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MEGALOBLASTIC ANAEMIA OF PREGNANCY AND THE PUERPERIUM

BY

L. S. P. DAVIDSON, M.D., F.R.C.P.Ed.&Lond.

L. J. DAVIS, M.D., F.R.C.P.Ed., M.R.C.P.Lond.

AND

JAMES INNES, M.B., Ch.B., M.R.C.P.Ed.

(*From the Department of Medicine, University of Edinburgh*)

Apart from the apparent anaemia caused by physiological dilution of the corpuscles resulting from increased plasma volume in pregnancy (Dieckmann and Wegner, 1934) and the hypochromic anaemia due to nutritional iron deficiency which has been shown by Davidson, Fullerton, and Campbell (1935) to be of frequent occurrence in pregnant women of the poorer classes, it has been recognized since 1842 (Channing, 1842) that a severe anaemia of the pernicious type may complicate pregnancy. Very occasionally it is of the classical Addisonian type, having antedated the onset of pregnancy, but more often it is an anaemia closely resembling Addisonian pernicious anaemia which develops during the course of pregnancy. Osler (1919) discussed this latter condition and pointed out that it differed from Addisonian anaemia in that recovery, when it takes place, is permanent. It should be noted, however, that the number of cases upon which this observation was based was small and that the haematological data submitted were inadequate and unsatisfactory—for instance, two of the cases had a colour index of 0.6.

A number of cases of this type of anaemia have been recorded in temperate climates during the past 20 years, but most authors have stressed its rarity. Thus Evans (1929) states that not one case of macrocytic anaemia was observed in 4,000 pregnancies. Whitby (1932), Wilkinson (1932), Bethell (1936), and Musser (1940) all indicate that the condition is encountered but seldom. On the other hand, Stevenson (1938) during six years studied 30 cases in Glasgow, which she classified as "pernicious, megaloblastic, or hyperchromic anaemia of pregnancy or puerperium." It is significant to note, however, that of her 30 cases only 17 had a colour index above unity, and that Price-Jones curves showed a shift to the right in only 6 cases. Leucopenia was present in 8 cases only. She concluded, on the basis of the frequency with which polychromasia, nucleated red cells, and immature leucocytes were observed, that the blood pictures reflected greater activity of the bone marrow than is found in Addisonian pernicious anaemia in relapse, and that an added iron deficiency sometimes complicated the picture. No observations on the bone marrow were recorded by Stevenson or the other workers mentioned above. Another significant observation by Stevenson was that achlorhydria was uncommon, being present in only 3 of her 19 cases.

Investigation of 16 Cases

In Edinburgh during the past two years we have studied 16 cases of this type of anaemia referred to us by our obstetrical colleagues. During this period there were approximately 8,000 confinements in the maternity hospitals concerned, but as no special study of anaemia in pregnancy was being undertaken by us, and as the cases were seen only in the course of our routine work as hospital physicians, it is reasonable to assume that many additional cases occurred during the period under review. Seven of the cases were seen by us prior to the use of liver therapy, but in the remaining 9 cases treatment had been instituted from two days to two months before we were called into consultation on account of their refractoriness to treatment.

Age.—The ages of the patients are set forth in the Table. It will be noted that 9 were between 23 and 30, 5 were between 30 and 40, and 2 were aged 41. It is evident that the ages are considerably lower than those commonly met with in Addisonian pernicious anaemia.

Number of Pregnancies.—Two of the patients were primigravidae, 6 were primiparae, 4 were in their seventh, and 4 were in their third, fourth, sixth, and ninth pregnancies, respectively. It is commonly held that pernicious anaemia of pregnancy occurs mainly in women who have borne several children, but it will be seen that this is not supported by our experience.

History of Anaemia.—Only 2 of the patients were seen by us before delivery, but examination of case records revealed a history of marked pallor and dyspnoea during pregnancy in 13. In 8 of these cases haemoglobin figures were available, ranging from 18 to 52%, and more detailed haematological data available in 4 of them indicated a severe anaemia of the pernicious type. It was repeatedly noted that the anaemia became progressively more severe during the last two months of pregnancy.

