

and in this group there is a foetal mortality of 5%. This means that foetal distress due to post-maturity may lead to four caesarean sections in 1,000 confinements, a figure which has been exceeded by several of the writers who advocate surgical induction of labour as the treatment of choice.

Summary

Case reports were obtained from 5,000 patients by means of a personal interview during the first week of the puerperium. These reports showed that in 53.1% of single vertex presentations labour began spontaneously during the 40th or 41st week of pregnancy. In 7.4% the pregnancy was prolonged for more than 14 days after the estimated date of confinement. There was no relationship between the length of the menstrual cycle and the duration of pregnancy, providing that the cycle was not unduly prolonged. There was an increase of foetal mortality to 5.1% if pregnancy was prolonged for more than 14 days after the estimated date of confinement. It is suggested that this mortality resulted from foetal anoxia *in utero*. By reference to a series of 564 stillbirths this foetal anoxia was mainly a risk occurring during the first and second stages of labour. Induction of labour did not appear to be the best means of combating this risk. A policy of "masterly inactivity" is advocated until labour starts spontaneously. Then the strictest watch for foetal distress is indicated, with resort to caesarean section at once in cases in which it occurs.

I am indebted to the honorary medical staffs of the Jubilee and Royal Maternity Hospitals, Belfast, for permission to interview their patients. I wish to acknowledge the encouragement and help which Professor C. H. G. Macafee has given me throughout this work.

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The United Nations is to publish an unabridged record of the International Conference on the Peaceful Uses of Atomic Energy, held at Geneva last month, the Secretary-General has announced. The English language edition will be ready early in 1956. Orders may be placed with any United Nations publications sales agent. The prepublication price for the full series of 16 volumes is £39. Mimeographed copies of most of the individual papers may be ordered through Her Majesty's Stationery Office at 1s. 9d. each.

FOETAL DEATHS FROM ANTENATAL ANTICOAGULANT THERAPY

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The incidence of thrombophlebitis in pregnancy is exceedingly low. Hallum and Newham (1951) reported only five cases of this condition in 13,144 deliveries—an incidence of 0.037%. F. J. Browne (quoted by Donaldson, 1950) saw only three cases in 10 years—an incidence of about 0.025%. Other published figures give an incidence of from 0.000001 to 0.1% (Westmann, 1936). Since, however, considerable success has accompanied the use of anticoagulants in general thrombotic disease and especially in post-partum thrombophlebitis (Davis and Porter, 1944; Barnes and Ervin, 1946; Stallworthy, 1954), their use in the ante-partum variety will inevitably have to be considered whenever a case is encountered.

In spite of experimental data which indicated that damage to the foetus might result from the use of anticoagulants in pregnancy (Quick, 1946) and evidence that foetal haemorrhage occurs in cattle who eat spoiled sweet clover (Schofield, 1924; Roderick and Schalk, 1931), there have been reports of the successful use of anticoagulants in pregnant women (Mansell, 1952; H. P. Wright, 1951; I. S. Wright, 1951). These authors think that there are good reasons for their use so long as adequate control of the prothrombin index is undertaken.

The following case records are reported to indicate that foetal catastrophes may occur even when the maternal prothrombin times are apparently controlled.

Case Histories

The mother was aged 39. Her last menstrual period was on January 11, 1952. The expected date of delivery was October 18, and the actual date October 17. She had had rheumatic fever at 6 years and scarlet fever at 10. She had had three previous pregnancies: (1) 1934, full-term normal delivery, 6 lb. 12 oz. (3.1 kg.), well. (2) 1947, six weeks premature delivery, 4 lb. 4 oz. (1.9 kg.), well. (3) 1949, miscarriage at three months.

During the early months of the present pregnancy there was a marked increase in the varicosity of her leg veins, and on July 14, 1952, she was admitted to hospital because of severe varicose eczema of the left leg. This responded satisfactorily to rest in bed and Lassar's paste. A twin pregnancy was diagnosed at this stage.

