THE INFLUENCE OF MATERNAL IRON-DEFICIENCY ANAEMIA ON THE HAEMOGLOBIN OF THE INFANT

BY

PHILIP LANZKOWSKY*

From the Department of Child Health, University of Cape Town and Red Cross War Memorial Children's Hospital, Rondebosch, Cape Town, South Africa

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The object of this study is to define the part played by maternal iron-deficiency anaemia in the pathogenesis of iron deficiency anaemia in infancy, a condition commonly found in Cape Town (Lanzkowsky and McKenzie, 1959; Lanzkowsky, 1959 and 1960a).

A number of early reports on the effect of maternal iron-deficiency anaemia on the newborn have indicated that maternal anaemia does not cause anaemia in the infant soon after birth and that the foetus avails itself of maternal blood-forming materials necessary for its own requirement irrespective of the condition of maternal blood (Baar and Stransky, 1928; Strauss, 1933; Strauss and Castle, 1933; Fullerton, 1937; Davidson and Fullerton, 1938). This view has been opposed by Maurer, Greengard and Kluver (1932). Paradoxically, Strean and Gottlieb (1936) found that the greater the maternal anaemia, the greater the foetal polycythaemia.

More recently Sisson and Lund (1958), basing the diagnosis of iron-deficiency anaemia on calculation of maternal and infant red cell volume and haemoglobin mass, concluded that infants of anaemic mothers frequently did have an iron-deficiency anaemia. Woodruff and Bridgeforth (1953) and Sturgeon (1959), on the other hand, are at variance with the work of Sisson and Lund and have convincingly shown in large and well-controlled series that there is no difference in the state of iron nutrition in groups of infants born to mothers with various degrees of iron nutrition.

Many authors have endorsed the statement that infants born to anaemic mothers become anaemic towards the end of the first year, although scientific evidence supporting this concept is very scanty. Mackay (1931), Abt and Nagel (1932), Neale and Hawksley (1933), Parsons (1933), Strauss (1933, 1935) and Hahn, Carothers, Darby, Martin, Sheppard, Cannon, Beam, Densen, Peterson and McClellan (1951) all favoured the view that maternal iron deficiency was a factor in the pathogenesis of iron-deficiency anaemia in infants during the first year of life due to deficient iron storage in the foetal liver. Most of these early reports are unsatisfactory for various reasons. Strauss (1933, 1935) has been widely quoted in support of the contention that maternal iron deficiency causes a reduction of the haemoglobin blood level in the infant during the latter half of the first year of life, but his investigation did not take into account such pertinent factors as birth weight, rate of growth, type of feeding and incidence of infection. In other similar reports the clinical data presented do not bear critical analysis, because control series were not undertaken and the evidence presented in favour of such a hypothesis does not appear to justify the conclusions drawn therefrom.

Fullerton (1937) alone of the earlier investigators did not accept the view that there was a relationship between maternal anaemia and anaemia in the baby during the latter half of the first year of its life. He followed a large number of cases, with a control series, over a long period and took into account such relevant details as birth weight and method of feeding. This earlier work has been verified more recently by Woodruff and Bridgeforth (1953) and Sturgeon (1959) who have shown that the state of an infant's iron nutrition at 1 year of age is not influenced by the level of maternal iron nutrition during pregnancy.

In any assessment of maternal influence on the iron nutrition of the infant it is essential to distinguish clearly between the nutritional state of the infant at birth and at a later stage of its development. If the recent view is accepted that at birth there is no substantial store of iron in any of the infant's tissues except in the circulating haemoglobin, it is apparent that after some months of extrauterine life the dietary iron intake may have influenced the haemoglobin level.

Most of the literature on the relationship between

* Cecil John Adams Memorial Travelling Fellow, 1960.
maternal and infant haemoglobin levels is confused and difficult to assess because the fundamentally important time factor had not been taken into account. The present study was undertaken to investigate the effect of maternal iron-deficiency anaemia on the haemoglobin of the infant during the first three months of life. This investigation consists of two parts: The first deals with the effect of maternal iron-deficiency anaemia at term on the haemoglobin level of the infant in the first 24 hours of life, and the second part with the effect of maternal iron-deficiency anaemia at term on the haemoglobin levels in these infants at 3 months of age, i.e. before dietary effects are likely to have exerted any material influence on the infants' iron nutrition.