Peripheral Blood Findings

The data recorded in the Table are those obtained when the patients were first seen by us. It has already been noted that liver therapy had previously been instituted for varying periods of time in 9 cases before they came under our observation.

The *red cell counts* are seen to vary from 0.57 to 3.2 millions per c.mm., being below 1.7 millions in 11 of the cases. *Haemoglobin concentrations* were estimated by the Haldane method, 100% being equivalent to 13.8 g. per 100 c.cm. The figures ranged from 12 to 52%, being below 40% in 12 cases. Ten of the patients had *colour indices* above unity. It is generally agreed, however, that the normal range is from 0.9 to 1.09. On this basis the colour indices were greater than normal in only 6 cases, within normal limits in 8 cases, and below normal in 2. Of the 7 patients seen before beginning treatment, only 3 had colour indices above 1.09, while of the 5 seen within a week of beginning liver therapy 4 had colour indices within the normal range. In view of the short time that had elapsed since treatment of these latter patients had been started, we consider it improbable that they had

previously displayed high colour indices. Of the 2 hypochromic cases, one (No. 9) was an unusual case, to which further reference will be made, while the blood picture of the other (No. 8) was modified by a blood transfusion given shortly before the recorded blood examination was made by us.

Anisocytosis and ovality of outline of the red cells were not considered by us to be so prominent in these cases of anaemia of pregnancy as we have been accustomed to find in classical Addisonian anaemia of equivalent severity.

Macrocytosis.—Price-Jones curves were not constructed, but the films were carefully inspected with a view to assessing the approximate frequency of cells of different sizes. We feel that, with experience and using a constant magnification, a very fair approximation can be obtained by visual inspection. In 9 of the cases we noted numerous macrocytes, and formed the opinion that the mean cell size was greater than normal, while in 7 the mean cell size did not appear to exceed normal limits.

Leucocytes.—In 9 patients the white cell counts were within or below normal limits. A leucocytosis was present in 4, all of whom were suffering from septic complications.

Table showing Details of 16 Cases of Megaloblastic Anaemia of Pregnancy

GROUP I.—CASES DISPLAYING A PROMPT RESPONSE TO LIVER THERAPY:

Case No., Age, etc.	Peripheral Blood: Hb %	R.B.C. (millions per c.mm.)	Colour Index	W.B.C. per c.mm.	Sternal Marrow	Free HCl	Amount of Liver Extract before Response	Time of Initial Reticulocyte Response
							c.cm.	
(A) Cases studied before starting liver therapy:								
No. 1, aged 41, para. 8	40	2·07	1·00	5,400	Megaloblastic	+	4	3 days
No. 2 „ 35 „ 5	34	1·74	0·98	8,800	„	+	8	4 „
(B) Cases first seen after starting liver therapy:								
No. 3, aged 33, para. 6	40	1·47	1·33	12,000	Not examined	—	1	4 days
No. 4 „ 32 „ 6	32	1·48	1·08	3,800	Megaloblastic, with early normoblastic differentiation	—	6	4 „
No. 5 „ 41 „ 3	22	1·01	1·09	19,800	„	—	6	4 „

GROUP II.—CASES DISPLAYING A DELAYED RESPONSE TO LIVER THERAPY:

(A) Cases studied before starting liver therapy:								
No. 6, aged 29, para. 6	17	0·58	1·45	5,200	Megaloblastic	+	28	26 days
No. 7 „ 25 „ 1	32	1·45	1·20	2,200	„	+	60	4 months
No. 8 „ 27 „ 1	30	1·70	0·84	2,500	„	+	24	6 „ (died from sepsis)
No. 9 „ 23 „ 1	48	3·20	0·75	5,200	Normoblasts preponderate, but megaloblasts numerous	+	30	7 weeks
(B) Cases first seen after starting liver therapy:								
No. 10, aged 38, para. 6	12	0·57	1·05	10,400	Megaloblastic	-	16	15 days
No. 11 „ 27 „ 1	18	0·95	0·95	7,400	Megaloblastic and normoblastic	-	18	11 „
No. 12 „ 24 „ 0	52	2·18	1·19	10,200	Not done	-	15	3 weeks
No. 13 „ 38 „ 1	29	1·20	1·21	3,400	Normoblastic*	-	42	4 „
No. 14 „ 23 „ 2	29	1·33	1·09	8,800	Not done	Not done	48	8 „
No. 15 „ 29 „ 1	32	1·58	1·01	4,000	Normoblasts preponderate, but megaloblasts numerous	—	22	10 „
No. 16 „ 29 „ 0, seen before liver therapy began	21	0·80	1·30	7,000	Megaloblastic	Not done	6	Died following transfusion 3 days after liver

