

Oral Contraceptives and Cerebral Arterial Occlusion

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Several cases of arterial occlusion have been described in young women taking oral contraceptives (see Nevin *et al.*, 1965).

It has been suggested, following these reports, that there is a causal relationship between the taking of oral contraceptives and the arterial occlusion. If such a relationship exists it might be expected that the incidence of cerebral arterial occlusion in women in the reproductive period of life would perhaps show an increase since the introduction of oral contraceptives. These were first used among the general population in Great Britain in 1960 (Family Planning Association, personal communication). Since then the number of women in Great Britain estimated by the Family Planning Association to be taking oral contraceptives has risen from 5,000 in 1961 to between 300,000 and 400,000 in the first six months of 1965 (H. Hill, personal communication, 1965). That is, in 1964, of women of child-bearing age in this country (about 8,000,000) roughly 2.5% were taking oral contraceptives, and in 1965 approximately 9%.

There has been no report so far of the results of a prospective study of the morbidity in women taking oral contraceptives. It therefore seemed of interest to examine the figures of this hospital for proved cerebral arterial occlusion occurring between 1 January 1955 and 30 June 1965 to see how many women with such occlusions were on oral contraceptives and to see if there was any detectable change in the incidence of occlusion in women in the reproductive period of life.

Method

Only arteriographically proved cases of occlusion were considered, because of the difficulty in distinguishing clinically between neurological syndromes due to arterial occlusion and those due to small intracerebral haemorrhages and other causes. With one exception the arteriograms were performed in this hospital. They were carried out either by direct puncture of the carotid or vertebral arteries or by catheterization of the aortic arch and its major branches by the axillary or femoral routes. Vertebral arteries are often congenitally asymmetrical, and one artery may be congenitally absent. In seven cases in the present series, none in the age group under discussion, it was impossible to decide whether apparent absence or occlusion of a vertebral artery was congenital, acquired, or due to a technical limitation. Because of this uncertainty these cases were excluded from the series.

Results

The diagnosis of occlusion of a cerebral artery or of the carotid or vertebral arteries was established by arteriography in 315 patients between 1 January 1955 and 30 June 1965. Of these, 39 were women aged 18-45 years. It can be seen from Fig. 1 that there is no obvious change in the annual incidence of cerebral arterial occlusion in women aged 18-45 in the years 1961-5 as compared with the years 1955-60. This is in contrast to the increase in total numbers of women taking oral contraceptives (Fig. 1 A) from 5,000 in 1961 to between 300,000 to 400,000 in the first six months of 1965.

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Fig. 2 shows the ages of women between 18 and 45 who sustained an arterial occlusion. There is no obvious change in the age incidence since the introduction of oral contraceptives.

From Table I it can be seen that of the 18 women with cerebral arterial occlusion diagnosed between 1961 and 1965 nine were definitely not taking oral contraceptives, four were definitely taking oral contraceptives, and in five it was impossible to obtain definite information.

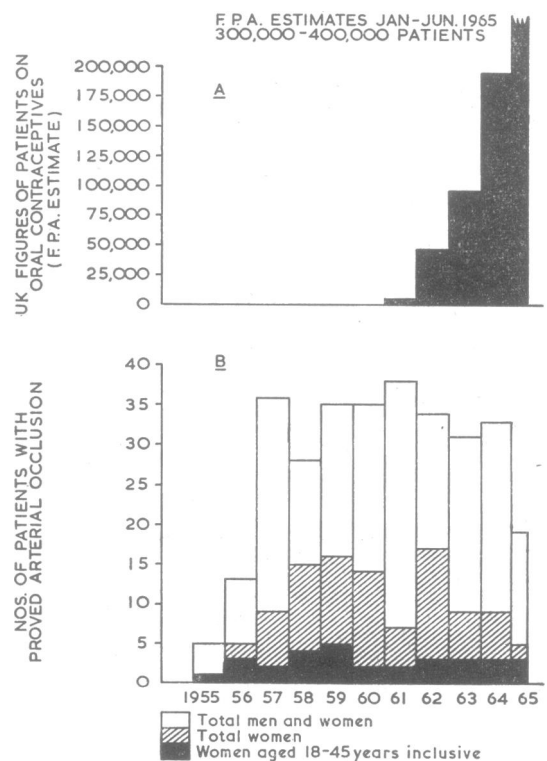


FIG. 1.—A, Annual incidence of the numbers of patients in the U.K. on oral contraceptives since the contraceptives were first used. The figure for 1965 is for the first six months only. B, Total number of cases, total women, and total women aged 18-45 who were found to have cerebral arterial occlusion in each year from 1955.

