ORIGINAL ARTICLES

MIGRAINE AND ORAL CONTRACEPTIVES

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SYNOPSIS

To ascertain the effect of oral contraceptives on migraine, an analysis was made of self administered questionnaires from 886 non-pregnant migraine sufferers aged 15-45 years (241 Pill takers, 290 ex-takers and 355 non-takers), together with a 3 months record of migraine attacks in 416 women covering 1,239 menstruations.

Migraine was worse on the Pill in 34% of takers and 60% of ex-takers. On stopping the Pill 39% of ex-takers improved. During menstruation 35% of attacks occurred in takers, 32% of attacks in ex-takers and 27% of attacks in non-takers. A significant increase in migraine at mid-cycle was most marked among those whose migraine increased on the Pill and those with severe attacks. Other significant differences are reported relating to length of menstrual cycle. Deterioration of migraine on Pill related to age, parity, cycle length, menstrual attacks, relief of migraine in late pregnancy and onset after pregnancy.

AN APPEAL WAS LAUNCHED by the British Migraine Association for the cooperation of migraine sufferers in a study of the hormonal aspects of migraine in women. Over 3,000 replies were received from Britain and overseas, covering an age range from 15-85 years; this paper deals only with the effect of the oral contraceptive Pill on migraine sufferers between 15-45 years in Britain.

METHOD

The volunteers initially completed a two page questionnaire and were then asked to keep a three month record from September to November of the dates of menstruation and headaches, noting the severity of headaches using the following grades:

1. Slight headache-no medication needed.

2. Mild headache-medication needed.

3. Moderate headache-unable to continue work.

4. Severe headache-sufficient to require bed rest.

In the analysis only moderate and severe headaches were considered.

Migraine was defined in accordance with the definition of the World Federation of Neurology. 'Classic' migraine was defined as an intermittent, one-sided headache preceeded or accompanied by visual, sensory, motor or gastrointestinal symptoms. 'Common' migraine was defined as an intermittent headache severe enough to require medication and interfering with working capacity.

In this paper `the Pill' refers to an oestrogen-progestogen oral contraceptive compound. No women were currently taking the progestogen-only Pill; there were four women who had used this preparation for a short time in the past but they had also used oestrogen-progestogen combinations for a longer period.

RESULTS

Completed questionnaires were received from 886 non-pregnant women between 15 and 45 years, of whom 241 were currently taking the Pill (takers), 290 had previously taken the pill (ex-takers) and 355 had never done so (non-takers). A three month record was received from 416 women covering 1,239 menstruations and 936 attacks. There was an even distribution of replies throughout Britain, and also between urban and rural areas.

The fallout on the Pill showed a steady rise with age, 26% of ex-takers in the under 25 years age group, rising to 67% for those between 41-45 years, (Fig. 1). Twenty six women (4.7%) blamed the Pill for the onset of their migraine. While taking the Pill migraine became worse in 34% of takers compared with 60% of ex-takers. Further, on stopping the Pill 39% of ex-takers found their migraine improved, only 15% noting further deterioration, (Fig. 2).

Fluctuations in hormonal levels occur at menstruation and this was reflected in the timing of migraine attacks. During days 1-4 of the menstrual cycle 35% of attacks occurred in takers, compared with 32% of ex-takers and 27% of non-takers, (Fig. 3). Among takers there was a marked increase in incidence at mid cycle. This is a time of fluctuations in hormonal levels. To assess its effect the incidence was significantly raised on days 13-14 in the takers, ($P = < 0.005$), but a normal distribution ocurred among ex-takers and non-takers, (Fig. 4).

This rise at midcycle was most marked among takers who claimed their migraine had been worse since taking the Pill (Table 1), and also among takers with severe attacks.

Examination of the three month records showed two types of patterns:

1. *Menstrual* attacks, occurring at the same time in each menstrual cycle.

2. *Sporadic* attacks unrelated to menstruation.