* Sternal marrow examined two weeks after beginning of response to liver therapy.

Other Findings

Sternal Marrow.—Sternal puncture was performed in 13 of the cases. The resulting films with one exception showed numerous primitive megaloblasts. In 6 of the 7 cases seen before beginning liver therapy the qualitative and quantitative erythroblast pictures were identical with those found in Addisonian pernicious anaemia in the stage of relapse. The remaining marrow film, from Case 9, contained many megaloblasts, but the normoblasts were more numerous than we should expect to find in a case of Addisonian pernicious anaemia at the level of 3.2 million erythrocytes per c.mm. The marrow films from the cases seen subsequent to starting liver injections presented the mixed megaloblastic and normoblastic pictures that have been previously described by us in Addisonian pernicious anaemia responding to treatment (Davidson, Davis, and Innes, 1942). The bone marrow in Case 13, which gave a normoblastic picture, was examined two weeks after a response to liver therapy had occurred.

Gastric Juice.—It was practicable to carry out gastric analysis in only 11 of our cases when they were first seen. Free hydrochloric acid was present in 7. In the course of subsequent examinations free hydrochloric acid was found in 3 of the cases that had not been tested previously. Thus of 14 cases tested only 4 were found to have a histamine-fast achlorhydria.

Sepsis.—Septic complications developed during the puerperium in 9 cases. The conditions were: mastitis in 4 cases, pyelitis in 3 cases, and pneumonia in 2. In 3 of these patients a streptococcal stomatitis had also been present during pregnancy.

Treatment and Progress

All the patients were given liver extract parenterally in ample doses. In 5 cases this resulted in a typical reticulocyte response within a week and a subsequent adequate rise in the red cell count. Ten patients were temporarily refractory to treatment for periods varying from eleven days to several months. All received intensive parenteral liver therapy, well-known preparations such as anahaemin, pernaemon forte, campolon, neohepatex, haemex, and reticulogen being used. In order to eliminate the possibility of the failure to respond being due to an inert batch, more than one brand was invariably administered to such refractory cases. In addition to liver extract, all the refractory cases were treated with iron, and many of them also received yeast and ascorbic acid. In spite of this treatment 6 cases continued to be refractory for a month or longer. In 12 of the severest cases life had to be sustained by blood transfusion because of the low blood level and the unsatisfactory clinical state. In some of the refractory cases blood had to be given repeatedly, sometimes over several weeks.

In some cases liver therapy resulted in the same dramatic haematological and clinical improvement as is seen in

Addisonian pernicious anaemia, but in others the response was delayed, and when it occurred the rise in red cells and haemoglobin was gradual and protracted. Fourteen of the cases eventually made a complete clinical and haematological recovery. One patient (Case 16) died after a transfusion reaction; another (Case 8) died six months after delivery, despite large doses of liver extract, iron, yeast, and ascorbic acid, and repeated blood transfusions; death was attributed to severe bronchiectasis and pyelonephritis.

Since all these patients have been under observation for only two years, or less, it is impossible to make any statement regarding the permanency of recovery. Four have been followed during periods of six to twenty-four months and have maintained satisfactory blood levels without further treatment.

