Today's Treatment

Blood and Neoplastic Diseases

Pregnancy Anaemia

MARION H. HALL

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During normal pregnancy there is a fall in haemoglobin concentration which is often referred to as "the physiological anaemia of pregnancy." This occurs because the red cell volume expands by at least 18% (reaching a maximum at term) but the plasma volume expands much more (by about half, reaching a plateau at around 34 weeks in the primigravida, but continuing to rise until term in the multigravida). Thus, though the total amount of haemoglobin in the body rises by 85g or so, its concentration drops by 1-2 g/ml. This fall in haemoglobin concentration is associated with a *reduced* arteriovenous oxygen difference, confirming that the increased oxygen requirements of pregnancy can readily be met. The disproportionate increase in the plasma volume is appropriate to the increased renal blood flow, which helps to eliminate the waste products of increased metabolism, and to the increased blood flow to the skin which is required to lose the excessive heat produced. Hence the fall in haemoglobin concentration does not signify "anaemia": it is a normal physiological event and does not require treatment.[1]

Iron Deficiency

DIAGNOSIS

In Western Europe and America iron deficiency is by far the commonest cause of pregnancy anaemia, occurring in 15-30% of women depending upon the diagnostic criteria used. In normal pregnancy, the serum iron concentration usually falls by about 35% and the iron-binding capacity rises by 60-100%, even when the diet is rich in iron or when iron medication is given. Morphological changes in the red cells (hypochromia and microcytosis), together with a fall in the mean corpuscular haemoglobin concentration, are the best guides to a diagnosis of anaemia, and a peripheral blood film should be examined when the haemoglobin concentration is less than 12 g/100 ml at booking, or less than 11 g/100 ml in late pregnancy. Iron deficiency may be present at booking but more commonly appears in the mid-trimester.

TREATMENT

Unless delivery is imminent or the anaemia very severe, the initial treatment of iron-deficiency anaemia in pregnancy should be with oral iron. The absorption of oral iron is increased in pregnancy, especially if there is iron deficiency, and oral iron is usually well tolerated, safe, and effective (though side effects such as nausea, heartburn, abdominal pain, constipation, or diarrhoea may occur). An inexpensive preparation such as ferrous fumarate 400 mg, or ferrous gluconate 600 mg, given in divided doses preferably with food, should be adequate and such a dose (70-130 mg elemental iron) certainly far exceeds the normal pregnancy requirement of 4-5 mg per day in the last trimester. (If the patient's diet is likely to be deficient in ascorbic acid, the addition of ascorbic acid 250 mg daily in divided doses may be helpful as it improves iron absorption. Dietary advice should also be given.)

The response to treatment should be checked by repeat haemoglobin estimation and examination of a stained blood film and a reticulocyte count after a few weeks (weekly if the anaemia is severe). If the haemoglobin level rises satisfactorily treatment should be continued for another three months to replenish iron stores. If the haemoglobin does not rise but the evidence of iron deficiency disappears, then another cause for the anaemia, such as folic-acid deficiency, should be suspected and sought. If iron deficiency remains apparent, parenteral iron therapy may be indicated. In patients of Mediterranean, African, or Eastern origin, β-thalassaemia minor should first be excluded by haemoglobin electrophoresis, which should in any case be routine at booking in these patients.

Parenteral iron therapy is useful when it is suspected that a patient is either not taking or not absorbing oral medication, or when a more rapid rise in haemoglobin is essential (though the response to parenteral medication is only marginally more rapid than that to oral treatment). The safest form of parenteral treatment in pregnancy seems to be iron sorbitol injection. Daily intramuscular injections of 2 ml (containing 100 mg elemental iron) should be given for seven to 10 days until the calculated iron deficit is made up and the iron stores replenished (remembering that about 30% of the dose is excreted in the urine). If necessary, twice-daily injections may be given.

Oral iron should be stopped two days before starting intramuscular therapy to avoid overloading the iron-binding capacity and a test dose of 0·5 ml should be given. Nausea and vomiting within half an hour of the test dose suggests that the iron-binding capacity is overloaded. The injections are commonly painful and the skin may become discoloured. Increased excretion of white cells in the urine may occur in patients with co-existing urinary tract infection, but there is no evidence of increased bacterial activity.

Unless anaemia is severe intramuscular iron therapy may usually be given to outpatients—for example, by asking the district nurse to visit the patient's home. Where this is impossible, if the patient is working or will not co-operate, there is a case for total dose intravenous iron infusion using iron dextran. This treatment is contraindicated by a history of

Department of Obstetrics and Gynaecology, University of Aberdeen
MARION H. HALL, M.D., M.R.C.O.G., Consultant

allergy or asthma, since there is a risk of severe anaphylactoid reaction, especially in pregnancy. The infusion of iron dextran (dose according to the concentration of not over 5%) must be started very slowly and speeded up only if no reaction occurs. Local venous thrombosis sometimes occurs.