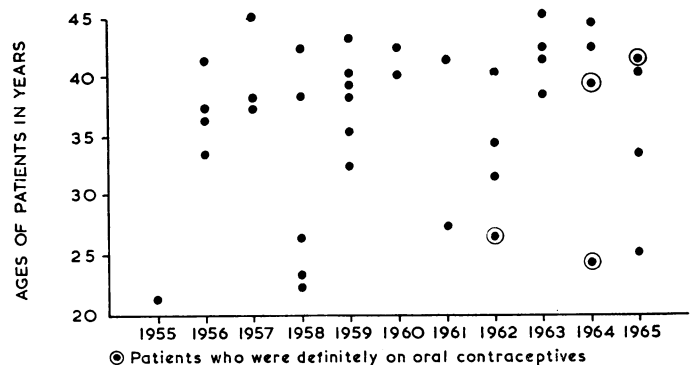


FIG. 2.—Actual ages of women aged 18-45 who sustained an arterial occlusion.

The clinical information about the patients taking oral contraceptives is of some interest.

TABLE I.—*Women Aged 18–45 Years (inclusive) with Cerebral Artery Occlusion*

	1961	1962	1963	1964	1965	Totals
On oral contraceptives ..	0	1	0	2	1	4
Not on oral contraceptives ..	1	2	2	2	2	9
Not definitely known ..	1	1	2	0	1	5

Case Reports

Case 1.—A woman aged 28 was admitted in November 1964 under the care of Dr. Macdonald Critchley for investigation of a two-year history of intermittent weakness of the left side of her body, and visual disturbances in her left field of vision. She was normotensive with signs of a minimal left hemiparesis. She gave a past history of five miscarriages, each during the fourth and fifth months of pregnancy. There was a family history of coronary artery disease (father) and of hypertension (paternal grandmother), and she had been noted to be mildly hypertensive in the past. She had taken oral contraceptives for two months only, in 1962. It was impossible to ascertain the exact time at which she had taken these pills, but it coincided roughly with the onset of the symptoms. Gynaecological investigations failed to reveal the cause of her frequent miscarriages. There was no evidence of any thrombotic tendency nor of cardiac disease or arteritis. Arteriography demonstrated a partial occlusion of the right middle cerebral artery.

Comment.—In this patient, in whom the first stroke symptoms occurred at about the same time as she started taking oral contraceptives, we found it impossible to determine the exact time relationship of the two events.

Case 2.—A woman aged 41 was admitted in June 1965 under the care of Dr. William Goody nine days after starting on Ovulen (ethynodiol), one tablet daily. She had suddenly developed a right-sided headache and a complete left hemiplegia, hemianopsia, and hemianaesthesia. Three years previously, five weeks post-partum, she had had an episode of sudden onset of pain and cyanosis of the right forearm, with absence of the brachial and radial pulses on that side for two days. Recovery from this episode was complete except for a persistently absent brachial pulse. A year later she had an uncomplicated pregnancy. Investigation in 1965 showed no evidence of a cardiac lesion or thrombotic disease and no cervical ribs; blood-pressure was 130/80. Aortic arch angiogram was normal except for complete occlusion of the right common carotid artery at the carotid siphon.

Case 3.—A woman aged 39 was admitted in 1964 under the care of Dr. Ross Russell. Within a few weeks of starting Anovlar (norethisterone) tablets she had a series of attacks of clumsiness of the left hand, each lasting about 30 seconds and recurring every two to three days. About two months later a more prolonged episode occurred, slowly spreading to involve the left face, arm, and leg. The father of this patient died of heart disease at the age of 47; a grandmother and an aunt suffered from diabetes; and a sister had hypertension. At the age of 30 the patient suffered intermittent claudication of the left foot, and arteriography showed occlusion of both anterior and posterior tibial arteries. Menstrual history was normal, but she had never been pregnant. She had smoked heavily for many years. On examination in 1964 she had a left hemiparesis. Blood-pressure was 140/70, the left dorsalis pedis and posterior tibial pulses were impalpable. The only abnormal finding was found on arteriography, which showed complete occlusion of the right internal carotid artery near its origin.

