who complained of discomfort or pain or who had to be taken out of the trial is shown in table v.

Again, groups 1 and 2, who were receiving stilbœstrol, show clear superiority over groups 3 and 4, who received only diuretic or placebo. Discomfort was at its height by the third day and continued unabated on the fourth day, after the course of treatment had finished.

Discussion

Investigations such as this one which depend on the reports of a multiplicity of observers and on the subjective as well as objective responses of a group of patients liable to be in a temporary state of emotional instability must always to some extent be suspect in point of reliability. The double-blind scheme at the least excludes the effects of prejudice and personal bias in the observer; the form that had to be filled in required the nurse to inspect and palpate the breasts as well as to listen to the patient's complaints. Some care was taken to exclude unreliable observations, and about a third more patients were started in each group than were included in the trial. The intention was to collect 100 patients in each group, but the trends were immediately obvious when interim checks were made, and by the time 50 or so patients had accumulated in each group, there seemed no justification for prolonging the sometimes severe discomfort experienced by the patients not receiving stilbœstrol. In addition, the use of œstrogens for this purpose may really be said to be generally accepted. Bendrofluazide was included in the trial because it appeared as the modern equivalent of purging and restricting fluids, and because of reports (Healy 1961, Stout 1962) that it was by itself actually superior in many ways to stilbœstrol. This was not our experience and the use of diuretics is not supported by any significant improvement in results. It does seem that, if diuretics are given, the dosage should be reduced gradually and not stopped abruptly.

Conclusion

A 12% failure-rate obtained in the present trial with stilbœstrol as against a rate of 65% without it support a general clinical impression of the efficacy of stilbœstrol which is difficult to reject.

I should like to thank all the nurses at the Rankin Memorial Hospital who helped to carry out this trial.

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"... The public will recollect that Mr. Abernethy, in December last, applied to the Court of Chancery for an Injunction to restrain the publication of his lectures in this work. The Lord Chancellor very properly, as we conceive, refused the application, but it appears that Mr. Abernethy's notion of law is that it can alter the past as well as the future. He may possibly have vanity enough to suppose that we shall *reprint* his lectures. On this point his mind may be perfectly at ease; our pages have been already obscured with his hypothetical nonsense during six tedious months, and when we read the proof of the last paragraph we felt relieved, as we formerly stated, of a most intolerable *incubus*."—*Lancet*, May 28, 1825, p. 225.

PUERPERAL THROMBOEMBOLISM AND SUPPRESSION OF LACTATION

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Summary The effect of suppression of lactation on the development of puerperal thromboembolism has been examined in 9324 women delivered in Cardiff in 1965 and 1966 who suffered 44 episodes. The incidence of thromboembolism was influenced by the age and parity of the mother, but even when allowance is made for these factors there was still a significantly higher incidence in the patients who had had lactation suppressed, There was a tenfold increase in low-parity women aged 25 and older who were not lactating compared with those who were. All 8 cases of pulmonary embolism were in women who were not lactating.

Introduction

PULMONARY embolism is now second only to abortion as a cause of death in obstetrics in this country (Ministry of Health 1966). Moreover, there is no evidence that its incidence is decreasing. Surveys by the Medical Research Council, the Royal College of General Practitioners, and the Committee on Safety of Drugs—reviewed by the *British Medical Journal* (1967)—have confirmed that the administration of œstrogen and progestogen mixtures for contraceptive purposes increases the risk of thromboembolism.

In the U.K. breast-feeding is now the exception rather than the rule, and œstrogens are widely used to suppress lactation. Other factors might influence the incidence of thromboembolism, but we decided to investigate the possible relation between the suppression of lactation and puerperal thromboembolism.

Method

The Cardiff Birth Survey provides information about every birth in the city. The record is completed within three weeks of delivery, and care is taken to ensure that later puerperal complications are added.