Among the 122 ex-takers 39% had predominantly menstrual attacks and 61% had sporadic attacks. (Table 2). However, among those with menstrual attacks 81% reported worsening of their migraine when

TABLE I

Migraine attacks between Days 9-18 of Menstrual Cycle

Day of Menstrual Cycle	*9-10*	*11-12*	*13-14*	*15-16*	*17-18*	*Total*
Migraine Attacks	*14%*	*20%-*	*30%*	*19%*	*17%*	*95*
Severe Attacks	*12%*	*25%*	*30%*	*16%*	*16%*	*67*
Worse on Pill	*6%*	*12%*	*47%*	*22%*	*12%*	*32*

on the Pill compared with 57% of those with a sporadic pattern (P = <0.005).

While the menstrual cycle of the takers was restricted to 28 days, that of the ex-takers and non-takers had a range from 20-36 days. A striking feature was that among the 122, ex-takers who completed the three month record, 60% of those unaffected by the Pill had a conventional cycle within the 27-30 day range, whereas only 44% of those whose migraine became worse on the Pill had a cycle within these limits (P = <0.05).

Deterioration of migraine on the Pill was significantly related to parity (P = <0.005), only 45% of nulliparious women having worse migraine on the Pill compared with 62% who had one or two children and 68% who had three or more children. Further 83% of those whose migraine was better during the last trimester of pregnancy claimed their migraine was worse on the Pill (P= <0.001). Of the 38 women whose migraine commenced after a pregnancy 79% were worse on the Pill (P= <0.05). There was no significant difference in the effect of the Pill in ex-takers in respect of common or classic migraine. (Table 2).

No differences were noted between the groups in relation to mean age of menarche, classic migraine, positive family history or age of onset of migraine (Table 3). Simmilarly there were no differences among takers and ex-takers in respect of the various formulations of the Pill.

DISCUSSION

Women who volunteered for this study were self-selected and motivated by a desire to assist in the relief of migraine. The wide

TABLE II
Migraine in Ex-takers

Taking Pill	*Same or Better*	*Worse*	*Total*	*Significance*
Pattern of Attacks				
Menstrual	19%	81%	47	
Sporadic	43%	57%	75	P = <0.05
Cycle Length				
Under 26 days	19%	29%	45	
27-30 days	60%	44%	84	P = <0.05
31-40 days	17%	21%	36	
Over 40 days	4%	6%	9	
Parity				
0	55%	45%	63	
1-2	37%	63%	162	P=<0.005
3 or more	31%	69%	64	
During late Pregnancy				
Better	61%	83%	138	
Same	25%	8%	27	P = <0.001
Worse	14%	9%	20	
Onset of Migraine				
Before pregnancy	38%	62%	188	P = <0.05
After pregnancy	21%	79%	38	
Type of Migraine				
Common	62%	53%	166	Not
Classic	38%	47%	126	Significant

TABLE III

Characteristics of Takers, Ex-takers and Non-takers

	Takers	*Ex-Takers*	*Non-Takers*
Number in group	241	290	355
Mean age of menarche	13.4 yrs.	1.34 yrs.	13.5 yrs.
Classic migraine	45%	41%	47%
Positive family history	55%	57%	56%
Onset of migraine			
Under 10 years	14%	16%	10%
11-20 years	54%	44%	28%
Over 20 years	38%	40%	62%
After childbirth	1.7%	1.4%	1.4%

geographical coverage, and the meticulous three months records of attacks in relation to 1,239 menstruations provided invaluable information which had not previously been available for analysis. Waters and O'Connor[1] found that there was no difference in the validity of information obtained from a postal questionnaire compared with that obtained from questionnaires administered by a trained field worker.

The finding that migraine occurs at midcycle in takers, and especially in those whose migraine deteriorates on the Pill, confirms Phillips's[2] observation in a series of 20 women whose migraine deteriorated on the Pill, that migraine commonly developed in the middle of their artificial cycle. It is possible that attacks occurred at midcycle in ex-takers and non-takers but owing to the variable length of their cycle the attacks were more evenly spread over days 11-18, however the significance of attacks at midcycle in takers is that ovulation has been suppressed in these women. The Pill is designed to inhibit ovulation and it would seem that in some women at least, it may cause a reaction in the hypothalamic-pituitary axis. This is known to occur in those developing amenorrhoea and anovular menstruation after stopping the Pill.

The finding that ex-takers with menstrual cycles outside the conventional 27-30 day range deteriorated on the Pill, also suggests that the imposition of a rigid 28 day rhythm disturbs the menstrual clock in the hypothalamus. It is comparable to the finding among some migraine sufferers who have had a hysterectomy, and still experience attacks at cyclical intervals[3] again suggesting a disturbance of the menstrual clock in the hypothalamus.

