# THE ANAEMIAS OF PREGNANCY

## ASPECTS PERTAINING TO THE INCIDENCE AND PATHOGENESIS OF THE ANAEMIAS OF PREGNANCY ENCOUNTERED IN SOUTH AUSTRALIA

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The regulations of the University of Adelaide for the degree of Doctor of Medicine require:

(1) A declaration that the thesis is the writer's own composition. This declaration may be found immediately following the list of contents.

(2) An indication of where the writer considers the thesis t advance medical knowledge or practice. This subject is contained in th Conclusion on page 109.

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# INTRODUCTION.

## An Outline of the Study Undertaken.

Owing to the emergence of unforeseen problems during the study, some modifications to its character were necessary during the three years over which it has extended. The purpose of this introduction is to outline the study as it was originally conceived, and to indicate briefly the problems which arose and the modifications which were required during its course.

The definition of anaemia of pregnancy is of necessity somewhat arbitrary, and it depends upon the average haemoglobin values found in the community. These are largely dependent upon the dietetic habits, living standard and environmental conditions of the population involved.

It is not surprising, therefore, to find that the values accepted as normal and anaemic respectively have varied considerably over the years. With the higher living standards of today, and the advancement of medicine, there is a general tendency to raise the lower limit of the haemoglobin level which is acceptable as normal in pregnancy. Scott and Govan (1949), working in Glasgow, found that 20.1% of their patients had haemoglobin values of less than 8.9 g. of haemoglobin per 100 ml. of blood at some stage during their pregnancy. They accepted from 8.9 g. to 9.9 g. of haemoglobin per 100 ml. of blood as low normal values.

By contrast, in a survey of the haemoglobin values of 177 randomly selected patients at the Queen Victoria Maternity Hospital Adelaide, the lowest haemoglobin encountered was 9.0 g. per 100 ml.

This survey of the anaemias of pregnancy was commenced at the Queen Victoria Maternity Hospital in March, 1958. The objects, at the outset, were to determine what proportion of patients with haemoglobin values below 11.0 g. per 100 ml. of blood were iron deficient, and what

proportion of patients resistant to iron therapy were of a frankly megaloblastic, or had an incipient megaloblastic, type of anaemia. This was initiated by the number of reports of a high incidence of megaloblastic anaemia in the British Isles, and also by the possibility that some patients might be suffering from an arrest of haemopoiesis before the development of a frank megaloblastic change in the bone marrow.

In Adelaide, a percentage scale was adopted in the past for the assessment of haemoglobin values, in which 100% corresponds to 15.3 g. of haemoglobin per 100 ml. of blood. From the point of view of the haematologist interested in comparative values, it is recognised that the percentage scale has serious disadvantages; but as this system is in current clinical use, it is necessary to deal in terms of this scale for local usage. Haemoglobin values are estimated using the oxyhaemoglobin method with a Unicam S. P. 300 absorptiometer, which has been calibrated from iron estimated haemoglobin standards. The optical density is then checked against a scale on which 11.0 g. of haemoglobin per 100 ml. of blood corresponds to 72%, and 10.7 g. of haemoglobin per 100 ml. of blood corresponds to 70%.

For the purpose of this investigation, the haemoglobin level of 10.7 g. per 100 ml. of blood (70%) was chosen as the arbitrary limit for the following reasons:

1. It would include all patients with haemoglobin values of less than 11.0 g. per 100 ml. of blood.
2. The figure of 70% provided an easy criterion for all members of the staff to recall, and would minimise confusion as to the level at which patients were referred for special investigation.
3. The numbers of patients referred would not be too excessive.
4. It was believed that this level would include all patients with

frank megaloblastic forms of anaemia.

5. The majority of obstetricians regard this level of haemoglobin as the minimum at which the risks of delivery are acceptable; and patients with haemoglobins below this value at the 39th week of gestation, are usually transfused before delivery.

It was arranged that all patients with haemoglobins of 10.7 g. per 100 ml. of blood, or less, should be referred to the Medical Complications Clinic organised by Dr. R. A. Burston at the Queen Victoria Maternity Hospital. It was hoped to obtain, as near as possible, a complete coverage of patients from all the clinics.

