FIG 4—Number of stillbirths and neonatal deaths (1/12) weighing 1500 g or less.

For England and Wales numbers in the 2500 g or less failed to rise after 1961 and started to fall before the numbers in the total live births group. Since 1970 the numbers in both groups have fallen together (fig 1). Numbers in the 2000-2500 g group rose and fell with the total live birth group (fig 2). The cause of the 2500 g or less group failing to rise after 1961 appears to lie with the 1500 g or less group (fig 3). In case these falls might be thought to be due to a changing fashion in diagnosis, stillbirths and live births over the years have maintained the same relationship to each other in the 1500 g or less group (fig 4).

Discussion

What can be the explanation of these facts? 1953-61 was the period of rising births with a uniform increase in all weight groups. During the period 1961-70 the contraceptive pill became available in Britain. The first effect may have been to

reduce the number of very small infants. This probably resulted from a reduction in the number of late, illegal abortions. The Abortion Act of 1967 with an expanded use of contraception must be responsible for the recent plunge from 1971 to 1975. But this by itself would not explain the disproportionate drop in the very small births, which again is probably due to the virtual disappearance of illegal abortion.

On this basis the much greater fall in Sheffield may be due to the greater necessity for, and availability of, illegal abortion in the cities before 1967.

But, of course, there must be more to it than that. Improvement in general health, proper spacing of pregnancies, adequate antenatal care, and great improvement in the obstetric services may all have helped to reduce the incidence of spontaneous premature labour. Future developments should reduce this even more.⁴

If the national figures develop along the same lines as Sheffield the number of very small infants is going to be drastically reduced in the future. Were that to happen the superintensive care units for preterm infants envisaged in the Court Report⁵ and other DHSS publications⁶ may be unnecessary. If they are established it may be impossible to measure their worth because what they would set out to do may well be occurring already.

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(Accepted 2 August 1977)

Post-"pill" amenorrhoea—cause or coincidence?

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British Medical Journal, 1977, **2**, 940-942

Summary

The relationship of contraceptive history to diagnostic category of amenorrhoea was analysed in 131 consecutively investigated cases of secondary amenorrhoea. Amenorrhoea occurred in 52 patients immediately after discontinuing the oral contraceptive. Twenty-two had had amenorrhoea before oral contraceptive treatment

and 23 patients before the episode of non-contraceptive-related amenorrhoea investigated here. When these cases were excluded from analysis there was no significant difference in the distribution of any of the diagnostic categories between those who had used the oral contraceptive and those who had not.

The results suggest that using oral contraceptives does not cause subsequent amenorrhoea.

Introduction

Many patients develop post-"pill" amenorrhoea (PPA)—that is, secondary amenorrhoea immediately after stopping oral contraceptives.¹⁻³ Usually it has been concluded that the amenorrhoea was caused by the contraceptive. With few exceptions,^{3,4} however, there has been no attempt to compare the clinical and endocrine features of patients with PPA with those in a comparable group of patients with amenorrhoea who have not taken the oral contraceptive (OC). We report the results of our analysis of 150 patients with secondary amenorrhoea and compare the distribution of various diagnostic categories in

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those presenting with PPA with that in those with amenorrhoea unrelated to contraceptives.

Patients and methods

The definition of secondary amenorrhoea used here was failure to menstruate for at least four months. All patients were investigated consecutively according to the protocol of Jacobs *et al.*⁵ When appropriate, laparoscopy was performed: the appearance of the ovaries was recorded, and tubal patency was established by the passage of dye. The patient's height and her present, premorbid, and lowest weights were recorded.

Based on these investigations the following diagnostic categories were recognised.

Primary ovarian failure (13 cases)—Serum follicle-stimulating hormone concentration exceeding 170 μ g/l.

Hyperprolactinaemia (41 cases)—Serum prolactin concentration exceeding 16 μ g/l. Pituitary tumours were diagnosed in 16 of these patients.