Discussion

Consideration of our own findings as well as those of previous investigators (e.g., Osler, 1919; Stevenson, 1938) reveal that a considerable proportion of cases of "pernicious anaemia of pregnancy" fail to satisfy all the criteria that are usually required for a diagnosis of Addisonian pernicious anaemia. In our opinion, for the diagnosis of the latter condition the following features should be present: a blood picture displaying anisocytosis, macrocytosis, ovalocytosis, hyperchromia, leucopenia, and thrombocytopenia, and a histamine-fast achlorhydria. In none of our group of 16 cases were all these features present. Basing a diagnosis solely on the peripheral red cell picture, we should have designated 5 of our cases as classical pernicious anaemia, while 7 more would have required careful consideration, since the colour indices were considerably higher than would be expected in iron-deficiency anaemias of comparable severity. The outstanding features serving to differentiate many of our cases from Addisonian pernicious anaemia were the presence of free hydrochloric acid in the gastric juice and a lower frequency and degree of macrocytosis and ovalocytosis.

Examination of the sternal marrow obtained before and after beginning liver therapy revealed with one exception (Case 9) pictures identical with those found in Addisonian pernicious anaemia at equivalent stages, and clearly indicated that these anaemias have for their immediate cause arrested maturation of the megaloblasts. Accordingly we propose that the term "megaloblastic anaemia of pregnancy" should be substituted for the misleading name "pernicious anaemia of pregnancy" on the grounds that the megaloblastic appearance of the bone marrow is characteristic and constant, while the peripheral blood findings are variable. The varying blood pictures are probably due to coexisting deficiencies of other haematinic factors.

Owing to the varying peripheral blood picture it does not appear practicable to establish adequate criteria for diagnosis without examination of the sternal marrow. Since severely anaemic patients with colour indices within or below the normal range may respond promptly to liver extract it would follow that the institution of rational treatment is dependent upon sternal puncture. The alternative is the empirical administration to all such patients of liver extract in addition to iron. Although manifestly undesirable, empirical liver therapy is perhaps less deserving of censure in this instance than in the treatment of other types of anaemia, since megaloblastic anaemia of pregnancy is of temporary duration, and the patient is accordingly not permanently condemned to an expensive and tiresome treatment.

The aetiology of megaloblastic anaemia of pregnancy is still unsettled. The most acceptable explanation is that the primary cause lies in a temporary failure of secretion of the intrinsic factor of Castle by the stomach during the later months of pregnancy (Strauss and Castle, 1933). That the secretion of hydrochloric acid may be temporarily impaired in a considerable proportion of pregnant women has been established by Strauss and Castle (1932). Other factors held to be of importance are: (1) reduced intake of extrinsic factor consequent upon poor diet, capricious appetite, anorexia, and vomiting; (2) impaired absorption from the small intestine due to altered hydrogen-ion concentration of its contents secondary to reduced gastric acidity; and (3) increased demands by the foetus for haematinic principles. We are unable to express any opinion on impaired production of intrinsic factor by the stomach or failure of absorption by the small intestine, as we have made no special investigation of these points. With regard to diet, in some of our cases it was apparently satisfactory, but in others it was undoubtedly poor. Furthermore, in some patients undue anorexia and vomiting were known to have occurred, whereas in others no note of such symptoms appeared in the case records. Nevertheless, since the bone marrows were megaloblastic, it can be safely assumed that there was an insufficiency of liver factor for normoblastic erythropoiesis.

Ten of our cases were refractory to treatment for longer or shorter periods before they eventually responded. This failure suggests the existence of a state of temporary arrest of erythropoietic function consequent on the absence of some essential factor additional to the liver principle. A similar state of affairs not infrequently occurs in sprue, in which a megaloblastic marrow may fail to react to parenteral liver extract. One of us has previously noted (Davidson, 1939) that in this condition a response may occur when liver therapy is supplemented by a high-protein diet. This would suggest that some factor in protein is necessary for erythrocyte production, possibly in connexion with stroma formation.

An alternative hypothesis is that refractoriness to treatment is related to a functional inability of the bone marrow to utilize the various haematinic principles because of the profound strain of pregnancy and the shock of labour occurring in a severely anaemic patient. In this connexion we wish to draw attention to the disastrous fall in the blood count which may result from a normal blood loss in such women during childbirth. Data available to us show that a haemoglobin level of 30 to 40% before labour may drop to a figure of 15 to 20% immediately subsequent to delivery.