Total dose iron infusion is certainly more dangerous than intramuscular iron sorbitol injection, but has the advantage that the patient has to attend hospital for one or two days at the most, so that it may be indicated in patients with social problems. There is some evidence that a more sustained haemoglobin rise is obtained than with iron sorbitol injections. With either form of treatment, the doctor must check the response to treatment by a repeat full blood count.

PROPHYLAXIS

In areas where iron deficiency is common, owing to dietary deficiency or to gastrointestinal blood loss from hookworm infestation, routine oral iron supplements should be prescribed in pregnancy. Nevertheless, as many as 30% of patients do not take such supplements,[2] so that careful haematological screening is still necessary even if iron is routinely prescribed. As a minimum the haemoglobin should be estimated at booking, at 30 and 36 weeks' gestation, and after delivery.

In areas where most pregnant women do not suffer from iron deficiency, such as the United Kingdom, it is more doubtful whether iron should routinely be prescribed. Even in women without iron deficiency, the haemoglobin concentration can be raised by pharmacological though not by physiological doses of iron; this is thought to be due to the erythropoietic effect of iron on the bone marrow. Nevertheless, there is no evidence that normal women feel better, or benefit in any way from having their haemoglobin concentration raised in this way,[3] and rationally iron therapy should be reviewed for those who actually show iron deficiency—especially since iron consumption in the first 56 days of pregnancy is associated with a higher incidence of major congenital abnormality in the fetus.[4]

It may also be reasonable to select for routine iron supplements in the second and third trimester women of low social class with inadequate nutrition, those with a history of iron-deficiency anaemia, and those with twin pregnancies.

Folic-acid Deficiency

DIAGNOSIS

Megaloblastic anaemia in pregnancy is virtually always due to folic-acid deficiency, since pregnancy does not occur in untreated pernicious anaemia. Megaloblastic anaemia is very common in some areas such as West Africa, where it is principally due to malarial haemolysis, though haemoglobinapathies (principally Haemoglobin SC disease) make a major contribution in a minority of cases. Women of African or Eastern origin should always be screened for haemoglobinopathy in pregnancy, since some who are normally asymptomatic may have serious problems in pregnancy.

Megaloblastic anaemia is uncommon in Western Europe and America and occurs in only 1-2% of pregnant women in the United Kingdom. A fall in the serum folate level occurs in normal pregnancy, perhaps partially due to increased fetal demands and malabsorption, but principally due to reduced renal tubular reabsorption of folate.[5] This fall in serum folate does not usually cause anaemia or any problem, and is not in itself an indication for treatment. Even in women with a low haemoglobin concentration a low serum folate does not mean that folic-acid deficiency is the cause of the anaemia, and megaloblastic anaemia can be diagnosed only if a peripheral blood film shows a macrocytic normochromic picture, if a buffy coat film shows nuclear hypersegmentation of the neutrophil polymorphs, or if examination of the bone marrow shows megaloblastic changes. Iron deficiency is common in women with folic-acid deficiency, but probably both are usually due to inadequate nutrition, and iron deficiency does not in itself predispose to folic-acid deficiency.[6]

In Britain megaloblastic anaemia usually occurs in the third trimester of pregnancy, but is diagnosed for the first time in the puerperium in as many as 20-30% of cases, perhaps precipitated by blood loss at delivery. Examination of a blood film or buffy coat is therefore mandatory in all cases of puerperal anaemia. Frequent full blood counts in the last few weeks of pregnancy should enable many of these anaemias to be diagnosed before delivery.

TREATMENT

Treatment of established or suspected megaloblastic anaemia is by oral folic acid 15-30 mg daily in divided doses. Toxic effects have not been reported in pregnancy. Treatment should be continued for a month after delivery, but should then be stopped because of the risk of precipitating subacute combined degeneration of the cord in a subsequently arising case of pernicious anaemia.

PROPHYLAXIS

Routine prescription of folic-acid supplements in pregnancy has been widely advocated and practised but with doubtful justification. What are they intended to achieve?

Certainly a supplement of 300 μg folic acid daily is necessary to maintain the serum and red cell folate at a normal non-pregnant level,[7] but it has never been shown that it is necessary or desirable to do so. In normal women the haemoglobin concentration is not raised by folic-acid supplements,[8] and there is no good evidence that the outcome of pregnancy is in any way improved. In developed countries, therefore, the practice of routine folic-acid prophylaxis in pregnancy is not justified, though it is probably not actually harmful.

In areas such as West Africa where dietary deficiency of folate is common and folate requirements are increased by malarial haemolysis and haemoglobinopathies routine folic-acid supplements of at least 300 μg daily are required.

In Western countries some specific groups of pregnant women may be selected for routine folic-acid prophylaxis. For example, in twin pregnancy there are likely to be increased urinary losses of folate and increased fetal demands, and megaloblastic anaemia is thought to be commoner, though this has not been confirmed in a large series of twin pregnancies in Aberdeen. Epileptic women on anticonvulsant therapy are prone to develop megaloblastic anaemia, but since administration of folic acid may increase the fit frequency of fits this should be prescribed only if megaloblastic anaemia actually occurs, and then only under close supervision.

