A CASE OF SYMPTOMATIC HAEMOLYTIC ANAEMIA IN PREGNANCY

BY

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This report describes a case of symptomatic haemolytic anaemia occurring during a young woman's first two pregnancies. She gave no previous history of jaundice or anaemia. The haemolytic process on both occasions followed the onset of gestation and ceased spontaneously after delivery.

In the older literature megaloblastic anaemia of pregnancy was often confused with haemolytic anaemia and pernicious anaemia, so the records are unreliable as regards the incidence of the disease. Within the last decade we could find few papers in the English literature specifically devoted to this complication of pregnancy. In our hospital the case described below was the only one which had occurred in over 12,000 pregnancies seen during the past five years. It would therefore appear to be rare.

First Pregnancy

A married woman aged 29 was first seen by one of us (G. A. C.) at St. Luke's Maternity Hospital in October, 1949. She was then in the last trimester of her first pregnancy. She gave a history of being quite well throughout that pregnancy until shortly before admission, when she felt sick and vomited, subsequent to which she became slightly jaundiced. She denied ever having been jaundiced or anaemic before in her life. There was no family history of haemolytic anaemia; her two sisters, both married, had had normal pregnancies. On examination the patient was found to be 32 weeks pregnant. She was clearly anaemic and jaundiced. Her liver and spleen were not enlarged and her body temperature was normal. No other clinical abnormality was found.

Investigations.—Haemoglobin, 8 g. per 100 ml.; red cells, 1,600,000 per c.mm.; reticulocytes, 25%. A marked polychromasia and scanty normoblasts were present in the peripheral film but no microspherocytes were seen. The red-cell-fragility test by the method of Creed gave a normal result. The total white cell count was 7,000 per c.mm., the differential count being normal. Platelets numbered 210,000 per c.mm. The sternal marrow showed a marked normoblastic hyperplasia. Blood chemistry: van den Bergh reaction—direct test negative, indirect test positive; serum bilirubin 3.2 mg. per 100 ml. Urine: bilirubin absent; haemoglobin absent; urobilinogen strongly positive.

A diagnosis of haemolytic anaemia was made. The patient was treated with folic acid and liver preparations, and was given blood transfusions, but did not respond to any of these. In fact, blood transfusion merely seemed to cause increased haemolysis. On December 14, after a surgical induction of labour, the patient delivered herself of a healthy female infant. Two weeks later her haemoglobin had risen for the first time since her admission to hospital, to 10.4 g. per 100 ml., and subsequently the haemolytic process rapidly ceased. The patient and her baby were seen three months after delivery and were then in good health. Laboratory examinations failed to give any evidence of haemolytic anaemia in either the mother or her baby. The mother's haemoglobin was then 15.6 g. per 100 ml.

Second Pregnancy

Clinical Features

The patient came under our care for the second time on December 8, 1952, being again pregnant. Her expected date of delivery was April 2, 1953. On inquiry she said she had been perfectly well since her last pregnancy, and had remained so during the early weeks of this one. In the two weeks prior to attending the antenatal clinic she had again noticed a slight jaundice accompanied by excessive tiredness.

Examination revealed a well-nourished woman aged 32. There was a slight icterus of the sclera and skin. No oedema was present. Her uterine enlargement corresponded to a 26-weeks pregnancy. Physical examination of her cardiovascular, central nervous, and respiratory systems showed no abnormality. Neither the spleen nor the liver was palpably enlarged. Her body temperature was normal.

Laboratory investigations, details of which are given below, showed that she had a recurrence of the haemolytic anaemia experienced during her first pregnancy. It was decided to allow the pregnancy to continue to term if her condition permitted, supporting her when necessary with blood transfusions.

Her progress continued fairly satisfactorily until March 12, when the maturity of her pregnancy was 37 weeks. On that date her haemoglobin level had fallen to 4 g. per 100 ml. Two pints (1,140 ml.) of whole blood was administered. This raised the haemoglobin level to 7.3 g. per 100 ml., but on March 14 it had fallen to 5.3 g. per 100 ml., and a cold agglutinin had appeared in her blood that temporarily rendered cross-matching difficult. As soon as this difficulty had been overcome a surgical induction of labour was performed. This was followed by the delivery of a normal live female child on March 15. The blood loss at delivery was normal.

