Fatal Brain Damage Associated with Cardiomyopathy of Pregnancy, with Notes on Caesarean Section in a Hyperbaric Chamber

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Summary: Three weeks after admission to a maternity hospital for observation following minor antepartum haemorrhage, a primiparous patient aged 22 suffered a sudden left hemiplegia and became comatose. Congestive cardiac failure ensued and because of the subsequent severe hypoxaemia she was transferred to the hyperbaric oxygen unit at the Western Infirmary, Glasgow, where it was found possible to improve her condition by means of oxygen at increased pressure. A caesarean section was successfully performed in the hyperbaric chamber, and a normal live female infant was delivered. Though the patient's general condition improved she never regained consciousness and died almost three months later. Necropsy confirmed the clinical diagnosis of cardiomyopathy of pregnancy with severe ischaemic changes in the brain.

Introduction

Cardiomyopathy of pregnancy is a relatively uncommon and frequently fatal condition. The following case presented some unusual features.

Case Report

On 26 December 1966 a 22-year-old primipara in the 37th week of pregnancy was admitted to a maternity hospital for observation because of minor antepartum haemorrhage. There was no record of any illness before her pregnancy, and until the time of her admission she had been in good health. On admission clinical examination was negative, her pulse rate being 84 per minute and blood pressure 110/70 mm. Hg.

She was kept under observation for three weeks, during which no alteration occurred in her condition, until suddenly, while in bed at 6.50 p.m. on 16 January 1967, she complained of tingling and pins-and-needles in her left limb and abruptly became unconscious and cyanosed with stertorous respiration. Within minutes

the pulse rate was 140 and the blood pressure 150/100. Neurological examination revealed an unconscious patient with left-sided hemiplegia, the right pupil being larger than the left.

To eliminate the possibility of intracranial haemorrhage or occlusion of a major artery which might be amenable to surgery, emergency transfer was arranged to the Institute of Neurological Sciences (Killearn Hospital). A right carotid angiogram showed no abnormality. The lumbar cerebrospinal fluid was clear though the protein level was 240 mg./100 ml. The diagnosis therefore remained in serious doubt.

By the following morning (17 January) the patient's general condition had deteriorated, the most clamant features being hyper-ventilation and gross cyanosis. There was a persistent tachycardia (120 per minute), and the blood pressure was 135/100. The arterial blood gas values while the patient breathed air were: pH 7.330 units; PCO_2 32 mm. Hg; base excess -8 mEq/l.; PO_2 48 mm. Hg. After the administration of 100 mEq of sodium bicarbonate a slight improvement in her condition was noted, and spontaneous movements of the left side were observed. Oxygenation of the patient, however, continued to be a source of anxiety, and during the subsequent administration of 100% oxygen the arterial oxygen tension was found to be only 50 mm. Hg. A chest radiograph showed a severe degree of pulmonary oedema with enlargement of the heart. On the afternoon of 17 January—that is, 24 hours after the initial collapse—the patient was transferred to the hyperbaric oxygen unit of the Western Infirmary for further assessment and therapy.

On her admission the blood pressure, which had been 100/80 before she left the neurosurgical centre, had fallen to 95/60, and the pulse rate was 144. The heart was clinically enlarged, and there was triple rhythm. No murmurs were noted. Clinical examination of the lungs showed widespread crepitations, and the jugular venous pressure was raised. An initial electrocardiogram (lead II only) showed sinus tachycardia. Blood gas values while the patient breathed 100% oxygen are shown in Table I.

Among other possible manoeuvres to relieve the patient's hypoxia, the question of early caesarean section was raised at this stage. There was, however, little evidence of foetal distress, nor were there any acute obstetrical indications for the procedure. Obstetrical opinion favoured at least some delay in the hope that continued oxygenation at normal pressure with relief of metabolic acidosis might improve the patient's condition without the necessity for operative intervention. The blood gas values two hours later with the patient breathing oxygen spontaneously are given in Table I. An electrocardiogram showed changes consistent with widespread anterolateral ischaemia (Fig. 2). Because of the marginal nature of the improvement which had taken place in the patient's condition with 100% oxygen at normal pressure, and because of the onset now