Clomiphene-responsive amenorrhoea (20 cases)—Ovulation proved by pregnancy or inferred from a serum progesterone concentration equal to or exceeding 25 nmol/l (7.9 ng/ml) during the putative luteal phase (17 days after starting a five-day course of clomiphene citrate 100 mg/day). Only patients ovulating in response to treatment with clomiphene who did not have any of the other causes of amenorrhoea described here were placed in this category.

Anorexia nervosa (21 cases)—Diagnosed by the psychiatric history according to Crisp's description,⁶ but regardless of the patient's current weight.⁷

Weight (loss) related amenorrhoea, without anorexia nervosa (12 cases)—Diagnosed in patients with loss of weight and an inappropriate desire to be thin but in whom primary anorexia nervosa could not be diagnosed with certainty.

Amenorrhoea associated with psychiatric disease, excluding categories 4 and 5 above (24 cases)—Diagnosed in patients with recent depressive reactions, severe psychological immaturity, or obvious personality disorders.

Polycystic ovary syndrome (seven cases)—Diagnosed by the appearance of the ovaries at laparoscopy.

Amenorrhoea due to miscellaneous causes (seven cases)—Two patients with lower genital tract occlusion, two patients with primary hypothyroidism, one with hypopituitarism (posthypophysectomy) and two non-clomiphene responsive patients in whom no diagnosis has so far been reached.

The patients in the PPA group had all used a combined (oestrogen + progestogen) OC for at least four months (mean 30.4 months, range 4-120 months) immediately before the amenorrhoea that caused the referral. The group of patients with amenorrhoea unrelated to OC treatment included those who had never used any form of contraception (75 cases) and those who had used them in the past but in whom at least six consecutive menstrual cycles had occurred between the patients discontinuing their use and the present investigations (17 cases). Two patients with amenorrhoea during and after treatment with the OC and three patients with amenorrhoea after discontinuation of mechanical methods of contraception, together with those in the last two categories above were excluded from further study, leaving the results of 131 patients for statistical analysis.

Laboratory methods

The reagents for measurement of serum luteinising hormone (MRC 68/40), follicle-stimulating hormone (MRC 68/39), prolactin (VLS No 1), and thyroid-stimulating hormone (MRC 68/38) were kindly supplied by the Medical Research Council of the UK, Dr W D Odell, and the National Pituitary Agency of the USA. The methods of measuring these hormones, serum thyroxine, and progesterone concentrations and their normal ranges have been described elsewhere.⁵

Results

Contraceptive history

Amenorrhoea unrelated to OC treatment occurred in 79 patients; previous episodes of amenorrhoea had occurred in 23 of them.

Amenorrhoea immediately after discontinuation of the OC (PPA) occurred in 52 cases; episodes of amenorrhoea preceding the OC treatment had occurred in 22. There was no difference in the duration of the present episode of amenorrhoea between the PPA group and the group with non-OC related amenorrhoea ($P > 0.05$ Mann-Whitney U test).

When the group of patients with PPA was compared with the group of patients with non-OC related amenorrhoea, there was no difference with respect to the mean age at presentation (26.6 years for the whole group), mean age at menarche (13.3 years), mean height (164 cm), or mean weight at first visit (58.1 kg).

Relationship of contraceptive history to diagnosis of amenorrhoea

Table I compares the distribution of diagnoses between the group of patients whose amenorrhoea was unrelated to OC treatment with the distribution in the group of patients with PPA.

Analysis of these data by the chi squared test (table I) showed there was no significant difference of the distributions of diagnoses between the two groups ($P = 0.15$; raw $\chi^2 = 8.09$; $DF = 5$). Nevertheless, since several reports of patients with PPA specifically describe a favourable outcome of treatment with clomiphene,⁸⁻⁹ a difference in the distribution of the clomiphene-responsive cases was sought by comparing their distribution between the two groups with that of the combined number of all of the other cases shown in table I: for this comparison $P = 0.0235$ (corrected $\chi^2 = 5.12$; $DF = 1$). When the distribution of the number of patients in each of the other diagnostic categories was compared with the distribution of the sum of all the remaining cases, no significant differences were found (in all cases $P > 0.2$).