Following delivery the haemolytic process persisted without apparent abatement for four weeks, and then gradually ceased. By May 20 it had stopped completely, so far as could be determined by laboratory tests.

The patient's clinical condition throughout the second pregnancy was much worse than during the first. The severity of the haemolytic process was evidently increasing with the parity. In view of this, sterilization was advised. For this purpose laparotomy was performed in the puerperium, when the patient was still showing some evidence of increased red-cell destruction.

At operation the abdominal organs, including the liver and the spleen, appeared normal. One ovary showed a number of small cysts, the other appeared atrophic. The genital organs were otherwise normal. Biopsy material was obtained from both ovaries, and a small inguinal lymph node was removed. Since the patient's discharge both she and her two children have been examined from time to time for the presence of haemolytic anaemia with negative results. The last examination of the patient, six months after delivery, showed haemoglobin 15 g. per 100 ml., reticulocytes less than 1%, serum bilirubin 0.8 mg. per 100 ml., and faecal urobilinogen 130 Ehrlich units per 100 g. of faeces. She was symptom-free and in good health.

Laboratory Investigations

Haemoglobin and Red Cells.—At her first attendance the patient's haemoglobin was 7.3 g. per 100 ml. Examination of the stained film showed a moderate degree of polychromasia. Normoblasts constituted 2% of the total nucleated cells present. No microspherocytes were seen, nor were any found in subsequent blood examinations. On February 12, 1953, the mean corpuscular volume was 114 cubic μ and the mean corpuscular haemoglobin concentration 30%. Reticulocyte counts when the haemolytic process was at its height varied from 20 to 32% of the total red-cell count, and normoblasts were found in every stained film examined during this period. The behaviour of the blood counts is given in Table I. The haemoglobin was estimated by the alkaline haematin method of King (1946).

TABLE I.—*Chronological Record of Laboratory Studies*

Date	R.B.C. mil./ c.mm.	Hb g./ 100 ml.	Reticulo- cytes %	Leuco- cytes per c.mm.	Plate- lets per c.mm.	Serum Bilirubin mg./ 100 ml.	Faecal Uro- bilinogen Ehrlich Units/ 100 g.
8/12/52	2.4	7.3	21	7,600	196,000	2.2	800
16/12/52		Transfusion 2 pints whole blood					
18/12/52		10.0		8,300		2.1	
23/12/52		9.9		5,100	185,000	1.9	1,200
14/1/53		9.6	30			1.7	1,980
12/2/53	1.4	4.5	32	9,800	250,000		
13/2/53		Transfusion 3 pints whole blood					
17/2/53	1.32	4.4	31	10,200	240,000		
2/3/53	1.35	4.4	30	10,300	180,000	2.0	
12/3/53	1.2	4.0	22	5,800			
		Transfusion 2 pints whole blood					
13/3/53		7.4	24	6,700			
14/3/53		5.3		8,100	190,000		
15/3/53		Patient delivered. Blood loss normal					
16/3/53	1.7	5.1	11	9,000	200,000	1.4	
25/3/53	1.6	5.3	25	9,200	251,000	1.3	2,650
30/3/53		Transfusion 2 pints whole blood					
14/5/53	2.6	8.9	27	8,900	196,000	1.3	2,700
8/4/53	2.64	8.8	28	10,100		1.6	
10/4/53		Transfusion 2 pints whole blood					
15/4/53	3.91	10.9	16	9,800	194,000	1.1	980
1/5/53	3.8	12.5	8	7,600	210,000	1.2	670
10/5/53	4.02	13.0	2	10,100		0.9	340
20/5/53	5.03	14.5	0.5	6,700	220,000	0.6	140

Red-Cell Fragility.—The patient's red cells were examined, using the combined fragility test of Varadi (1951), on December 23, 1952, and February 24 and May 30, 1953, and no increase in fragility was demonstrated.