Case 4.—A woman aged 24 was admitted in 1964 under the care of Dr. Ross Russell. About one month after starting on Conovid E this patient developed recurrent episodes of weakness of the right side of her body, occurring over the four months before admission. In the last episode she had dysphasia. There was nothing relevant in the past or family histories. She was normotensive, and the only abnormal signs were weakness of the right face and arm, nominal dysphasia, and right-left confusion. Investigations showed no evidence of thrombotic tendency or arteritis. Cerebral angiography showed a complete left internal carotid occlusion just above the bifurcation.

Discussion

The general impression that cerebral arterial occlusion was very rare in young women until two or three years ago has not been confirmed. From Figs. 1 and 2 it is clear that in a specialized neurological hospital there were many such cases before the introduction of oral contraceptives. As in all specialist institutions, there is a tendency to admit patients of a younger age group and a higher social group than in a general hospital, but the policy in this hospital has probably remained unchanged over the period covered by this report. Since 1957 there has been an increased interest in the radiological investigation of strokes (see Table II). The fact that the annual inci-

TABLE II

Year	1955	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965*
No. of carotid, vertebral, and arch angiograms	600	631	743	767	786	781	871	782	878	721	428

* To June 30.

dence of cerebral arterial occlusion in women aged 18–45 years has not changed in this hospital in recent years is of little significance, since the total numbers are small, and the proportion of women of child-bearing age in the country taking oral contraceptives is still only about 8%, so that a small change in incidence would not be detected.

The finding of four patients on oral contraceptives in a total of 18 is at first sight striking, but must be examined with caution before assuming any causal relationship. One of the difficulties is that, while figures for the total number of patients in the country on oral contraceptives can be obtained, no information is available on variations with regions, social class, etc. If the women considered in this report were representative of the country as a whole then the proportion on oral contraceptives in our series (22%) is three times greater than would be expected in a random sample (approximately 8% in 1965), but this is almost certainly not the case, since all our patients were selected for admission to a specialist hospital and were all from the south of England, where the practice of contraception is probably more common.

The history of previous vascular disease (two cases) or of a strong family history of vascular disease (two cases) is a feature of our patients, and suggests either that the cerebral arterial occlusion on oral contraceptives was not more than a coincidence or that a predisposition to vascular occlusion was present in these patients and might have been aggravated by oral contraceptives. However, this is capable of more than one interpretation, and familial or past vascular disease, especially if this occurred during pregnancy (Case 2), may in fact have been the reason for taking contraceptives. For the same reason the prevalence of contraceptive taking in other young women in this hospital is of little value, since some patients with neurological disease may wish to avoid pregnancy on eugenic grounds. The occurrence of thrombosis in three cases out of four within a few weeks of starting oral contraceptives is probably the strongest reason for suspecting a causal relationship in this series, but until the number of women on oral contraceptives is accurately known and a systematic prospective inquiry for complications is completed the question must remain open.

The present report has dealt only with the most serious manifestation of arterial disease, because this objective assessment is possible. Less grave effects may occur but are not within the scope of this communication.

Summary

Between January 1955 and July 1965 of the 315 cases of cerebral arterial occlusion at this hospital 39 have been in women aged 18–45 years; of these, 21 occurred before the introduction of oral contraceptives in 1961, and 18 since then.

Four, or perhaps three, of these 18 patients developed their symptoms within a few weeks of starting on oral contraceptives. Two of these four patients had a previous arterial occlusive episode, in one of these five weeks post-partum. On the basis of these figures, involving such a small number of cases, we are unable to draw any conclusions about the possible causal relationship between oral contraceptives and cerebral arterial occlusion, and consider that this can only be demonstrated in patients by a prospective long-term study.

We would like to thank Dr. James Bull, of the Lysholm Department of Radiology, for permission to use the records and films of the department; Dr. R. W. Ross Russell for helpful criticism; and the physicians and surgeons of the National Hospital, Queen Square, for permission to publish this report.

REFERENCE

Nevin, N. C., Elmes, P. C., and Weaver, J. A. (1965). *Brit. med. J.*, 1, 1586.

Medical Memoranda

Pregnancy in a 31 in. (77.5 cm.) Dwarf

Brit. med. J., 1965, 2, 1166

This report concerns pregnancy in a woman who was only 31 in. (77.5 cm.) tall.

