	NS
3	15,4	7	50,0	0,01
4	27,8	5	20,0	NS
4	27,8	6	12,5	NS
4	27,8	7	50,0	0,05
5	20,0	6	12,5	NS
5	20,0	7	50,0	0,05
6	12,5	7	50,0	0,01
8 A	22,0	8 B	24,0	NS
8 A	22,0	8 C	28,0	NS
8 A	22,0	8 D	32,0	NS
8 A	22,0	8 E	14,3	NS
8 B	24,0	8 C	28,0	NS
8 B	24,0	8 D	32,0	NS
8 B	24,0	8 E	14,3	NS
8 C	28,0	8 D	32,0	NS
8 C	28,0	8 E	14,3	0,05
8 D	32,0	8 E	14,3	0,05

Group 1 Normal premenopausal
2 Premenopausal, investigated immediately post-oöphorectomy
3 Premenopausal, investigated 6 months post-oöphorectomy
4 Premenopausal, investigated 2 years post-oöphorectomy
5 Postmenopausal, investigated immediately post-oöphorectomy
6 6 months post-hysterectomy with conserved ovaries
7 2 years post-hysterectomy with conserved ovaries
8 All patients investigated and treated post-oöphorectomy (i.e. groups 2 + 3 + 4 + 5)
8 A Control — variable time < 2 years post-oöphorectomy
8 B 3 months' continuous oestradiol valerate therapy
8 C 6 months' continuous oestradiol valerate therapy
8 D 3 months' continuous placebo therapy
8 E 3 months' continuous conjugated oestrogen therapy

to modify the attitude of the patient towards the discomfort.

Larsson-Cohn and Lundberg,[7] recognising the limited size and lack of controls of previous studies, set out an investigation to compare, in a large group of subjects, the frequency of headache before and during treatment with different contraceptives. Their results are of some interest. Of women without pretreatment headache, 10,3% experienced headaches during treatment—a significantly higher than expected finding. Some variation of the frequency of headaches was noted among subjects taking different groups of drugs. However, the differences were of low significance.

Aetiology

The discrepancy in incidence makes an analysis of the aetiology even more difficult. Grant[2] found a strong association between headache and arteriolar development in the endometrium; the implication being that the excessive arteriolar development in the endometrium may be representative of similar vascular changes elsewhere. Thus the cerebral vasculature could be involved in an analogous way and hence be the cause of headache. Grant showed, moreover, that there is a considerable difference between one oral contraceptive and another as far as headache is concerned. She felt that this depended mainly on the particular progestogen concerned. The dose is also of importance, the incidence of well-developed arterioles rising to a peak as the dose of progestogen (always of the 19-nor-17α-ethinyl configuration) is increased, and then falling off if larger doses of progestogen are given. That is, the progestogen/oestrogen combinations which produce a high incidence of headache also have a high incidence of endometrial arteriolar development.

Schenker *et al.*[8] assessed the retinal vessels of women taking oral contraceptives. Their results were somewhat inconclusive, although they suggested that fundoscopy was of possible help in deciding when to discontinue medication in selected patients. Similar changes were noted in patients with hypertension after they had used ergometrine preparations.

There are few data on the effect of progestogen alone on headache, and it is most probable that some oestrogen is essential to the progestogenic effect. Mears *et al.*[9] evaluated 4 oral contraceptives containing only progestogens. There was a consistent incidence of headache of 9 - 11% among the various groups, nausea and breast tenderness being the only minor side-effects occurring to a greater extent. However, no-one has shown any association between oral therapy alone, including those commonly contained in oral contraceptives, and development of headache.[10] A collaborative dose-response clinical study[11] using decreasing doses of combination oral contraceptives, showed a dose-response relationship in regard to the usual clinical side-effects. The formulations used contained 40 - 60% less oestrogen and progestogen than the currently available combination products. Their low-dose combination did, nevertheless, show adequate conception control.

West and West[12] studied the personality and electroencephalograms (EEGs) of women with headache on oral contraceptives. They found a significantly higher proportion of abnormal EEGs in women with troublesome headaches on oral contraceptives compared with headache-free controls. They concluded, however, that the EEG abnor-

malities were not caused by the oral contraceptives, but pre-exist and probably indicate a state of latent migraine which can be activated by oral contraceptives.

An odd feature of many oral contraceptive headaches is that they seem to be most severe while the patient is *not* taking the compounds, i.e. they present in the interval between courses. It may be that loss of hormonal support causes shrinkage of cerebral blood vessels in much the same way as menstruation results from kinking of the endometrial coiled arterioles. This is, of course, conjecture; in many cases, severe headaches are associated with medication.[13]

CONCLUSIONS

It may be concluded, therefore, that there is a definite relationship between oral contraceptive medication and the development of non-specific headache. The precise incidence is not known, but appears to depend on the type of hormonal combination and also to be in direct proportion to the dosage of hormone present in the pill, the lower dosed pills being associated with a lower incidence of headache. Most evidence is in favour of the progestogenic component being the aetiological agent, but it would appear that some oestrogen is necessary. There is very little information on the effect of pure progestogenic contraceptive agents on headache. Most information on the oestrogenic component, including the present study, would appear to clear this group of steroids from any direct aetiological relationship. Any patients developing headache on the contraceptive pill should be investigated for coincidental causes; even if excluded, contraceptive pill therapy should probably be discontinued. However, where the symptoms are not severe and the patient is willing or keen to continue with the pill, then the lower dose combinations should be selected.

The immediate future is likely to witness the introduction of combination-type oral contraceptives with far lower doses of both oestrogen and progestogen than those currently available, and hopefully this will be paralleled by a direct decrease in all minor side-effects of oral contraceptive medication, including headache.

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