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TABLE I.—Arterial Blood Gas Values during Period of Acute Resuscitation

Hours after Admission to Western Infirmary, Glasgow	pH (Units)	PCO ₂ (mm. Hg)	Base Excess (mEq/l.)	PO ₂ (mm. Hg)	Ventilation	Inspired Oxygen (%)	Comments
0	7.255	43	-9	75	Spontaneous	100	On admission
2	7.405	45	+3	61	Spontaneous	100	After bicarbonate
4	7.160	65	-8	69	Spontaneous	100	After convulsions
Compression							
6	7.455	47	+8	310	I.P.P.V.	103	At 2 atmospheres absolute
7	7.500	43	+9	490	I.P.P.V.	103	
Decompression							
9	7.550	35	+8	121	I.P.P.V.	103	Normal pressure

I.P.P.V. = Intermittent positive-pressure ventilation.

of foetal distress (the foetal heart rate had risen to approximately 200 per minute and was irregular), it was decided to assess the effect of oxygen administration at 2 atmospheres absolute.

FIG. 1.—Electrocardiogram taken during period of hypoxaemia, showing evidence of widespread anterolateral ischaemia.

Before compression started, however, the patient began to have generalized convulsions, which became continuous within minutes, and her general condition deteriorated until death was thought to be imminent. Curare was administered intravenously and positive-pressure ventilation begun, which brought the convulsions under control. The blood gas values after this episode, at four hours, are given in Table I. Ventilation with 100% oxygen and administration of bicarbonate promptly corrected the respiratory and metabolic acidoses, but the arterial oxygen tension remained unchanged at 70 mm. Hg. Over the next 20 minutes the blood pressure rose to 90/60, though gross peripheral vasoconstriction was present and the pulse rate was 166.

Following compression to 2 atmospheres absolute there was a marked improvement in the patient's condition: the blood pressure rose to 100/70 mm. Hg and the periphery became warm and pink. The blood gas values shortly after reaching the increased pressure are given in Table I. The foetal heart rate, which had been 220 and irregular immediately before compression, fell to 165 and became regular. Caesarean section was now performed (Professor I. Donald, University Department of Obstetrics and Gynaecology), and proceeded remarkably smoothly, though it was noted that the uterus remained slight cyanosed in spite of the high maternal arterial oxygen tension. A normal live female child was born with an Apgar score of 9 (Apgar *et al.*, 1958).

After two hours at 2 atmospheres absolute the chamber was decompressed to normal pressure, ventilation of the patient being continued by means of an East Radcliffe ventilator with 100% oxygen. The maximum arterial oxygen tension at increased pressure was 490 (Table I): a few minutes after reaching normal pressure it was 121 mm. Hg (Table I). Phenytoin sodium and phenobarbitone were given as anticonvulsants; hydrocortisone and digoxin as non-specific therapy for cardiomyopathy. Mannitol was administered as prophylaxis against cerebral oedema.

Over the next few days the patient's general condition improved until, breathing air without added oxygen, she was able to remain well oxygenated. Her conscious level rose until she could grip to command with her right hand, but the left hemiplegia persisted. No further clinical improvement occurred, though serial electroencephalography showed resolution of the profound abnormalities seen in the early stages. She remained in this state of unconsciousness until her death two and a half months after admission.

During the period which succeeded the caesarean section attempts were made to clarify the primary diagnosis. Biparietal burr-holes

revealed normal intracranial pressure; a brain biopsy specimen was taken, the appearances being suggestive of recent ischaemic neuronal necrosis: viral studies on the biopsy fragments were negative. Enzyme studies on the blood were carried out (Table II). Evidence of continuing destruction of cells was present, the myocardium being especially incriminated in view of the continued raised levels of the heart-specific fraction of lactic dehydrogenase.