Although the varicose veins remained quite prominent the eczema stayed under control, but on October 2 she presented with all the signs of a deep femoral thrombosis of the left leg. She was promptly readmitted to hospital. Treatment included ethyl biscoumacetate 200 mg. immediately, followed by 100 mg. twice daily. On October 4 the dosage was increased to 100 mg. eight-hourly, and this amount was continued until October 9, when, because of macroscopic haematuria, the drug was stopped. The prothrombin time was measured daily by the one-stage method of Quick, and the Table shows the results up to, and after, the cessation of treatment.

On October 16 spontaneous labour started, and after a first stage of 4 hours 50 minutes and a second stage of 1

hour she was delivered of the first boy spontaneously. This was a vertex delivery, but the child was stillborn. The birth weight was 7 lb. 4 oz. (3.3 kg.) and he was noticed to have

Date	Control	Patient	Prothrombin Index
3/10/52	25 secs.	20 secs.	80%
4/10/52	15 "	15 "	100%
5/10/52	22 "	32 "	70%
6/10/52	10 "	20 "	50%
7/10/52	15 "	25 "	60%
8/10/52	15 "	30 "	50%
9/10/52	15 "	30 "	50%
10/10/52	16 "	35 "	46%
11/10/52	15 "	28 "	53%
12/10/52	15 "	20 "	75%

a large head. Thirteen minutes later the second boy was born. The breech presented, but there was no difficulty with the aftercoming head. This child weighed 6 lb. 10 oz. (3 kg.). He was asphyxiated at birth and responded poorly to resuscitation.

Further History of Twin 2

Two hours after delivery he had a brisk haemorrhage from the cord. An extra ligature was applied and vitamin K, 10 mg. six-hourly subcutaneously, was prescribed. At this stage a "blood blister" was observed on his upper lip that had not been present at birth. Although his haemoglobin level after this haemorrhage was found to be 114% his condition never became satisfactory. He became even more feeble, with an irritable, high-pitched cry, and he refused most of the fluids offered him. In addition to the haemorrhagic blister on his lip he developed an apparently spontaneous ecchymosis on the anterior chest wall. At 3 days of age the skull circumference was 14½ in. (37 cm.) and the sutures were markedly separated. X-ray examination of the skull showed marked "starting of the sutures," and in the original films there appeared to be some flakes of calcium present. This could not, however, be shown in further films, and its significance is therefore doubtful. Ventricular puncture revealed the presence of dark-red, heavily blood-stained C.S.F. It was clear that there had been extensive intracranial haemorrhage, and the nature of the C.S.F. indicated that this had probably occurred before birth, since the fluid at 3 days of age already appeared to be "old."

The child's general condition continued to be poor and the hydrocephalus increased. By the age of 13 days the head circumference was 18½ in. (47.6 cm.). He took feeds badly and gradually lost weight, being a miserable marasmic infant when he died on November 21 at the age of 35 days.

Post-Mortem Reports (Dr. D. E. Price)

Twin 1 (Stillborn).—A little haemorrhagic fluid was present in the nose and mouth. Central nervous system: The right side of the brain was covered by extensive blood clot; the falx cerebri and the tentorium appeared intact; the precise origin of the haemorrhage could not be made out. Cardiovascular system: The pericardium was distended by blood-stained fluid and blood clot; the heart valves and muscle were normal, as were the aorta and other great vessels. Gastro-intestinal system: The stomach contained about 1 oz. (28 ml.) of blood, otherwise there was no abnormality. Testes: Both were surrounded by a blood clot, and extensive haemorrhage into the testicular tissues was present. Lungs: Completely atelectatic, and sank in water. Other systems: No abnormality noted.

Twin 2.—An emaciated male child with marked hydrocephalus. Central nervous system: Extensive internal hydrocephalus; large amount of organizing blood clot at the base of the brain. Lungs: Patchy peribronchial consolidation of the lungs; also pale areas of consolidation pyramidal in shape, with the base towards the pleura; no pleural effusion or adhesions. Other systems: No abnormality noted. Microscopic examination confirmed that the tissue surrounding the base of the brain was organizing blood clot. No calcium deposits were seen microscopically.

Discussion

We believe that both twins died as a result of the anticoagulant therapy given to the mother. There is no doubt that they died of generalized haemorrhages which occurred before birth, and there is no known natural disease which presents in this way. So-called "haemorrhagic disease of the newborn" does not demonstrate itself until after birth. Cerebral haemorrhage of the kind found in the second twin can occur spontaneously, but usually it occurs after a difficult delivery; so far as the first is concerned there seems to be no other explanation of the very widespread bleeding other than the therapy given to the mother. Unfortunately in neither case was a prothrombin time obtained, since the first twin was stillborn and the second twin had already received vitamin K as an emergency measure.