The inhibitory effects of sepsis on liver therapy have been widely accepted. In 6 of our cases it is possible that sepsis played a part in this delayed response to liver therapy, but one of us has had cases of Addisonian pernicious anaemia with severe pneumonia with blood counts of a million or less which responded promptly to liver therapy (Davidson, 1933). Furthermore, in some of our present group of pregnancy cases refractory to treatment no sepsis could be found.

Conclusions

The practical conclusions drawn from our experience on which we wish to lay particular emphasis may be stated as follows.

1. It should be recognized that a severe megaloblastic anaemia may occur during pregnancy or the puerperium although the colour index may be unity or less.

2. Despite the administration of large quantities of liver extract, iron, and yeast, no response may be obtained for a considerable time in a proportion of such patients.

3. Our experience indicates that the great majority of refractory cases eventually make a complete recovery if life is maintained by blood transfusions while persevering with vigorous haematinic treatment. A study of the Table will show that, no matter how severely anaemic the patient, a good prognosis can be given if these measures are carried out.

4. The paramount importance of recognition of anaemia during pregnancy cannot be stressed too strongly, as only by this means can the acute exacerbations which tend to occur during the last two months of pregnancy be prevented.

Summary

A severe type of anaemia associated with a megaloblastic bone marrow occurring during pregnancy and the puerperium has been defined and its points of resemblance to and distinction from Addisonian pernicious anaemia considered.

Sixteen cases have been recorded and their haematological, clinical, and therapeutic aspects discussed.

Ten of the cases were temporarily refractory to treatment with massive doses of liver extract, iron, and other haematinics.

Attention has been drawn to the vital importance of perseverance with intensive therapy in refractory cases and to the necessity for sustaining life by blood transfusions until a response is obtained.

On a basis of bone-marrow cytology, the term "megaloblastic anaemia of pregnancy and the puerperium" has been proposed for this type of anaemia.

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ASPHYXIA FOLLOWING DENTAL EXTRACTION IN A HAEMOPHILIAC

WITH A NOTE ON THE SPREAD OF INFECTION IN LUDWIG'S ANGINA

BY

C. L. ENDICOTT, L.D.S.
Director, Eastman Dental Clinic

J. H. MITCHELL, L.D.S.
Chief of Staff, Eastman Dental Clinic

AND

G. QVIST, F.R.C.S.
Late Surgical Registrar, Royal Free Hospital

The dangers of dental extraction in haemophilia are well recognized, and numerous cases of persistent haemorrhage are on record. The case here described is of interest on account of the anatomical extent of the haemorrhage, the extravasation of blood involving the deep cervical tissues as far down as the larynx, so that tracheotomy was necessary.

Case Report

The patient, a man aged 35, attended the Eastman Dental Clinic on Oct. 14, 1941, complaining of pain for two days localized to the right second lower molar tooth. He did not admit any previous history of bleeding, so that when dental extraction was performed it was not known that he was a haemophiliac.

His history, which was obtained later, showed that he had in fact suffered from recurrent haemorrhages from the age of 19. There was no abnormality of bleeding among his parents and six brothers. When 19 years old he was admitted to St. Bartholomew's Hospital with a large haematoma of the thigh following a trivial injury, and was readmitted a year later for haemorrhage after dental extraction, when bleeding continued for one week and 550 c.cm. of blood was given. On this occasion the blood-coagulation time was 17½ minutes; after the blood transfusion it was 8¾ minutes. At the age of 24 he was admitted to Guy's Hospital with a haematoma of the rectus abdominis and haemarthrosis of the left knee. Bleeding-time was normal and coagulation time was 13 minutes on one occasion (12/5/30) and 16 minutes on a second occasion (24/12/30) (control, 6 minutes). He was readmitted to St. Bartholomew's at the age of 31 with a haematoma of the forearm. The bleeding-time was then 2 minutes 10 seconds and coagulation time 3 minutes 30 seconds (27/8/37) (control, 2 minutes 10 seconds); platelets, 244,000.