Faecal Urobilinogen.—The semi-quantitative method of Watson as described by Wintrobe (1951) was used. The results are summarized in Table I. The upper limit of normal by this method is 350 Ehrlich units per 100 g. of faeces.

Blood Chemistry.—No abnormality was found on estimating the serum proteins and blood urea. Schumm's test for methaemalbumin was negative. Haemoglobinaemia was never demonstrated. The direct van den Bergh reaction was negative, and the indirect strongly positive. Serum bilirubin estimations varied between 1.7 and 2.2 mg. per 100 ml. during pregnancy.

Fractional gastric analysis showed the presence of free hydrochloric acid.

Sternal Marrow.—This was examined on February 12. The myelogram (Table II) showed a richly cellular marrow. There was a marked normoblastic hyperplasia. Apart from the reduction in relative proportions the myeloid series appeared normal.

TABLE II.—*The Myelogram*

Proerythroblasts	..	..	..	..	4.0%
Early normoblasts	..	..	..	..	18.0%
Late and intermediate normoblasts	..	..	..	..	43.0%
Myeloblasts	..	..	..	..	0.5%
Premyelocytes	..	..	..	..	0.5%
Myelocytes	..	..	..	..	6.0%
Metamyelocytes	..	..	..	..	10.0%
Polymorphonuclear leucocytes	..	..	..	..	15.0%
Lymphocytes	..	..	..	..	1.0%
Normoblasts in mitosis	..	..	..	..	2.0%
Megakaryocytes	..	..	..	..	Present
Myeloid:erythroid ratio	..	..	..	..	0.3:1

Leucocytes.—The total white cell counts varied from 5,000 to 10,300 per c.mm. Scanty myelocytes (under 1%) were present from time to time during pregnancy, otherwise the differential count showed no abnormality.

Platelet counts varied between 180,000 and 300,000 per c.mm.

Urine.—Urobilinogen was present in the urine in increased amounts during pregnancy. Its presence was demonstrated by the techniques described by Wintrobe (1951). Tests for haemoglobin, bilirubin, and haemosiderin were negative.

Coombs Test.—The direct and indirect tests were invariably negative during pregnancy and following the patient's recovery. The technique used was that described by Dacie (1950).

Circulating Haemolysins.—The patient's blood was examined, using the presumptive tests described by Wintrobe (1951), for the presence of cold and warm haemolysins on February 12, March 27, and April 20. They were not demonstrated.

In Vitro Erythrophagocytosis.—The method described by Zinkham and Diamond (1952) was used. The index was less than 0.1%—a normal result.

Cold Agglutinins.—On March 13, two days before delivery, a cold agglutinin in low titre (1/32) was noticed in the patient's blood. Its presence had not been detected previously and it disappeared within five days of its first appearance. It may have been due to the transfusion given on March 12.

Serology.—The patient was Group O, Rh positive; no atypical antibodies were present in her serum. The Kahn test was negative.

Baby's Cord Blood.—Blood Group A, Rh positive. No agglutinins active against the mother's cells in saline or albumin or by the Coombs technique were detected in the cord serum. The haemoglobin was 19.3 g. per 100 ml. No evidence of a haemolytic anaemia was found at birth or in subsequent examinations of the baby.

Histology of Biopsy Material.—One ovary showed the presence of multiple small follicular cysts; in the other a corpus albicans was present but no active follicles were seen. The inguinal lymph node showed fibrous scarring due to past attacks of lymphadenitis.

Discussion

O'Grady *et al.* (1953), in a short review of haemolytic anaemia in pregnancy, state: "Although pregnancy does not cause haemolytic anaemia it may be a precipitating factor." In our case, however, the intimate association of the anaemia with the patient's two pregnancies and its cessation following delivery suggest that gestation plays an important part in its causation. The mechanism of the increased red-cell destruction is obscure. The failure to demonstrate either autoagglutinins or haemolysins in the circulating blood indicates that abnormal antibody formation in cases of symptomatic haemolytic disease due to other causes (Allibone and Collins, 1951). Lescher (1942), in a review of eight cases of haemolytic anaemia in pregnancy, states that there is no evidence of the development of a haemolysin in either the maternal or the foetal structures. He also notes that neither nutrition nor infection seems to play any part in the abnormal haemolysis.