TABLE I—Relationship of diagnosis to contraceptive history in 131 patients with amenorrhoea

	Amenorrhoea not related to contraception (60%)	Amenorrhoea immediately after contraception (40%)
Primary ovarian failure	10 (12.7%)	3 (5.8%)
Hyperprolactinaemia	28 (35.4%)	13 (25.0%)
Clomiphene-responsive amenorrhoea	7 (8.9%)	13 (25.0%)
Anorexia nervosa	12 (15.2%)	9 (17.3%)
Weight (loss) related amenorrhoea	7 (8.9%)	5 (9.6%)
Psychiatric disease	15 (19.0%)	9 (17.3%)
Total	79	52

Raw $\chi^2 = 8.09$; $DF = 5$; $P = 0.15$.

TABLE II—Relationship of diagnosis to contraceptive history in 86 patients in whom there were no previous episodes of amenorrhoea

	Amenorrhoea not related to contraception (65%)	Amenorrhoea immediately after contraception (35%)
Primary ovarian failure	5 (8.9%)	2 (6.7%)
Hyperprolactinaemia	22 (39.3%)	8 (26.7%)
Clomiphene-responsive amenorrhoea	3 (5.4%)	4 (13.3%)
Anorexia nervosa	11 (19.6%)	7 (23.3%)
Weight (loss) related amenorrhoea	6 (10.7%)	3 (10.0%)
Psychiatric disease	9 (16.1%)	6 (20.0%)
Total	56	30

These results suggested a possible association of clomiphene-responsive amenorrhoea with previous treatment with the OC. Episodes of amenorrhoea, however, had preceded OC treatment in 22 patients and preceded the episode of non-contraceptive-related amenorrhoea investigated here in 23 cases; moreover, 13 of these patients were in the clomiphene-responsive category (nine PPA, four non-OC related). Since OC treatment could not have started a form of amenorrhoea that had preceded it, the numbers of patients who had had amenorrhoea before oral contraception, or before the current episode of amenorrhoea, were subtracted from the total number of cases (table II). When this was done, more than 20% of the diagnostic categories had less than five cases in them, so comparison of the groups by the χ^2 test was not possible.¹⁰ When the distribution between the two groups of cases of clomiphene-responsive amenorrhoea was compared with the distribution of the sums of the remaining cases, however, no significant difference was found ($P = 0.18$, Fisher's exact test).

Discussion

Amenorrhoea immediately after discontinuation of the OC occurred in 40% of our patients. This figure, similar to that reported by Shearman,¹¹ most probably reflects partly the referring habits of the doctors using the clinic and partly our known interest in this condition. Nevertheless, we have avoided the problems of bias inherent in selecting referred cases by comparing the distribution of diagnostic categories in patients with PPA with that in patients with amenorrhoea unrelated to treatment with the OC.

Primary ovarian failure occurred in 5.8% of the patients with PPA. This observation has been reported by others¹² and is almost certainly a coincidental finding, because the condition occurred with a similar frequency in the group of patients with non-OC related amenorrhoea.

Hyperprolactinaemia occurred in 25% of the patients with PPA. Since treatment of normal women with oestrogen-containing OC raises serum prolactin concentrations¹³ while oestrogen treatment may cause hyperplasia of pituitary lactotrophs in animals,¹⁴ we expected that disorders of prolactin secretion might have occurred more commonly in the group of patients with PPA.¹⁵ The data shown in tables I and II, however, indicate that a similar proportion of the patients who had non-contraceptive related amenorrhoea also had hyperprolactinaemia. Moreover, four of the hyperprolactinaemic patients with PPA and 12 of those with amenorrhoea unrelated to OC treatment had pituitary tumours.