Other Anaemias

CHRONIC RENAL DISEASE

Normochromic anaemia often occurs in pregnant women with chronic renal disease, and renal disease should be suspected and searched for in women with pregnancy anaemia not responding to treatment. In known renal disease treatment should be with the appropriate haematinics, but is unlikely to be successful, since erythropoeisis is depressed.

PICA

Pregnant women often show dietary fads and deficiency of iron or folate may result. They may also consume unusual foods in large quantities; fortunately, this is generally harmless but occasionally toxic substances such as lavatory fresh-

eners or newsprint may be taken and give rise to anaemia. The history may be difficult to elicit and should always be carefully checked in cases of refrectory anaemia in pregnancy. The treatment, of course, is to withhold the toxic substance.

MICROANGIOPATHIC ANAEMIA

Microangiopathic anaemia is a rare complication of eclampsia, intrauterine death, or amniotic fluid embolism, and is associated with disseminated intravascular coagulation. Fortunately, it is usually self-limiting but in a severe case intravenous heparin may be helpful.

Blood Transfusion

In developed countries anaemia in pregnancy is rarely sufficiently severe to require blood transfusion. Nevertheless, occasional women who have had little antenatal care are found to have a severe anaemia when near term, or in labour. Appropriate haematinic therapy should be instituted and blood should be cross-matched in preparation for delivery, in case caesarean section should be required or postpartum haemorrhage occur. If the blood volume is normal, however, a blood transfusion should be given only if the haemoglobin concentration is less than 7 g/100 ml, in view of the risk of serum hepatitis. Even severe anaemia hardly ever necessitates blood transfusion in the puerperium; a brisk response to haematinics may be expected.

If the packed cell volume is less than 13%, as is quite common in underdeveloped countries—where the anaemia is haemolytic and progressive—cardiac failure is likely to develop, and blood transfusion is therefore dangerous, but necessary. Pulmonary oedema may be prevented by the simultaneous administration of a rapidly acting diuretic such as ethacrynic acid, or by exchange transfusion.[9] Where gross iron-deficiency anaemia produces a very low haemoglobin concentration, however, the response to iron is excellent and should be accompanied by attention to diet and treatment of the hookworm infestation.

References

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3 Paintin, D. B., Thomson, A. M., and Hytten, F. E., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1966, 73, 181.
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Any Questions?

We publish below a selection of questions and answers of general interest

Does tetracycline Cause Dysphagia?

Is there any evidence that tetracycline causes dysphagia?

It is unlikely that any of the tetracyclines could cause dysphagia by a direct pharmacological action. The drugs may, however, cause local irritation of the oropharyngeal or lower oesophageal mucosa and this would result in dysphagia. Oxytetracycline is more likely to cause such local irritation than are the other tetracyclines. A well recognized complication of therapy with the tetracyclines is secondary fungal infection usually due to *Candida*. This may affect the pharynx or oesophagus and thus give rise to dysphagia. The diagnosis of such a secondary infection is frequently not as simple as might be expected so careful examination of the pharynx should be done in any patient on a tetracycline who complains of dysphagia. This would include taking swabs for fungal tests.

Excessive Salivation in Retarded Youth

What measures can be taken to alleviate excessive salivation in a mildly mentally retarded youth with cerebral palsy?

I suspect that the presenting symptom is drooling or dribbling and that the postulated underlying disorder—excessive salivation—has no solid evidence to support it. If the patient was taught to keep his month closed and to swallow accumulating saliva, there would probably be no problem whether the amount of saliva secreted was normal or excessive. Speech therapists are often interested in such training or the patient might have behaviour therapy under a specialist in mental handicap or child psychiatry. Reduction in output of saliva by drugs, surgery, or *x* rays is inadvisable as are operations designed to transplant salivary ducts so that the saliva runs into the throat instead of the mouth.

Notes and Comments

Routine Use of Penicillin for Sore Throat.—Dr. R. J. FALLON (Department of Laboratory Medicine, Ruchill Hospital, Glasgow) writes: Though I would agree in general terms with the advice of your expert ("Any Questions?" 26 January, p. 156) it is unfortunate that he said that the number of tetracycline-resistant Group A streptococci is now falling, based upon the paper by Dr. M. H. Robertson[1] whose observations related to streptococci isolated in South-west Essex. Though there is no doubt of the validity of the findings for that area I think it is important to point out[2] that Dr. Robertson's experience was not the same as mine in Scotland where, in the Glasgow area, there has been no fall in the proportion of tetracycline-resistant Group A haemolytic streptococci over the last four years. One cannot necessarily generalize for the country as a whole on observations made in any particular area because, even in this small country, epidemiological patterns may well vary from area to area. It would be interesting to know of current surveillance of tetracycline resistance in streptococci from other areas of Britain to see whether there are any other noteworthy regional variations.

1 Robertson, M. H., *British Medical Journal*, 1973, 4, 84.
2 Fallon, R. J., *British Medical Journal*, 1973, 4, 300.