Present Investigation

The Newborn Infant. Fifty-nine mothers and their newborn infants were investigated. These mothers were drawn from a random selection of women attending antenatal clinics and were confined at various maternity institutions attached to the University of Cape Town. All these women were given a general medical examination at their first attendance and were found to be healthy. Sero-logical tests for syphilis were negative in all cases. Only those who had full-term normal pregnancies and a normal labour and who had been delivered without untoward incident were included in this series. Women with a history of haemorrhage before, after or during delivery or whose delivery was in any way abnormal, were excluded from this investigation. None had received prophylactic iron therapy during pregnancy.

The mean income per week of the families from which these women came was £14.09 and £5.27 for White and Cape Coloured women respectively. According to the criteria adopted by Bronte-Stewart, Keys, Brock, Moodie, Keys and Antonis (1955) and Moodie (1959) these amounts place these women in the 'medium income' groups of their respective sections in the community.

Fifty-nine cases were selected from this random sample designed to provide two groups, one comprising women who were severely anaemic at term and the other women who were not anaemic at term. It was hoped that such a division based on the presence or absence of severe iron-deficiency anaemia would yield clear-cut results.

The diagnosis of maternal iron-deficiency anaemia was made on the basis of mean corpuscular haemoglobin concentration (M.C.H.C.) values. Most investigators in this field have diagnosed maternal iron-deficiency anaemia solely on the basis of a low haemoglobin level; the fallacy of using such a criterion for the diagnosis of anaemia especially in pregnant women is well recognized.

The 59 cases were divided into two groups.

Group A: 33 women (18 White, 15 Cape Coloured) all with M.C.H.C. levels of 27% or less;

Group B: 26 women (11 White, 15 Cape Coloured) all with M.C.H.C. levels of 31% or more.

The difference in the average mean corpuscular haemoglobin concentration levels in the two groups of mothers was highly significant statistically.

The slight difference between the mean birth weights of the infants born to mothers in group A and the infants of the mothers in group B was not statistically significant.

In the total series of 29 White babies in both groups there were 12 cases (eight in group A and four in group B) in which the umbilical cord had been clamped immediately after birth and 17 (10 in group A and seven in group B) in which the cords were stripped and clamped later. The results in so far as they concerned the infants were analysed separately, because of the variation in haemoglobin levels that occur when umbilical cords are clamped at different times after birth (Lanzkowsky, 1960b). This variability amongst the White infants was taken into account in analysing the results and the White infants therefore were considered under two sub-groups for both group A and group B. The method of cord management was the same in all 30 Cape Coloured infants; the results in these infants were therefore analysed simply on the basis of whether they belonged to either group A or group B. How these cases were divided and the number of cases in each group and sub-group is shown below in simplified form.

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<thead>
<tr>
<th>59 parturient women</th>
<th>33 group A (low M.C.H.C.)</th>
<th>8 White, early clamped</th>
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<tr>
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<td>10 White, late clamped</td>
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<td></td>
<td>15 Cape Coloured</td>
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<tr>
<td>26 group B (high M.C.H.C.)</td>
<td>4 White, early clamped</td>
<td>15 Cape Coloured</td>
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<td>7 White, late clamped</td>
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Methods. Blood investigations were done on venous blood in mothers and on capillary blood in infants. The haemoglobin estimations were carried out by the oxyhaemoglobin method with a Klett-Summerson colorimeter previously calibrated against standard haematin and cyanmethaemoglobin solutions. Packed cell volume estimations were made in accordance with the standard Wintrobe procedure (Wintrobe, 1929).
RESULTS. The Table shows that the mean haemoglobin levels in the first 24 hours of life in infants born to mothers in group A were 19-04, 18-70 and 18-99 g. % for the White early-clamped, White late-clamped and Cape Coloured infants respectively, as compared with values of 20-30, 19-47 and 18-90 g. % obtained from the corresponding sub-groups of infants born to mothers in group B. The difference in haemoglobin values between the corresponding sub-groups of infants born to mothers in group A and in group B was not statistically significant.