It would be interesting to know if women who develop other side effects on the Pill, especially depression and weight gain, have the same characteristics as migraine sufferers who deteriorate on the Pill. Do they have an unconventional cycle length and menstrually related symptoms? It should not be difficult for manufacturers to produce oral contraceptive packs suitable for those with cycles of 24 or 31 days. Unfortunately few women are aware of the precise length of their cycle, and most welcome the ability of the Pill to regulate it to a conventional length.

The finding that an increase in migraine on the Pill is unrelated to either dosage or type of oestrogen or progestogen confirms clinical experience which suggests that deterioration of migraine on the Pill is not likely to be improved by changing to a different Pill.

Headaches are a troublesome and common side effect of the Pill. The Oral Contraceptive Study of the Royal College of General Practitioners[4] found-"the highest difference in frequency of reporting in respect of any symptom to be migraine and headache". While there may well have been a bias towards over or under reporting of an increase in the number of migraines whilst

on the Pill, such bias would not extend to the length of menstrual cycle in ex-takers or the finding of severe attacks at midcycle among takers whose migraine deteriorated on the Pill.

The Family Planning Association advise that women with classical migraine should not be given the Pill, and that if classical migraine develops in the course of Pill taking it should be stopped. They recognize that for this reason some women, determined to have the Pill, withhold information about their headaches and visual auras.

Many workers,[2,5,6,7,8,9,10] have noted that the use of the Pill causes headaches and migraine in those who did not previously suffer from them, or increases the frequency and severity in those who previously suffered. Estimates on the frequency of headaches on the Pill vary from 0.2% to 60% depending on the proportion and type of oestrogen and progestogen used in the preparation. Grant[6] has demonstrated the relationship between headaches on the pill and the development of endometrial arterioles. All these workers have applied their studies to establishing a relationship between the Pill and migraine. This present study would appear to be the first to investigate why the severity of migraine increases in some women who are on the Pill, while others are not affected or even improve, and to ascertain the factors responsible. This study suggests that the factors likely to cause deterioration of migraine among Pill takers are:

1. Age, increasing rapidly after 30 years.
2. Parity.
3. Length of menstrual cycle outside the conventional 27-30 days.
4. Menstrual pattern of migraine.
5. Relief of migraine during the last trimester of pregnancy.
6. Onset of migraine after a pregnancy.

It also suggests that any woman on the Pill who develops migraine at midcycle should adopt another method of contraception.

REFERENCES

1. Waters, W.E., & O'Connor, P.J., "The Clinical Validation of a Headache Questionnaire", "Background to Migraine", 3rd Migraine Symposium (Ed. Cockraine A.L.), William Heinemann Medical Books Ltd, London, 1970. 1-8.
2. Phillips, B.M., "Oral Contraceptive Drugs and Migraine", *Brit. med. J.* 2, 99, 1968.
3. Dalton, K., "The Aftermath of Hysterectomy and Oophorectomy," *Proc. roy. Soc. Med.* 50, 6, 415-418, 1957.
4. Roy. Coll. Gen. Practit. "Oral Contraceptives & Health," (Ed. Kay C) Pitman Medical, London, 84, 1974.
5. Lundberg, P.O., "Migraine Prophylaxis with Progestogens," *Acta Endocr.* (Kbh) 40, Suppl 68, 1-22, 1962.
6. Grant, E.C.G., "Relation of Arterioles in the Endometrium to Headaches from Oral Contraceptives," *Lancet* 1:1143-1144, 1965.
7. West, J., & West, E.D., "The electroencephalogram & personality of women with headaches on Oral Contraceptives," *Lancet* 1:1180-1182, 1966.
8. Whitty, C.W.M., Hockaday, J.M. & Whitty, M.M., "The Effect of Oral Contraceptives on Migraine," *Lancet* 1:856-859, 1966.
9. Grant, E.C.G., "Relation of Arterioles in the Endometrium to Headaches from Oral Contraceptives," *J. Obstet. Gynae Brit Cwlh.* 74:908-918, 1967.
10. West, J., "Headache and the Pill," *Brit. med. J.* 3:742-743, 1968.

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