The incidence of thromboembolism was studied in all mothers delivered of a single child in 1965 and 1966, and the records of patients who developed the complication were scrutinised. Twin deliveries were excluded since lactation was almost always suppressed.

The patients were classed as breast-feeding at seven days (lactating) or not breast-feeding at seven days (including mothers of stillborn infants and non-lactating mothers of infants who died in the neonatal period). They were also divided into parity groups, into two age-groups under and over 25 years, and into normal and other type of delivery.

The exact method of suppression of lactation was not recorded for all cases but in all the women with a thromboembolus investigated diethylstilbœstrol was used in doses ranging from 30–60 mg. daily for three days followed by 20–30 mg. daily for the next three days and 20 mg. daily for a final three days. This is the usual method used to suppress lactation in all Cardiff hospitals.

Thromboembolism is difficult to define and diagnose but for

the purposes of this study it has been defined as any case of pulmonary embolism or deep-vein thrombosis which showed signs definite enough to require the administration of anti-coagulants.

Results

In the two years, there were 9324 single deliveries, and of these only in 33 cases was the method of feeding at seven days not noted. Of the total, 3064 (33%) mothers were lactating and 6227 (67%) were not: 3049 (33%) were nulliparous, 4363 (47%) were of parity 1 or 2, and 1879 (20%) were of parity 3 or above. Spontaneous vaginal delivery occurred in 8198 (88%); assisted vaginal delivery in 728 (8%); and delivery by Cæsarean section in 368 (4%).

The pattern of feeding at the seventh day after delivery is shown in table I. Mothers of higher parity are less likely to breast feed than those of lower parity. Within parity groups, older mothers are more likely to breast feed than younger mothers. Cæsarean section and assisted vaginal delivery slightly reduces the incidence of breast-feeding.

The 44 cases of thromboembolism gave an incidence of

TABLE I—NUMBER OF MOTHERS AND PERCENTAGE LACTATING AT 7 DAYS

—	No. (and % lactating) of mothers of parity:			
	0	1 and 2	⩾3	All
Delivery:				
Normal ..	2392 (42%)	4058 (30%)	1748 (30%)	8198 (33%)
Assisted ..	657 (37%)	305 (25%)	131 (15%)	1093 (31%)
Age:				
<25	2247 (39%)	1827 (24%)	186 (21%)	4260 (32%)
⩾25	802 (46%)	2536 (33%)	1693 (30%)	5031 (34%)
Total	3049 (41%)	4364 (29%)	1879 (29%)	9291 (33%)

4·7 per 1000 single deliveries. In lactating women there were 7 cases in 3064 deliveries (2·3 per 1000) whereas in non-lactating women there were 37 cases out of 6227 (5·9 per 1000). 8 of the 44 cases (18%) were pulmonary emboli and in 5 of these there were no signs in the legs. 1 mother died. All the pulmonary emboli developed in women who were not lactating. Table II shows the incidence of thromboembolism per 1000 single deliveries in both lactating and non-lactating women for the three parity groups. The 2517 mothers of parity 0, 1, and 2 who were lactating had 3 cases of thromboembolism (1·2 per 1000), whilst the 4895 women of similar parities who were not lactating had 25 cases of thromboembolism (5·1 per 1000)—a fourfold increase.

Those mothers who required obstetrical intervention either by means of assisted delivery or by Cæsarean section were at increased risk of thromboembolism; 8198 normal deliveries gave a rate of 4·3 per 1000 and 1093 other deliveries 8·2 per 1000. But in both types of delivery there was an increased risk with suppression of lactation (table III).