When seen on Oct. 14, 1941, the patient had a tender loose second right lower molar, which was removed under gas anaesthesia. There was no undue difficulty or bleeding, and the patient went home. He returned in the afternoon, 5 hours later, bleeding from the tooth socket, which he stated had begun on the way home. The usual methods of control were attempted—plugging with dry gauze, adrenaline gauze, etc.—without relief. The patient was kept in the casualty ward, but in spite of repeated packing slow bleeding continued. Early the next morning, 18 hours after extraction, examination of the mouth showed that bleeding was proceeding from the gum at the site of extraction just behind the lower right first molar. Blood was welling up slowly from the depths of the socket, and there was no evidence of any tear of the mucosa other than at the actual situation of the extracted second molar. There was some swelling of the floor of the mouth just medial to the molar region, with the appearance of a submucosal haematoma. Two catgut stitches were introduced, closing over the gum, and external bleeding ceased immediately. Bleeding returned after two hours, and a third stitch was put in; no further haemorrhage occurred from this site. At this time, 24 hours after extraction, it was noted that the submucous swelling of the right side of the floor of the mouth had increased considerably, and there was now in addition a haematoma of the right side of the tongue and swelling of the right submaxillary region of the neck. It was believed that, bleeding from the gum having been controlled, tension in the tissues would not have to be very great to check what was regarded as a capillary ooze. Blood transfusion was begun.

During the next few hours the haematoma of the tongue spread to involve the whole organ, and swelling of the neck extended downwards, mostly on the right. During the course of the next day it became obvious that the larynx was being involved. Stridor was present and respiration was embarrassed, so that tracheotomy was necessary (54 hours after extraction). Actually breathing became extremely difficult on lowering the patient into the semi-supine position, and consciousness was lost just after incising the skin under local anaesthesia. On re-establishment of an airway with the tracheotomy tube, consciousness was recovered rapidly. The tracheotomy wound oozed continually and severe epistaxis started, and in spite of continued blood transfusion the patient died a few hours later, 66 hours after the extraction.

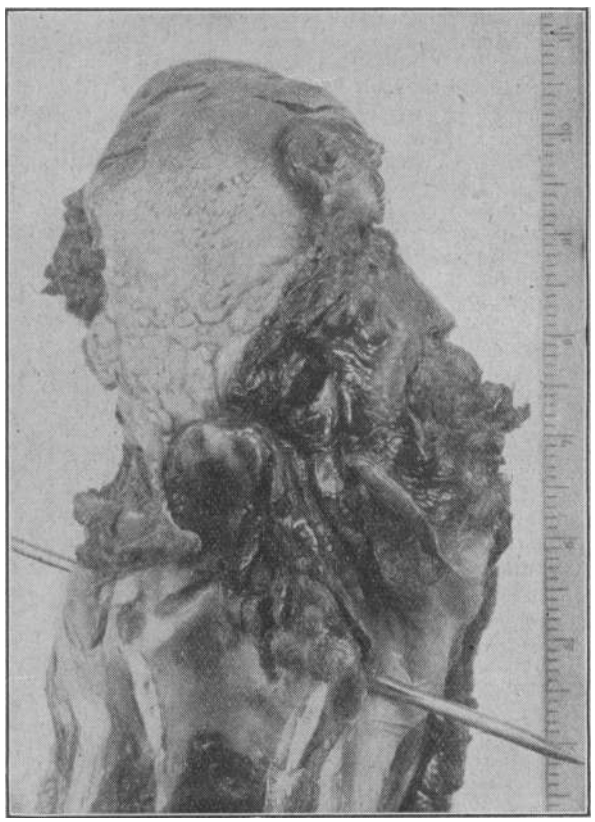

FIG. 1.—Specimen showing infiltration of blood into the mucous membrane of the larynx and upper part of the trachea.

Necropsy confirmed the presence of massive infiltration of the cervical tissues with blood, extending from the floor of the mouth and tongue down to the larynx and upper part of the trachea. The epiglottis and aryepiglottic folds were much swollen with blood and oedema in the submucosa, and the mucous membrane of the larynx and upper part of the trachea was infiltrated with blood, more marked on the right (Fig. 1). Careful search was made for a source of bleeding outside the gum, but none could be found.