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Oral Contraception and Serious Psychiatric Illness: Absence of an Association

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Summary: The incidence of serious psychiatric illness, as measured by first referral to hospital for specialist advice and treatment, has been investigated among 16,746 women taking part in the Oxford Family Planning Association contraceptive study. Of these women, 9,504 were recruited while using oral contraceptives, 4,144 while using a diaphragm and 3,098 while using an intrauterine device.

The results are reassuring with respect to oral contraceptive use. First referral rates per 1000 woman-years of observation in the oral contraceptive, diaphragm, and intrauterine device entry groups were 3.0, 2.6, and 2.8 respectively for non-psychotic psychiatric disorders and 0.46, 0.43, and 0.53 respectively for psychotic disorders.

Attempted suicide occurred only 40% as often amongst diaphragm users as amongst users of oral contraceptives or intrauterine devices; this finding presumably reflects the characteristics of women who choose the diaphragm as their birth control method.

During the nineteen sixties and seventies, many studies were published concerning the possible association between oral contraceptive use and the occurrence of psychiatric disorders, especially depression (Nilsson & Almgren, 1968; Murawski *et al,* 1968; Lewis & Hoghughi, 1969; Grounds *et al,* 1970; Herzberg *et al,* 1970; Goldzieher *et al,* 1971; Cullberg, 1972; Adams *et al,* 1973; Weissman & Slaby, 1973; Royal College of General Practitioners, 1974; Kane, 1976; Fleming & Seager, 1978; Ramcharan *et al,* 1981). The results obtained were conflicting, and even now there appears to be no clear consensus on this topic. We present here some findings about the occurrence of psychiatric illness among the women taking part in the Oxford/Family Planning Association (FPA) contraceptive study.

Method

The methods used in the Oxford/FPA contraceptive study have been described in detail elsewhere (Vessey *et al,* 1976). In brief, 17,032 women were recruited to the study during the interval 1968-74 at 17 family planning clinics in different parts of England and Scotland and they have remained under observation ever since. At the time of recruitment, each woman had to be: (a) aged 25-39 years (b) married (c) a white British subject (d) willing to participate and (e) either a current user of oral contraceptives of at least five months' standing or a current user of a diaphragm or an intrauterine device (IUD) of at least five months' standing without prior exposure to the pill. During follow-up, each woman was questioned at return visits to the clinic, and certain items of information noted on a special form. These included details of pregnancies and their outcome, changes in contraceptive practices and reasons for changes, and particulars of any referrals to hospital either as an out-patient or as an in-patient. Diagnoses on discharge from hospital were confirmed by obtaining copies of discharge letters or summaries. Women who stopped attending the clinic for any reason were sent a postal version of the follow-up form and, if this was not returned, were interviewed by telephone or at home. The work in each clinic was co-ordinated by a part-time research assistant, and follow-up has been maintained with an annual loss rate (for reasons other than death or emigration) of only about 0.3%.

The diagnostic data reported here should be treated with considerable caution. First, as already indicated, out-patient diagnoses are generally not confirmed by correspondence with the hospital concerned. Secondly, psychiatric discharge summaries are often purely descriptive and fail to include a specific diagnosis, in which case the coder (MPV) had to allocate the disorder to what appeared to be the most appropriate rubric in the Eighth Revision of the International Classification of Diseases (ICD), which has been used as the basis for the coding of all diagnoses in the Oxford/FPA study.

Particular difficulty was experienced in deciding whether some illnesses should be coded to ICD 300.4 (depressive neurosis) or to ICD 296.2 (manic-depressive psychosis, depressed type).

In the analyses which follow, psychiatric diagnoses have been divided into the following broad groups:

1. ICD Code 300.0—anxiety neurosis
2. ICD Code 300.4—depressive neurosis
3. ICD Codes 300.1-300.3 and 300.5-300.9—other neuroses
4. ICD Codes 301.0-309.9—other non-psychotic mental disorder
5. ICD Codes 295.0-295.9—schizophrenia
6. ICD Codes 296.0-296.9—affective psychosis
7. ICD Codes 290.0-294.9 and 297.0-299—other psychoses
8. Attempted suicide

Some women, of course, have more than one psychiatric diagnosis.

A total of 286 women known to have had a psychiatric illness requiring hospital referral before entering the study were excluded from all analyses (amounting to 1.6% of those in the pill entry-group, 1.6% of those in the diaphragm entry-group and 1.9% of those in the IUD entry-group).

Results

The main analysis of psychiatric illness rates was according to the contraceptive method in use at entry to the study; by using this approach, we considered that illnesses starting during oral contraceptive treatment and leading to discontinuation of medication in advance of hospital referral would still appear in the oral contraceptive group. Table I gives the numbers of woman-years of observation in each of the three entry-groups, and indicates the extent to which women persisted with the entry method during follow-up. Just under half of the woman-years of observation in the oral contraceptive entry group were spent actually using the pill, while there was relatively little use of oral contraceptives by those who entered the study while using a diaphragm or an IUD.