The age of the mother is important. Of 4260 mothers under 25 years of age, only 9 had thrombosis (2·1 per 1000) while of 5031 mothers of 25 years and over, 35 had thrombosis (7·0 per 1000). There is an interaction between age, parity, method of feeding, and incidence of thrombo-

TABLE II—INCIDENCE THROMBOEMBOLISM

—	Incidence (per 1000 births) in mothers of parity:			
	0	1 and 2	⩾3	All
Lactating ..	1·6	0·8	7·3	2·3
Not lactating ..	5·0	5·2	9·0	5·9
Total ..	3·6	3·9	8·5	4·7

TABLE III—VARIATIONS IN INCIDENCE OF THROMBOEMBOLISM WITH TYPE OF DELIVERY, PARITY, AND FEEDING

—	Incidence (per 1000 births) in mothers of parity:			
	0	1 and 2	⩾3	All
Normal delivery:				
Lactating ..	2·0	0·8	7·6	2·6
Not lactating	4·3	4·5	7·4	5·1
Total ..	3·3	3·4	7·4	4·3
Assisted delivery:				
Lactating ..	(0)	(0)	(0)	(0)
Not lactating	(7·2)	(12·2)	(27·3)	12·0
Total ..	4·6	(9·8)	(22·9)	8·2

Figures in parentheses based on fewer than 500 deliveries.

embolism. Table IV attempts to distinguish these effects separately. It shows that if a mother is under 25 years of age, she is at a low risk of developing thromboembolism, and that this risk is not appreciably affected either by increased parity or suppression of lactation. However, if a mother is 25 or over, there is an increased risk both with higher parity and with suppression of lactation. There were 1201 lactating mothers of 25 years and older of parities 0, 1, and 2 who had one thrombosis (0·8 per 1000) whereas 2137 mothers aged 25 and older who were not lactating and were of similar parity had nineteen thromboses (8·9 per 1000). This is a tenfold difference. In mothers who were in their fourth puerperium or more and who were over 25 years of age the incidence of thromboembolism after lactation was 5·9 per 1000 whereas after suppression of lactation it was 10·1 per 1000, almost double. The probability that results happened by chance in the incidence of thromboembolism is less than 0·001 if there were no difference between the lactating groups of mothers over 25 years of age.

Other factors such as previous medical history including previous thromboembolism, days in hospital before delivery, weight, anæmia, social class, length of labour,

TABLE IV—VARIATIONS IN INCIDENCE OF THROMBOEMBOLISM WITH AGE, PARITY, AND FEEDING

—	Incidence (per 1000 births) in mothers of parity:			
	0	1 and 2	⩾3	All
Mothers under 25:				
Lactating ..	2·3	(0)	(25·6)	2·2
Not lactating ..	2·9	1·4	(0)	2·1
All	2·7	1·1	(5·4)	2·1
Mothers of 25 and over:				
Lactating	(0)	1·2	5·9	2·3
Not lactating ..	11·5	8·2	10·1	9·3
All	6·2	5·9	8·9	7·0

Figures in parentheses based on fewer than 500 deliveries.

and third-stage and other puerperal complications and were not relevant. In 4 cases, however, there were factors predisposing to thromboembolism. In 3 of the women who were not lactating, 1 had biliary peritonitis, another had a venous cut-down on the leg, and the third had a puerperal tubal ligation. 1 who was lactating had a puerperal tubal ligation. These 4 cases have been included in all the statistical analyses, but their exclusion would not alter the main conclusions.

Discussion

The results suggest that the inhibition of lactation by the administration of diethylstilbœstrol significantly increases the risk of thromboembolism in the puerperium, and show that in mothers of parities 0, 1, and 2 the risk

is increased fourfold, and the increase is tenfold in those mothers who are 25 years and older. Parity has an effect which is separate from the effect of suppression of lactation, but is not striking until parity 3 and above. Mothers under 25 years of age have a low risk of thromboembolism, and this is not increased by suppression of lactation. The effect of parity at this age cannot be judged on our figures as the number of women of high parity under 25 years old are too small.

Assisted delivery and cæsarean section also increase the risk of thromboembolism. After cæsarean section no lactating mother developed thromboembolism, whilst 7 developed this after the operation in cases where lactation was suppressed.