Whitby and Britton (1950) regard the haemolytic anaemia occurring during pregnancy as similar to Lederer's anaemia. Our case differs from the usual description given of the latter condition in that it ran a less fulminating course and, apart from the symptoms due to the low haemoglobin concentration *per se*, there was no constitutional upset. It did not respond dramatically to blood transfusion. The haemolysis, moreover, was not accompanied by pyrexia or leucocytosis.

The failure of the spleen to enlarge and the fact that the process ceased completely after delivery, in the absence of splenectomy, indicates that this organ does not play any dominant part in the production of the disease. The possibility that this was a case of congenital acholuric jaundice can be dismissed in view of the absence of spherocytosis, the negative Varadi test, and the lack of a familial or personal history of such a disease. As the patient belonged to Group O, red-cell-survival studies were not attempted. The very transient rise produced in the haemoglobin concentration by transfusions (see Table I) suggests that the normal transfused cells were eliminated as fast as the patient's own cells. It is unlikely, therefore, that the process was due to any intrinsic effect induced by pregnancy in her red-cell structure.

In this case the haemolytic process seems to be due to overactivity of the normal mechanisms for the removal of red cells from the blood stream. The nature of such mechanisms is at present obscure. It is known, however, that they are influenced by the sex hormones. Hyperhaemolysis has been demonstrated in normal women during the latter part of the menstrual cycle (Ashby, 1921; Berlin, 1951). These authors, while admitting the obscurity of the nature of this hyperhaemolysis, conclude that it is due to hormone influences; Berlin also believes that the spleen plays no part in its production, as he found it to persist after splenectomy. Presumably, during a normal pregnancy the hyperhaemolysis is inhibited, to prevent the increased concentration of sex hormones following gestation from causing a haemolytic anaemia. In our case the inhibitory mechanisms would appear to have failed.

Summary

A case of symptomatic haemolytic anaemia associated with pregnancy is described. The haemolytic process occurred during a young woman's first two pregnancies and ceased spontaneously on both occasions during the puerperium. Neither circulating haemolysins nor atypical agglutinins were demonstrated. The mechanism of the hyperhaemolysis was obscure. We suggest that it may be related to that occurring during the pre-gestational phase of the normal menstrual cycle.

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REFERENCES

- Allibone, E. C., and Collins, D. H. (1951). *J. clin. Path.*, **4**, 412.
 Ashby, W. (1921). *J. exp. Med.*, **34**, 127.
 Berlin, R. (1951). *J. clin. Path.*, **4**, 286.
 Dacie, J. V. (1950). *Practical Haematology*, 1st ed. Churchill, London.
 King, E. J. (1946). *Micro-analysis in Medical Biochemistry*. London.
 Lescher, F. G. (1942). *Lancet*, **2**, 148.
 O'Grady, J. W., Riva, H. L., and Ritzenthaler, J. G. (1953). *Amer. J. Obstet. Gynec.*, **65**, 1338.
 Varadi, S. (1951). *J. clin. Path.*, **4**, 221.
 Whitby, L. E. H., and Britton, C. J. C. (1950). *Disorders of the Blood*, 6th ed. Churchill, London.
 Wintrobe, M. M. (1951). *Clinical Haematology*. Kimpton, London.
 Zinkham, W. H., and Diamond, L. K. (1952). *Blood*, **7**, 592.

ROSEOLA INFANTUM

13 CASES SEEN IN GENERAL PRACTICE

BY

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Very little has been published in Britain on this relatively common condition, also known as exanthem subitum or sixth disease. The *British Medical Journal* (1950) draws attention to this "common but little-known infectious disease of young children which has received too little attention in the past."