Table II shows the incidence rates of the various psychiatric illnesses (as measured by first referral to hospital) in women who entered the study while using either oral contraceptives, a diaphragm, or an IUD. The rates are adjusted by indirect standardisation (see Vessey *et al*, 1976) for the effects of age (five groups), parity (four groups), cigarette smoking (five groups), and social class (five groups). The two statistically significant differences concern hospital admission for 'other non-psychotic mental disorder', where the rate is about 80% higher in oral contraceptive users than in users of the other two methods, and 'attempted suicide', where the rate in diaphragm users is only about 40% of that in users of oral contraceptives or an IUD.

We wondered whether the rate of diagnosis of psychiatric illness in the oral contraceptive entry group might vary according to whether or not the pill was actually being used, and this question is examined in Table III. None of the differences is statistically significant, but there is a suggestion that psychotic illnesses were diagnosed a little more often in ex-pill users, and that attempted suicide was a little more common in current pill users.

We also wondered whether there might be a relationship between diagnosis of psychiatric illness and duration of oral contraceptive use. To investigate this possibility, we limited our analysis to women experiencing their first segment of pill use, and considered only those diagnoses occurring in current users. Not surprisingly, numbers were small, but the results for non-psychotic mental disorders (Groups one to four) and for attempted suicide (Group eight) are shown in Table IV. There is little indication of any trend, but the low rates in the longest duration of use group should be noted for both diagnoses.

Finally, we attempted to see whether there was any association between psychiatric illness and the progestogen content of oral contraceptives. For this purpose, we looked at diagnosis rates in users of the 'ovlar' series of pills, as described by the Royal College of General Practitioners (1977). The numbers of women using Anovlar (50 μg ethinyloestradiol, 4 mg norethisterone acetate), were too few for analysis, but there was no obvious difference in diagnosis rates between those using Gynovlar (50 μg ethinyloestradiol, 3 mg norethisterone acetate), and those using Minovlar (50 μg ethinyloestradiol, 1 mg norethisterone acetate).

Discussion

Our study has a number of important limitations as a source of information about possible associations between oral contraceptive use and psychiatric illness. First, as explained above, the reliability of our data on psychiatric diagnoses is uncertain, but at least all the coding was done by one medically qualified person (MPV). We did consider asking a psychiatrist to re-code all the in-patient material, but decided against it because the major problem seemed to be the basic inadequacy of the information provided in the discharge summaries and letters, rather than anything

TABLE I

Woman-years of observation and contraceptive methods used

Contraceptive method at entry	*No. of women*	*Woman-years of observation*	*% of woman-years spent using:—*				*Total*
			Oral contraceptives	*Diaphragm*	*IUD*	*Other or no method*	
Oral	9504	101,229	45.1	2.5	6.0	46.4	100.0
Diaphragm	4144	45,864	7.0	54.4	6.1	32.5	100.0
IUD	3098	33,530	4.2	1.1	65.1	29.6	100.0

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TABLE II

Psychiatric illness in relation to contraceptive method at entry to the study. The figures given are incidence rates (as measured by first referral to hospital) per 1000 woman-years of observation. Numbers of women affected given in parentheses.

Diagnostic group	*Type of referral*	*Contraceptive method at entry:—*			*Chi-square (d.f. 2)*
		Oral	*Diaphragm*	*IUD*	
Anxiety neurosis (1)	IP	0.11 (12)	0.25 (9)	0.18 (6)	3.8
	IP or OP	0.49 (53)	0.51 (21)	0.50 (15)	0.1
Depressive neurosis (2)	IP	0.51 (54)	0.36 (14)	0.46 (16)	1.4
	IP or OP	1.25 (131)	1.15 (49)	1.11 (37)	0.5
Other neurosis (3)	IP	0.16 (16)	0.17 (7)	0.19 (7)	0.2
	IP or OP	0.52 (54)	0.58 (24)	0.63 (22)	0.7
Other non-psychotic mental disorders (4)	IP	0.54 (57)	0.28 (12)	0.31 (10)	6.4*
	IP or OP	0.93 (100)	0.56 (23)	0.69 (22)	5.8
All non-psychotic mental disorders (1–4)	IP	1.21 (128)	0.98 (40)	1.04 (36)	1.6
	IP or OP	2.99 (316)	2.58 (108)	2.78 (92)	1.9
Affective psychosis (6)	IP	0.31 (33)	0.24 (9)	0.27 (10)	0.6
	IP or OP	0.36 (38)	0.31 (12)	0.34 (12)	0.2
All psychosis (5–7)	IP	0.38 (40)	0.36 (14)	0.45 (16)	0.4
	IP or OP	0.46 (49)	0.43 (17)	0.53 (18)	0.4
Attempted suicide (8)†	All IP	0.58 (61)	0.23 (9)	0.56 (20)	7.0*

*P <0.05 IP = inpatient OP = outpatient

The numbers of patients with schizophrenia (10) and 'other psychoses' (15) were too few to be worth showing separately.