The Infant at the Age of 3 Months. The investigation outlined above was continued until the infants were 3 months old. A number of variables, such as body weight, diet and infections, had to be considered in making deductions from observations. Were such an investigation to be continued beyond the third month of the infant's life, it would not be possible to interpret the significance of the results thereof accurately.

Material. The 59 infants of the mothers comprising group A and group B described earlier in this paper, were kept under observation until they were 3 months old. None received prophylactic iron medication during this time. Eleven mothers failed to bring their infants back for a final blood examination and this part of the investigation is therefore based on a total of 48 infants. None of these had suffered from any illness since birth. The two groups of infants were similar as regards birth weight and body weight at 3 months of age. The Table shows that the White early-clamped group A infants and the White late-clamped group A and group B infants (totalling 21 out of 24 White infants) had similar mean weights. The slightly higher mean weight of the three White early-clamped infants in group B is not of sufficient significance to disturb the homogeneity of the group.

RESULTS. The Table shows that the mean haemoglobin levels at 3 months of age were 11-42 g. %, 10-85 g. % and 10-65 g. % for the White early-clamped, White late-clamped and Cape Coloured infants respectively born to mothers in group A, as compared with values of 11-93 g. %, 11-07 g. % and 11-44 g. % in the corresponding sub-groups of infants born to mothers in group B. These differences are not statistically significant. The fall in haemoglobin level between birth and 3 months of age was approximately 8 g. % in all infants. Such a fall is normally to be expected (Lanzkowsky, 1959 and 1960a).

If more evidence were required it could doubtless be obtained by the examination of haemoglobin levels in infants born to extremely anaemic mothers. A case of such severity was seen after the conclusion of this investigation. The maternal haemoglobin was 4-5 g. % at six weeks before term and fell to 2 g. % at the time of delivery. This mother had all the manifestations of an iron-deficiency anaemia. The haemoglobin level of her infant when first recorded at 3 weeks of age was 15-5 g. % and at 3 months of age, it had fallen to 11 g. %.

Discussion

The theoretical explanation usually given for the pathogenesis of anaemia in infants born to iron-deficient mothers is that their hepatic store of iron is inadequate and that early exhaustion of that store occurs during the milk-feeding period of early infancy (Mackay, 1931; Neale and Hawksley, 1933; Strauss, 1933).
The above postulate has been tested experimentally in animals. Happ (1922) and Mitchell and Vaughn (1927) showed that when rats were fed on a diet low in iron, anaemia occurred in the second and third generations of their offspring. Similar observations have been reported for mice (Schmidt-Marburg, 1912) and for pigs (Mc Gowen and Crichton, 1924). Alt (1938), experimenting on rats, studied the offspring of female rats made anaemic by low iron diets. He showed that a single pregnancy in these female rats caused a decrease in the iron store in the liver without affecting the haemoglobin content of the blood. A second pregnancy, however, resulted in moderate anaemia due to iron deficiency. First litter offspring of these female rats with mild iron deficiency had normal haemoglobin values at birth, but they had a considerable reduction in their iron store. Second litter offspring of the female rats who were more iron deficient showed a decrease in haemoglobin content at birth and a reduction of the total iron content of these new-born rats to one-fourth of normal. Alt's work demonstrated that reduction of foetal liver iron store preceded the development of anaemia.

It is unsafe to presume an analogy between anaemia in infants and in animals without considering the fundamental differences which exist between the iron metabolism of experimental animals and of humans (Fullerton, 1937). Rabbits increase their weight six-fold during the almost exclusive period of milk-feeding during the first four weeks of life, and rats grow even more rapidly. A normal human infant gains approximately one-sixth of its birth weight in that time and it is obvious that its iron requirement is relatively much less than that of the rabbit or the rat. The liver store of iron at birth is not comparable in humans and animals. Moreover, the ratio of total foetal weight to maternal weight is much higher in experimental animals than in humans. For example, a female rat weighing 250 g. has an average litter of eight or nine young with a total weight of 36 to 45 g., giving a foetal to maternal ratio of about 1 in 6, whereas the human ratio is much less, approximately 1 in 16. In the rat it is far more likely than in human beings that maternal iron deficiency will result in foetal iron deficiency. Inferences to be drawn from animal experimental investigation cannot be applied unreservedly, if at all, to man.