The significance of weight loss and of the psychiatric features of anorexia nervosa in patients with amenorrhoea has been emphasised,¹⁶⁻¹⁸ and these factors accounted for many of our patients. The recent suggestion that low body weight renders patients more susceptible to impairment by the OC of subsequent reproductive performance¹⁹ seems improbable: patients with loss of weight occurred with equal frequency in both groups, and probably the cause of the reproductive disturbance was not the previous OC treatment but the psychiatric components of anorexia nervosa and the metabolic effects of self-starvation.²⁰⁻²² Similarly, a significant number of patients in both groups had other obvious psychiatric disorders. Several of these patients had stopped using contraceptives when a close emotional relationship had ended and the need for contraception had ceased. In these patients the reasons for stopping the OC were more likely to be the cause of the amenorrhoea than the effect of withdrawing sex steroid treatment.

Many reports have emphasised the favourable response of patients with PPA to treatment with clomiphene, so it was interesting to note a possible association of clomiphene-responsive amenorrhoea with previous contraceptive treatment (table I). It is also a feature of several reports of PPA, however, that many patients have had episodes of amenorrhoea before starting OC treatment.²³ Since a condition that had occurred before treatment could not have been caused de novo by that treatment, the numbers of cases with previous episodes of amenorrhoea were subtracted from the total numbers in each of the diagnostic categories in both of the groups (table II). There was then no significant difference between the two groups when the distribution of cases of clomiphene-responsive amenorrhoea was compared with the distribution of the remaining cases. The question remains, however, of whether treatment with the OC exacerbated the disturbance in the patients with a history of previous amenorrhoea. Although this history accounted for the statistically significant association of clomiphene-responsive amenorrhoea and OC treatment referred to above, it was not specific and occurred in all diagnostic categories and in both groups (tables I and II). While we think that a previous reproductive disturbance would be more likely to persist than be cured by treatment with the OC, the possibility remains that in this small category of patients the OC may have contributed to the amenorrhoea that followed its use. None the less, the response of these patients to simple treatment with clomiphene is so good that it need not be a matter for serious clinical concern.

This study of patients with PPA is retrospective, and it might be argued that conclusions would be drawn more safely from a prospective analysis of the subsequent menstrual history of a group of patients starting OC treatment. Problems of bias exist in prospective studies, however, because clinicians vary so widely in their indications for the OC, some using it to provide regular cycles while others exclude patients with irregular menstruation from treatment. Evaluation of the prospective studies so far reported²⁴⁻²⁵ is also difficult because complete endocrine investigation of the patients developing PPA and comparison of their results with those of a matched control group has not been performed.

Finally, there are two practical consequences of these results. The first is the importance of undertaking thorough investigation in all patients with amenorrhoea, regardless of their contraceptive history. Reference to table I shows that serious conditions causing the reproductive disturbance—including pituitary tumour and primary ovarian failure—occurred with a similar frequency in both groups of patients; moreover, neither a previously normal, nor a previously irregular, cycle in a patient with PPA precludes a serious disorder. The second practical consequence concerns the subsequent contraceptive advice to be given to patients presenting with PPA. We consider that, providing investigations exclude hyperprolactinaemia, amenorrhoea due to psychiatric disorders and weight loss is recognised and treated on its own merits, and other diseases are identified and corrected, a history of PPA does not itself contraindicate using oral contraceptives.

It is a pleasure to acknowledge the help and interest of the gynaecologists of St Mary's Hospital, and to thank them for permission to investigate patients under their care. We thank Mr John Fox for technical assistance and the department of chemical pathology of St Mary's Hospital for the measurements of thyroxine, thyroid-stimulating hormone, and progesterone. We are grateful to Mr Jack Thurwell for help with computer analysis of data and to Miss Elizabeth Belsey for statistical advice. During this study UAK was supported by a grant from the Studienstiftung des deutschen Volkes.

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(Accepted 5 July 1977)