Nearly all the published accounts of the disease come from the U.S.A., where Zahorsky, of St. Louis, first described it as a clinical entity and gave it the descriptive name in 1910. Up to 1940 he had seen about 300 cases in private practice (Zahorsky, 1940). Cases have been reported from all over the world, including Brazil, Formosa (Itagaki, 1933), Canada, Germany (Fischhof, 1936), South Africa (Witkin, 1937), Sweden, and Australia (Jackson, 1949). In Britain, only Schlesinger (1937) refers to a few cases seen in London.

The purpose of this paper is to show that, despite the paucity of references to it in the journals and textbooks, it arises quite frequently in general practice.

Age Incidence.—The disease affects infants between the ages of 6 months and 2 years. The youngest in Clemens's (1945) series of 80 cases was 5 months old, but he quotes one 2 months old. My youngest patient was 4½ weeks old.

Older children and adults have been involved in other series. The sexes are equally affected.

Aetiology.—Although the infective nature of the disease was accepted, proof was not established until Kempe *et al.* (1950) succeeded in transmitting the disease by injecting serum from an 18-months-old child in the pre-eruptive stage into a 6-months-old susceptible baby kept in isolation, who developed typical roseola infantum on the ninth day. In young apes these workers produced a fever without a rash after a similar period. While they consider the causal agent to be a virus, they have been unable to isolate it or to transmit it through any of the usual media. Hellström and Valquist (1951), at Upsala, have confirmed these findings in a larger series of 14 human cases.

Epidemiology.—Although most cases arise sporadically, epidemics have been reported, and the cases which I noted in my practice presented as a mild epidemic, although I can identify in recollection a number of sporadic cases over the years. American writers believe that it is endemic and almost universal in infancy, but that in favourable circumstances it appears in epidemic form. They find that the highest incidence is in the spring and to a less degree in the autumn.

Pathology.—No deaths have been reported. The blood changes seem to be important—they are a neutrophil leucopenia, appearing during the febrile stage and falling to a total white-cell count as low as 2,000 per c.mm. This process is reversed as soon as the rash appears, and the count returns to normal within a week. The incubation period is 5 to 15 days.

Clinical Course

The individual case presents on the following lines. A call is received to an infant who "has come out in a rash all over. He's been feverish for a few days, and I nearly sent for you yesterday, doctor. When I saw the rash to-day I thought it must be measles, but he seems better now." In fact, the child appears well apart from a rash in the form of discrete rose-coloured macules, most marked on the trunk but spreading on to the thighs and upper arms, up to the neck and often behind the ears. In severe rashes some coalescence may occur.

If the case is seen earlier the child has a fever extending over three to five days, the temperature rising to 101–102° F. (38.3–38.9° C.) or higher, with symptoms of inflammation and congestion of the nose and throat, and frequently of the tympanic membranes. He is restless, may refuse feeds, and is obviously unwell. Examination of the fauces shows redness of the tonsils and pharynx, and of one or both ear-drums. A cough may be present without signs in the chest. With the appearance of the rash the child rapidly improves, the catarrhal signs disappear, and normal lustre returns to the ear-drums. Posterior cervical and occipital lymph-node enlargement can nearly always be found: in my experience this is more obvious when the rash is severe, especially on the neck and behind the ears. The glands in the groins and armpits do not become palpable. All signs disappear in a day or two in most cases, but occasionally congestion of the nose or Eustachian tubes persists and frank otitis media may develop (as in one of the present series).

Clemens (1945), in a series of 80 cases, reports a pre-eruptive enanthem in 87%: this took the form of erythematous specks and streaks on the soft palate which preceded the typical exanthem by 48 hours and coincided with the period of maximum tubotympanitis and faucial congestion. I noted this in one case, but would be inclined to dismiss it as part of the general congestion of the mucous membrane of the palate.

Differential Diagnosis

In a clear-cut case the disease which is most like roseola infantum is rubella. In that condition the pyrexia and malaise coincide with the rash and are usually less pronounced. There is not the three to five days' pre-eruptive