No folic acid or vitamin $B_{12}$ was administered except through the channels provided by this clinic; and throughout the thirty-eight months during which these investigations have been carried out, only four patients have had folic acid given to them outside the survey.

The scheme of treatment and investigation commenced with the routine administration to all antenatal patients of 15 gr. (0.9 g.) of ferrous gluconate per day. Routine haemoglobins and haematocrit estimations were carried out on the patient's first attendance at the antenatal clinic; and subsequently at 28 weeks and 34 weeks of gestation.

All patients with haemoglobin values of less than 11.0 g. per 100 ml. at the first visit were given a trial therapy of oral ferrous gluconate (1.8 g. daily). Only in exceptional cases of severe anaemia, with evidence of severe iron deficiency, or failure of response to oral iron, was parenteral iron therapy commenced before the 28th week of pregnancy. In all cases where the haemoglobin level was below 11.0 g. per 100 ml., a red cell count and a packed cell volume was carried out with calculation of the red cell indices. The reticulocyte count was estimated, using the method of incubation in brilliant cresyl blue (Dacie, 1956). The white cell count was

estimated, and a differential count of the white cells carried out on a stained blood smear, together with an examination of the red cell morphology.

The majority of the patients entered the survey between the 28th and the 32nd weeks of pregnancy, as calculated from the expected date of delivery. Each patient had a loose leaf card compiled (Appendix 1) on which was entered most of the relevant haematological data, and from which it was possible to assess her progress, and to summarise the investigations.

In the initial phase of this investigation, all patients who were anaemic at 30 to 32 weeks gestation were treated with iron-dextran (Imferon, Bengers Ltd.).

In this initial phase of the investigation, lasting twelve months, it was found that the anaemias fell into three main groups, which can be classified as follows:

1. Normocytic or microcytic cases responding to parenteral iron therapy.
2. Normocytic or macrocytic cases not responding to parenteral iron therapy:
    - i. Responding to Folic Acid and $B_{12}$
    - ii. Not responding to Folic Acid or $B_{12}$:
        - (a) of toxic aetiology
        - (b) of unknown aetiology.
3. Microcytic cases showing no response to parenteral iron therapy.

The first case investigated in the survey fell into group 3, and it was soon appreciated that in these cases I was probably dealing with the thalassaemia trait. Owing to the relative infrequency of gross folic acid deficiency in this preliminary evaluation, and the relatively large numbers of iron refractory microcytic anaemias occurring in the Greek, Italian and

Cypriot patients, the emphasis of the investigation had, of necessity, to be shifted from the original objectives to the investigation and diagnosis of thalassaemia minor.

This group, in many respects, resembled severe iron deficiency anaemias when regarded from the haematological aspect; and in the second phase of twelve months, intensive efforts were commenced in an attempt to discriminate between the iron deficiency cases and the thalassaemia minor group at an early stage, and to obviate any necessity for parenteral iron therapy in these cases.

Pre-treatment serum iron values were taken, and the results assessed in conjunction with the response to iron therapy and the pre-treatment red cell indices.

Owing to the fact that the time available for treatment of the anaemia is limited during pregnancy, and that the results of the serum iron values were not immediately available, it was usually necessary to initiate parenteral iron therapy pending the receipt of the results of this estimation. It was found that some patients showed an apparent response to parenteral iron therapy in spite of a serum iron level which was within the normal range. This resulted in an increased necessity for the evolution of a reliable method for the discrimination between the iron deficiency and the thalassaemia cases.

Paper electrophoresis, using a barbiturate buffer, was tried but the separation of the $A_2$ haemoglobin component was neither satisfactory nor constant. Starch gel electrophoresis was used with an 0.25 m. barbiturate buffer, as modified by Dr. Curtain; and good separation of the haemoglobin $A_2$ component was obtained. No satisfactory method of quantitation could be found, however, and evaluation could only be made by visual inspection.