The incidence of venous thrombosis in the puerperium was 4·7 per 1000 single deliveries which is comparable to that reported by Ullery (1954) and Parker et al. (1957) but lower than that shown by Bauer (1946).

The ætiology of thromboembolism remains uncertain. Many factors may be involved, including changes in the vein wall, in the pattern of venous blood-flow, in platelets, and in coagulation mechanisms and in the fibrinolytic system. In the puerperium, changes in all these factors have been described (Wright 1942, Biezenski and Moore 1958, Gillman et al. 1959, McCausland et al. 1961, Nagayama et al. 1965, Shaper et al. 1965, Goodrich and Wood 1966, Poller and Thomson 1966, Shaper et al. 1966). Furthermore there is experimental evidence that œstrogens can influence these factors (Reynolds and Foster 1940, Tagnon et al. 1955, Johnson et al. 1957, Gillman et al. 1959, Phillips et al. 1959, Berkarda et al. 1965, Nagayama et al. 1965, Musiatowicz 1966, Poller and Thomson 1966). It may be that œstrogen administration, by accentuating the natural puerperal changes, increases the incidence of venous thrombosis.

The use of diethylstilbœstrol to suppress lactation requires review, particularly when it has been shown that it is associated with recurrence of lactation in 70% of cases and with prolonged lochial discharge. If no œstrogens are given to suppress lactation there is little more discomfort than if œstrogens are used, and no recurrence of lactation (Auld 1967).

The relation between œstrogen therapy and puerperal thromboembolism is being further investigated statistically in a larger series. Laboratory work is in progress on the effects of œstrogens in various doses on factors which may predispose to the development of thromboembolism.

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References continued at foot of next column

Hypothesis

CEREBRAL VULNERABILITY TO ISCHÆMIA

Summary The lipoprotein mozaic of the dendritic surface of cerebral neurones requires for its maintenance a continuous supply of adenosine triphosphate (A.T.P.) derived from oxidative metabolism. This A.T.P. is constantly being consumed at active sites in the cell membrane. Cerebral neurones which have the greatest relative surface area of all cells thus become rapidly depleted of A.T.P. when its synthesis is retarded by ischæmia. The unique vulnerability of cerebral neurones to ischæmia is thus seen as a consequence of their exceptionally extensive dendritic ramifications with vast areas of active lipoprotein membrane, which requires A.T.P. for its stabilisation. This view is supported by the relative insusceptibility to ischæmia and anoxia of cerebral neurones in newborn animals before the development of extensive dendritic branches. The immense area of dendritic lipoprotein surface at risk is also emphasised by the nature of remnants produced by disintegration of dendrites. After ischæmic necrosis of the cerebral cortex conspicuous lipoprotein granules persist in cerebral histiocytes which consume the dead neurones and their dendrites; this lipoprotein may be a resistant remnant formed by disarray of the extensive dendritic membranes.

INTRODUCTION

CEREBRAL neurones are exceptionally vulnerable to ischæmia. Not only is their activity rapidly interrupted by ischæmia but also they are killed by relatively short periods of ischæmia which leave other cells unharmed. Thus arrest of blood-supply for as short a time as 1 or 2 minutes may be followed by irreversible injury.[1 2] Both loss of consciousness and irreversible neuronal damage are determined by diminution in the supply of free energy which is normally provided by oxidative metabolism in cerebral grey matter.[3 4] During ischæmia, anaerobic glycolysis can provide only a temporary and inefficient substitute [4] for aerobic oxidation in replenishing the cellular reserves of adenosine triphosphate (A.T.P.); consequently the concentration of A.T.P. falls to low levels [5] in ischæmic brain. The question then arises how lack of A.T.P. can cause irreversible injury to the cell and why this happens so much more rapidly in cerebral neurones than in other cells. These problems are especially urgent now that, with the advent of cardiac and respiratory resuscitation, it has

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