A primigravida aged 34 was seen in November 1963 when she was 14 weeks pregnant. She was 2 ft. 7 in. (77.5 cm.) tall, with gross distortion of her lower limbs, pelvis, and spine with marked kyphoscoliosis, but her upper limbs were only slightly bowed (Fig. 1).



FIG. 1.—Radiograph of patient.

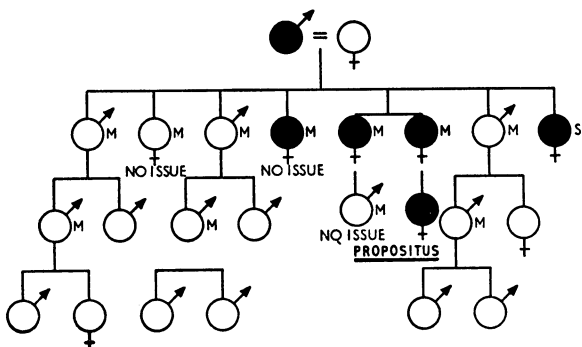


FIG. 2.—Patient's family tree. M=married, S=single.

She had never walked, but moved around either in a wheelchair or on a small stool fitted with rockers which she "worked" along. She was of normal intelligence and with no apparent inferiority complex. She had been married for 15 months and her husband was of normal physique and 5 ft. 7½ in. (169 cm.) in height.

The cause of the dwarfism was osteogenesis imperfecta. The first affected member of her family had been her maternal grandfather, and the disorder had shown itself in Mendelian dominant fashion in four of his eight children, including the patient's mother and the latter's twin sister (Fig. 2). But the patient herself was the only affected grandchild or great-grandchild. None of the affected members of the family exhibited blue sclerotics or otosclerosis.

The patient's pelvic cavity was so very small that the upper border of the 15-weeks-pregnant uterus was well above the umbilicus (Fig. 3). There was little room for it to extend further upwards,

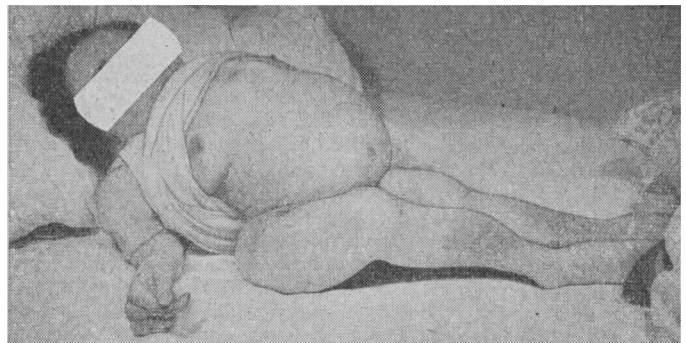


FIG. 3.—Photograph of patient, demonstrating upper border of uterus well above umbilicus at 15 weeks.

for the distance from xiphisternum to symphysis pubis was only 8 in. (20 cm.).

Her weight was 2 st. 12½ lb. (18.5 kg.); blood-pressure, 120/90 mm. Hg; E.C.G., normal but low voltage; vital capacity, 500 ml.; blood urea, 22 mg./100 ml.; haemoglobin, 80%; serum calcium, 9.3 mg./100 ml.; serum inorganic phosphate, 3.4 mg./100 ml.

As will be seen from these facts the outstanding physiological feature of this case was the grossly restricted vital capacity of 500 ml. Because of this and because there is a considerable maternal mortality, usually from pulmonary hypertension and cardiac failure, associated with pregnancy in kyphoscoliotic patients of greater height than this woman (Berge, 1962; Jones, 1964; Schüssling, 1964) the pregnancy was terminated at the sixteenth week. Anterior hysterotomy and sterilization were carried out under general anaesthesia (by Dr. R. G. Snow), which was well tolerated.

The post-operative course was smooth and the patient soon returned to being a wife to her husband and a book-keeper to her father. The foetus removed at hysterotomy showed an extensive spina bifida and rachischisis.

The photograph (Fig. 3) was taken by Dr. D. A. P. Cooke, F.R.P.S.

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REFERENCES

Berge, J. E. (1962). *J. Obstet. Gynaec. Brit. Cwlth*, 69, 81.
 Jones, D. H. (1964). *Lancet*, 1, 517.
 Schüssling, G. (1964). *Zbl. Gynäk.*, 86, 425.