TABLE II.—Blood Enzyme Values Throughout Postpartum Period

Enzyme:	L.D.H. (mu./ml.)	L.D.H. (H.S.) (mu./ml.)	S.AsT. (Frankel Units)	S.AIT. (Frankel Units)	Aldolase (mu./ml.)	C.P.K. (mu./ml.)
Normal upper limits	195	70	40	40	6	1.0
Day:						
1			365	90		
3	474	195	185	22		
6	444	202	90	88		
8	390	181	80	85	4.1	
9	477	200	130	180	4.8	
12	328	166	105	125	3.6	0.64
13	328	155	90	100	3.1	0.53
14	312	141	105	125	2.5	0.42
16	220	135	80	125	2.7	0.64
19	314	121	125	260	4.3	0.32
22	264	—	96	188	2.3	0.53
26	248		49	108	2.1	
29	218		50	98	1.8	
37	394		85	136	2.2	
47	306		115	63	2.2	
55	194		120	112		
75	162		10	8	1.5	

L.D.H. = Lactic dehydrogenase. L.D.H. (H.S.) = Lactic dehydrogenase (heart specific fraction). S.AsT. = Serum aspartate aminotransferase. S.AIT. = Serum alanine aminotransferase. C.P.K. = Creatine phosphokinase.

Necropsy Report

Significant abnormalities were restricted to the cardiovascular and central nervous systems.

Cardiovascular System.—The heart (415 g.) was increased in its transverse diameter owing mainly to enlargement of the right ventricle. The valve cusps and the endocardium appeared normal, and there was no intramural thrombus. The coronary arteries, the aorta, and the major neck arteries were of entirely normal appearance. On section the myocardium was uniformly pale and rather waxy in appearance. Microscopical examination disclosed many lightly collagenized foci devoid of muscle fibres throughout the myocardium, but particularly in the subendocardial portion of the left ventricle. At the margins of these foci there were histiocytes and empty sarcolemmal envelopes. There was no diffuse inflammatory process, but there were very occasional small discrete foci of lymphocytes and eosinophil leucocytes.

Central Nervous System.—In the brain (1,320 g.) the only external abnormalities were small rather ill-defined bilateral depressions in the cortex of the frontal, parietal, and occipital lobes about 1–2 cm. lateral to the interhemispheric fissure. Coronal sections of the cerebrum after fixation showed that these depressions were due to bilateral essentially symmetrical bands in the boundary zone ("watershed") between the anterior and middle cerebral arterial territories where the cortex was shrunken, soft, and rather granular. In all of the many large sections examined microscopically the central part of each lesion had the appearance of old total infarction. These foci of total necrosis were continuous on either side, with a narrow zone of subtotal and often pseudolaminar neuronal loss beyond which the cortex was normal. The entire lesion was rarely more than about 1.5 cm. wide and affected the cortex on the gyral crests as well as within sulci (Fig. 2). Where infarction of the cortex was complete there was a narrow subcortical band of myelin loss.

No other naked-eye abnormalities were observed in the brain or spinal cord, but a full neurohistological study showed more widespread morbidity. On the inferior aspect of the left occipital lobe, in the boundary zone between the middle and posterior cerebral arterial territories, there were two large foci of subtotal neuronal loss in the cortex. In each insula and in the temporal gyri there was a mild laminar thinning of neurones. In Ammon's horns there was subtotal neuronal loss and gliosis in each endfolium and mild focal neuronal loss in the Sommer sectors. In the thalamus there was a profound bilateral loss of neurones in the dorsomedial nuclei and in the anterior and lateral complexes. There was also a

moderate neuronal loss in the corticomedial and central segments of the amygdaloid nuclei. In the cerebellum there was a considerable loss of Purkinje cells.

FIG. 2.—Diagrams of (a) posterior part of frontal lobes and (b) parietal lobes based on tracings made from large celloidin sections. The distribution of neuronal loss in the cortex is shown by the dotted areas. These lie in the boundary zones ("watersheds") between the anterior and middle cerebral arterial territories. Neuronal loss affects the full thickness of the cortex in the central part of each abnormal area but becomes subtotal on each side. The reduction in thickness of the cortex secondary to the ischaemic damage is not shown.

There was no naked-eye or microscopical evidence of vascular occlusion or of intrinsic arterial disease.

Discussion

This patient presented problems both in diagnosis and in management. There was clear evidence of abnormality in the brain and in the heart.