In a survey of the literature we have been able to find only two similar cases. Sachs and Labate (1949) described the case of a woman, seven months pregnant, who had deep femoral thrombosis with multiple pulmonary emboli. She was so improved by the initial dicoumarol therapy that they decided to keep her on it until she was delivered. In spite of keeping her prothrombin time at "about 30 seconds" she had one further, non-fatal, embolism. Twenty days before delivery the foetal heart became inaudible, and eventually she produced, at term, a stillborn macerated foetus. The mother survived. Necropsy on the foetus revealed massive generalized haemorrhages, including a haemopericardium. A similar case was reported by v. Sydow (1947) in which dicoumarol was given for a month and was stopped only two days before delivery, when the prothrombin index (P.I.) was 33% of normal. The baby was born uneventfully but a few hours later developed extensive subcutaneous haemorrhages, and its P.I. was found to be less than 10% of normal. In spite of vitamin K it developed a massive intracranial haemorrhage with subsequent hydrocephalus somewhat similar to that in our second twin.

The fact that anticoagulants could cause haemorrhagic manifestations in the offspring of experimental animals was shown early on by several workers (Field, 1945; Quick, 1946; Kraus *et al.*, 1949), and on the basis of their animal experiments these authors condemned the use of anticoagulants in pregnant women. In spite of this, however, there were a considerable number of reports of their successful use in either single cases or small series (Felder, 1949; Weiss and Turner, 1949; Adamson *et al.*, 1950; Davis, 1951; Thornton, 1951; H. P. Wright, 1951; I. S. Wright, 1951; Mansell, 1952). Most of these authors believe that the danger to the mother may be so great that even in uncomplicated thrombosis the use of anticoagulants is justified. They assert that if the P.I. is properly "controlled" the danger to the foetus is negligible. Most of them recommend that the P.I. should be kept at about 30% of normal. H. P. Wright (1951), however, does extend the warning that anticoagulants should not be used in the "last few days" of pregnancy; and a more recent warning is issued by I. S. Wright *et al.* (1954), who say that their use is contra-indicated "in late pregnancy." With this we would heartily agree.

There seems no reason to believe that inaccurate estimations of the P.I. may have played a part in the fatal outcome in our cases. Anticoagulant therapy always carries with it a risk of haemorrhage, and this applies to every substance so far in general use. I. S. Wright *et al.* (1954) reported haemorrhagic incidents in 13% of patients being treated for myocardial infarction by means of anticoagulants. The fact that haemorrhage can occur in the presence of a normal (or only slightly reduced) P.I. is well known, and would appear to be partly explained by Donald *et al.* (1954), who have shown that in certain people the prothrombin, as estimated by the two-stage method of Biggs and Douglas (1953), may be considerably reduced, while by the ordinary one-stage method of Quick it may be only slightly reduced. In these

cases bleeding occurs because of a reduction in true prothrombin, whereas in most cases of haemorrhage due to anticoagulants the bleeding occurs because of depression of Factor VII.

In the case which we describe here the prothrombin time was estimated by the one-stage method of Quick, and it is possible that the maternal and foetal bleeding was due to true prothrombin depression in both. Whatever the anticoagulant employed, however, and whatever method is used to estimate the effect, we shall never be sure that the effect on the foetus is the same as on the mother. It will obviously be safer in the future, if anticoagulant therapy must be used, to rely on both the one-stage and the two-stage methods of estimation, although the one-stage method is still considered to be the best for routine use (Biggs and Douglas, 1953; Donald *et al.*, 1954; Hunter and Walker, 1954).