The iron store in the livers of human newborns was estimated by Gladstone (1932), Sheldon (1932) and Toverud (1935). They found an average of approximately 32, 50 and 60 mg. respectively. In such investigations failure to obtain livers in a blood-free state (presumably an impossibility) vitiates the results, especially if current opinion is correct in maintaining that the circulating haemoglobin carries most of the baby's supply of iron. Fullerton (1937), working on the assumption that there is no iron reserve in the liver at birth, calculated that a hypothetical deficit of 50 mg. of liver iron at birth would only reduce the blood iron from an estimated 333 mg. to 283 mg. by the time the infant reached the age of 9 months, and this would give a haemoglobin level of 73%. If this is correct, a partial deficiency in the liver iron store at birth could have only a slight effect on the haemoglobin level in later infancy.

Smith, Rosello, Say and Yeya (1955), having given transfusions of erythrocytes tagged with Fe$^{55}$ to mothers, judged that transplacentally acquired iron, not present in haemoglobin at the time of birth, was meagre in relation to the amounts of iron contained in circulating haemoglobin. The view that the blood of the newborn baby is the major source of the iron to be used later in maintaining haemoglobin levels is well documented (Lintzel, Rechenberger and Schairer, 1944; Hemmeler, 1946; Neander and Vahlquist, 1949; Langley, 1951; McCance and Widdowson, 1951; Josephs, 1953).

Smith et al. (1955) also showed that transplacental Fe$^{55}$ was 'diluted' by dietary iron when the infants were 3 to 4 months old. They showed that between the third or fourth month and the second year of age the haemoglobin level increased only slightly, while the total amount of haemoglobin was doubled, primarily by the addition of haemoglobin derived from dietary iron. This indicates that the older the infant, the less the importance of transplacental iron as compared with dietary iron. Even if at birth there should be a deficiency in total body iron associated with frank maternal iron-deficiency anaemia, this can be compensated for at 1 year of age by the iron in the infants' diet.

There is no reliable evidence to support the contention that a close relationship exists between maternal haemoglobin levels and those in the infant at any age after birth in human beings. The present work is in agreement with that of Woodruff and Bridgeforth (1953) and Sturgeon (1959) who have shown that the two levels are not interdependent at birth. The available evidence supporting the presence of a substantial store of iron in the liver is not convincing.

The work done by Sturgeon and the results of the present investigation do not support the concept that maternal iron deficiency has any effect whatsoever on the haemoglobin level of the baby at 3 months of age in infants of normal birth weight.
who have remained well since birth. It certainly seems that, so far as normal infants are concerned, they are parasitic on maternal iron and look after their own well-being in this respect very efficiently while in utero. Contrary views appear to have been based on observations which have ignored certain essentials. A careful attempt was made to control these factors in the present investigation. Many of the earlier workers cannot be blamed for not having taken such factors into consideration. The advancement of knowledge and development of interest in research has thrown into prominence many facets in this regard which were previously considered to be of little importance.

Summary

A review of the literature indicates that there is controversy as to whether maternal iron-deficiency anaemia influences the level of haemoglobin in the blood of infants or not. The present survey was designed to investigate this problem.

The possible influence of maternal iron-deficiency anaemia on the infant was considered under two headings: (a) in the newborn infant and (b) at 3 months of age, before dietary effects are likely to have influenced the infant's iron nutrition.

Selected mothers (White and Cape Coloured) were divided into two groups: one consisting of women whose mean corpuscular haemoglobin concentration values were 27% or less at term and the other, whose values were 31% or more. The infants of these mothers were investigated.

It was found that there was no significant difference of mean haemoglobin level in the infants, during the first 24 hours of life or at 3 months of age, born to either the anaemic or non-anaemic mothers.

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