A diagnosis of cardiomyopathy of pregnancy was supported by the presence of an enlarged heart, triple rhythm, sinus tachycardia, and electrocardiographic abnormalities (Meadows, 1960); the blood enzyme disturbances were also consistent with this diagnosis. There was no clinical or electrocardiographic support for the diagnosis of myocardial infarction, and at no time was there evidence of a valvular lesion. The presence of cardiomyopathy was confirmed after death because of the presence of many discrete collagenized foci devoid of muscle fibres in the myocardium in the absence of any arterial abnormalities.

The search for a specific aetiological factor in this condition, or group of conditions, has failed in the past, and exhaustive investigations in the present case were also unsuccessful. The only tenuous connecting factor was that promethazine hydrochloride, a phenothiazine drug, had been administered in the antenatal period, and such drugs have been implicated in cardiomyopathies. Whether there is a cardiomyopathy specific to pregnancy is still an open question, but in a recent review Brown *et al.* (1967) reported three cases in which this diagnosis was entertained.

It had been suggested in the past that embolism is the usual cause of strokes in patients with cardiomyopathy of pregnancy (Rosen, 1959), but there was no evidence of embolism in this case nor was there any mural thrombus in the heart. Connor and Adams (1966) have, however, emphasized that profound and fatal ischaemic cerebral damage apparently caused by an acute episode of cerebral perfusion failure may occur in cases of pregnancy cardiomyopathy. The bilateral essentially symmetrical watershed cortical infarcts in the present case associated with profound neuronal loss in the thalamus, moderately severe loss of Purkinje cells, and only focal abnormalities in the Ammon's horns with relative sparing of the "vulnerable" Sommer sectors, are in keeping with a severe though short-lived episode of cerebral perfusion failure. Adams *et al.* (1966) have argued that neuropathological abnormalities of this type are due to systemic hypotension, and it would appear that in the present case, a young woman with no occlusive arterial disease, the acute cerebral perfusion failure must be attributed to an episode

of severe hypotension possibly associated with a transient dysrhythmia, a known complication of cardiomyopathy of pregnancy. Another speculation is that in pregnancy there may be some disturbance of vascular reflexes predisposing to perfusion failure.

Management of such patients is limited to the standard therapy of congestive cardiac failure. Bed rest, digoxin, and diuretics remain the main pillars of treatment. The position of steroids in cardiomyopathies is debatable. Some success with this therapy has been reported, but there is no convincing evidence that these drugs are of definite value.

The management of the acute episode of hypoxaemia was of interest in relation to the administration of hyperbaric oxygen. An arterial oxygen tension of 70 mm. Hg would not by itself be a cause of serious anxiety even if, as in this case, it were achieved when using positive-pressure ventilation and 100% oxygen. The improved clinical condition of the patient, however, following the increase of the arterial oxygen tension to over 300 mm. Hg at 2 atmospheres absolute was striking, as was the relief of the signs of foetal distress. The finding of an increase in arterial oxygen tension from 70 mm. Hg with oxygen at normal barometric pressure to about 300 mm. Hg as a result of oxygen administration at 2 atmospheres absolute would be expected, assuming that there was no change in the amount of venous admixture (shunting) or in cardiac output. The later rise in arterial oxygen tension at increased pressure to nearly 500 mm. Hg is consistent with an increase in cardiac output in the immediate postpartum period (Adams, 1954). Sustained improvement in oxygenation probably resulted from the effects of the increase in cardiac output combined with the disappearance of the acute pulmonary oedema for which intermittent positive-pressure ventilation was most likely to have been responsible.

Cardiomyopathy does not usually present in such a dramatic fashion, and there may even be unsuspected cases among pregnant women, some of whom develop cardiac failure for no obvious reason. Screening of the antenatal population with 12-lead electrocardiography may bring the problem to light. It would seem logical to keep under close observation any patients who show unexplained electrocardiographic abnormalities in order that immediate hospital admission might be arranged if early signs of cardiac decompensation occur. On the other hand, when catastrophic cerebral events develop within minutes, as in this patient, it would be impossible to suggest any specifically effective prophylactic or therapeutic measure.

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