In order to determine what place anticoagulants should play in the treatment of antenatal thrombophlebitis it is essential to know what is the risk to the mother if they are not given. The incidence of the condition is so low that it is impossible to assess the dangers from such small series as those of Donaldson (1950) and Mansell (1952). One has therefore to turn to thrombophlebitis in general and draw conclusions on what is likely to happen in pregnancy. In several large series mentioned by I. S. Wright (1951), in which the thrombophlebitis was post-operative, the incidence of pulmonary embolism in the diagnosed cases was 50%: where one pulmonary embolism had occurred the incidence of a further, fatal, embolism was 20% (the diagnosis of pulmonary embolism does, however, depend to a great extent on the enthusiasm expended on its detection). In the obstetric cases, most of which must have been post-partum, the incidence of pulmonary embolism in cases diagnosed as having thrombophlebitis was 19-36% and the incidence of a further, fatal, embolism was only 5%. If, in addition, one takes into account Ochsner's differentiation between phlebothrombosis and thrombophlebitis and considers that the latter is by far the commoner in pregnancy and less apt to cause embolism (Ochsner, 1951), it would appear likely that the incidence of fatal pulmonary embolism in antenatal thrombophlebitis, untreated by anticoagulants, is well below 1%. It should be noted, however, that the danger to life is greatly increased after the first embolism has occurred, and also that in about 50% of cases of fatal pulmonary embolism there are no preceding signs of thrombophlebitis (Allen, 1946; Ochsner *et al.*, 1950).

It would appear to us that the danger to the life of a woman with antenatal thrombophlebitis is not sufficiently great to warrant the use of the present anticoagulants as a routine. They should not be used in the last four weeks of pregnancy if at all possible, but if a pregnant woman is having multiple pulmonary emboli then the risk to the foetus will have to be taken and anticoagulants given. Under these circumstances the laboratory control of therapy should be by both the one-stage and the two-stage methods.

Summary

Twin boys of a woman who had received anticoagulant therapy antenatally both died of haemorrhage. It is believed that the foetal haemorrhages resulted from the treatment given to the mother.

Since the risk to the mother from antenatal femoral thrombosis is so small it is recommended that anticoagulant therapy should not be given unless one pulmonary embolism has occurred. This applies especially to the last four weeks of pregnancy.

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Medical Memoranda

Penicillin Anaphylactoid Shock Successfully Treated with Adrenaline

The following cases have occurred within my practice during the period May 12, 1953, to August 8, 1955.

Case 1.—A man aged 75 was suffering from bronchial cancer, although at the time he was thought to have only bronchitis, for which condition a course of injections of crystalline penicillin had been given a year previously, without signs of intolerance. On May 12, 1953, one mega unit of crystalline penicillin was injected into the deltoid muscle. The patient at once complained of severe pain at the site of injection, became pale, sweated, and within a minute his breathing had become stertorous and his colour greyish. Two minutes later he was incapable of speech and pulseless. Adrenaline was now available, and 4 minims (0.24 ml.) of adrenaline 1:1,000 was injected subcutaneously. Within fifteen seconds his breathing had improved; in a quarter of an hour he was pale but could speak easily.

Case 2.—A man aged 30-35, a temporary resident, had a dental abscess and a very heavy purulent post-nasal discharge. His temperature was 101.2° F. (38.4° C.). He stated that he had never been treated with penicillin in any form. On June 27, 1953, having adrenaline ready for immediate use, I injected one mega unit of crystalline penicillin into the deltoid. The patient collapsed almost at once, becoming limp, blanched, and pulseless within half a minute. He was immediately given 4 minims (0.24 ml.) of adrenaline 1:1,000, and he responded by movement within ten seconds. Injections of 1 minim (0.06 ml.) at intervals of a minute were given for a further five minutes. He spoke naturally after a quarter of an hour. My impression at the time was that, had the adrenaline injection been delayed for perhaps two minutes, the patient might well have died.

Case 3.—A man aged 25-35, a temporary resident, was suffering from an early quinsy. On September 14, 1954, one mega unit of crystalline penicillin was injected into the deltoid, and within a minute he became pale and sweating, the pulse was weak, and he complained of pain at the site of injection. Adrenaline was given and the patient recovered sufficiently to leave the surgery in about a quarter of an hour.

Case 4.—A girl aged 14 had a septic foot. Her mother stated that she had never had an injection of penicillin but that she had been given penicillin lozenges on one occasion without untoward reaction. On August 8, 1955, after one mega unit of crystalline penicillin had been injected into the deltoid, the girl blanched rapidly, sweated, and her pulse