All rates are adjusted for the effects of age, parity, cigarette smoking, and social class.

† 7 women succeeded in a suicidal attempt. Of these, 3 were oral contraceptive users, 2 were diaphragm users and 2 were IUD users.

else. Secondly, our study is concerned only with conditions of sufficient severity to require referral to hospital for specialist advice and treatment—a very small proportion of all psychiatric morbidity; however, referral to a psychiatrist is a definite 'event' which can be counted, so at least we do know what we have measured. Thirdly, women recruited to the oral contraceptive entry-group had to have at least five months' use of the pill; this implies that any adverse psychiatric reactions occurring at the start of pill use would be missed in our investigation.

The study also has a number of obvious strengths, of which its large size, the inclusion of appropriate control groups, the high quality of the data on contraceptive use, and the completeness of follow-up are important examples.

Our results are reassuring with respect to oral contraceptive use. The one statistically significant difference concerns a heterogeneous diagnostic group ('other non-psychotic mental disorder'), and it seems reasonable to ascribe this finding to chance, in view of the large number of significance tests undertaken. The low rate of attempted suicide in diaphragm users is, however, most likely to be a reflection of the cautious, conscientious type of woman who chooses this method of birth control; the rates of accidental injury in our study are also low for diaphragm users.

It is of interest to compare our results with those reported from the other two large-scale cohort studies of women using oral contraception. In the Walnut Creek Study (Ramcharan *et al*, 1981) in California, which was also concerned with conditions leading to hospitalisation, there was a tendency for most psychiatric disorders to be diagnosed a little more often in past oral contraceptive users than in controls, but the same was not true for current users. The association was strongest for depressive neurosis, but even for this condition, it did not approach statistical significance. Homicides, accidents, and suicides were also commoner in oral contraceptive users, but again not statistically significantly so. In the Royal College of General Practitioners study (1974), the most disturbing finding was an approximately 30% increase in depressive illness in pill users, in comparison with controls, a difference which was highly significant statistically. This effect was apparent both in those with illness leading to hospital admission and in those with less severe conditions. In addition, deaths from

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TABLE III

Psychiatric illness in the oral contraceptive entry group classified according to whether or not the pill was in use at time of first hospital referral (inpatient or outpatient). Data are rates per 1000 woman-years of observation Numbers of women affected given in parentheses

Diagnostic group	*Contraceptive method in use:-*		*Chi-square (d.f. 1)*
	Oral	*Not oral*	
Anxiety neurosis (1)	0.44 (23)	0.54 (30)	0.4
Depressive neurosis (2)	1.27 (62)	1.24 (69)	0.1
Other neurosis (3)	0.60 (29)	0.45 (25)	0.8
Other non-psychotic mental disorder (4)	0.84 (42)	1.01 (58)	0.7
All non-psychotic mental disorders (1–4)	3.00 (149)	2.98 (167)	0.1
Affective psychosis (6)	0.28 (14)	0.44 (24)	1.5
All psychosis (5–7)	0.35 (18)	0.57 (31)	2.4
Attempted suicide (8)	0.73 (36)	0.45 (25)	3.1

The numbers of patients with schizophrenia and 'other psychosis' were too few to be worth showing separately.
All rates are adjusted for the effects of age, parity, cigarette smoking and social class.

TABLE IV

Diagnosis of psychiatric illness in relation to duration of oral contraceptive use. First segment of observation only. The data concern first hospital referrals (inpatient or outpatient) and are rates per 1000 woman-years of observation. Numbers of women affected given in parentheses.

Diagnostic group	*Duration of oral contraceptive use (mths)*				
	–24	*25–48*	*49–72*	*73–96*	*97+*
All non-psychotic mental disorders (1–4)	4.91 (16)	4.70 (28)	2.37 (13)	4.69 (18)	1.20 (4)
Attempted suicide (8)	1.00 (3)	1.43 (8)	0.56 (3)	1.24 (5)	0.25 (1)

All rates are adjusted for the effects of age and cigarette smoking.

suicide were rather commmoner in pill users, but the total number of deaths from this cause (13) was judged to be too small for reliable analysis.

Our findings are more reassuring than those in the other cohort studies. This may perhaps be because our comparison groups, which include only sexually active women, are more appropriate than those used by Ramcharan *et al* and by the Royal College of General Practitioners. For example, we might have drawn a misleading conclusion about the possible association between oral contraceptive use and attempted suicide if we had not included a group of IUD users in the study.

Finally, it should be stressed that the data collected in all three cohort studies relate largely to oral contraceptives which are no longer used. Accordingly, even if the older preparations were associated with some adverse psychiatric effects, the same might not be true for modern low-dose pills.

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