



## PREGNANCY- AND LACTATION-RELATED FOLATE DEFICIENCY IN SOUTH AFRICA — A CASE FOR FOLATE FOOD FORTIFICATION

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**Objective.** Characterisation of patients presenting with megaloblastic anaemia according to clinical, sociological, haematological and aetiological aspects of their disease, and use of these findings to increase awareness among clinicians and to make recommendations regarding changes in national health policy.

**Methods.** This study included 104 patients presenting with megaloblastic anaemia to a large referral hospital over a 1-year period. Data were collected and analysed in terms of age, gender, parity, gravidity, duration of lactation, socio-economic status, geographical origins, diet, previous haematitic treatment, clinical presentation and haematological measurements.

**Results.** The most common cause of megaloblastic anaemia was pernicious anaemia or probable pernicious anaemia (50%), followed by pregnancy- and lactation-related folate deficiency (32%); of these patients, the majority (28) presented postpartum while lactating; 5 patients were in the immediate puerperal period of 6 weeks, and a further 16 were seen during the first year and 7 during the second year following delivery. Only 4 patients were pregnant, and it is noteworthy that 2 of these were still lactating at 34 weeks' gestation.

**Conclusion.** Pregnancy- and lactation-related folate deficiency up to 2 years after delivery remains a common cause of megaloblastic anaemia in South Africa. Certain communities in rural South Africa have recently been shown to have high incidences of both neural tube defects and folate deficiency. The fortification of a staple food (e.g. maize or flour) with folic acid is feasible, inexpensive, safe and likely to be beneficial. This practice should reduce the prevalences of

megaloblastic anaemia in fertile women, neural tube defects, other congenital abnormalities, intra-uterine growth retardation, prematurity and possibly cardiovascular disease. There is urgent need for a national policy in this regard.

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Prolonged lactation as a common cause of folate deficiency has been a neglected area of study since the reports of its importance in South Africa 30 - 40 years ago.<sup>1-4</sup> Lactating women commonly present many months and up to 2 years following delivery with megaloblastic anaemia, sometimes profound, due to folate deficiency. These women are mostly of low socio-economic status and high parity, have breast-fed for months or years, and eat a sub-optimal diet.<sup>5,6</sup> The staple food, maize, has a low folate content of approximately 4 µg/100 g.<sup>7,8</sup> The main potential source of folate is green leaf vegetables, which have wide variations of availability during the year, and are liable to be cooked for long periods and reheated several times, in this way destroying most of the folate content.<sup>9</sup>

In many areas of rural South Africa, folate deficiency is a more common cause of anaemia than iron deficiency in pregnant black women.<sup>9,10</sup> The daily dietary requirement for food folate during lactation (600 µg/day) is only slightly less than the requirement for food folate during pregnancy (800 µg/day),<sup>11</sup> but lactation can continue for much longer than the duration of pregnancy, and in southern Africa it is possibly the more important cause of severe depletion. The diagnosis is probably missed in many non-pregnant women presenting to clinics or medical departments.

The present study documents the aetiology of megaloblastic anaemias in patients attending Chris Hani Baragwanath Hospital in Soweto, Johannesburg, over a 1-year period. The objective was to ascertain the common causes of megaloblastic anaemia occurring in the black population so as to be able to make recommendations regarding management and prevention.

### SUBJECTS AND METHODS

#### Subjects

Consecutive patients over 15 years of age presenting to Chris Hani Baragwanath Hospital with megaloblastic anaemia from January 1994 to January 1995 were included in this study. The present communication contains detailed analysis of pregnant and lactating women only.

#### Methods

Peripheral blood criteria for suspecting megaloblastic anaemia were oval macrocytes together with any one of the following: red blood cell macrocytosis, tear drops, basophilic stippling,

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Howell-Jolly bodies and red cells containing nuclear remnants, or right shift of neutrophils (> 5% with > 5 lobes).

Once a diagnosis of megaloblastic anaemia was suspected, several investigations were performed. Haemoglobin (Hb) and full blood counts (FBC) were analysed on a H3 Technicon blood analyser. Reticulocyte counts were performed manually, according to the method described by Dacie and Lewis.<sup>12</sup> Serum vitamin B<sub>12</sub>, folate and red cell folate concentrations were analysed using the Becton Dickinson Simul TRAC-SNB Radioassay kit (Catalogue No. 257117-100 tube kit, Becton Dickinson & Co., Orangeburg, New York) and a Packard Cobra II autogamma counter. Lymphocyte immunoassay control standards were included in each run of specimens. Bone marrow as aspirated from the right posterior iliac crest or other sites, and smears stained by the May-Grünwald-Giemsa stain and the Prussian blue (Perls) stain for iron, were assessed by a haematopathologist. Diagnostic criteria for megaloblastosis on bone marrow aspirates were based on Chanarin's scoring system.<sup>13</sup> Further investigations were dependent on the clinical presentation of the patient and the above results.

### Treatment and progress

With the aid of semi-structured questionnaires subjects were questioned as to socio-economic status, diet, alcohol and other substance use, medical and obstetric history and previous intake of haematinics. They were subjected to a full physical examination.

Patients were assessed on admission regarding the need for a blood transfusion. As a general rule, patients with an Hb of > 5 g/dl did not receive transfusion unless they were in cardiac failure or had evidence of cardiac ischaemia. Platelet transfusions were given to those patients with severe bleeding and for whom coagulation studies were normal. These were not rigidly applied rules but guides to treatment. Once the specimens for the necessary investigations had been collected, patients were started on oral folic acid 5 mg daily if the history was suggestive of folate deficiency, e.g. pregnancy, chronic haemolysis or ethanol-related anaemia. Vitamin B<sub>12</sub> was given with folate therapy if the history and/or clinical presentation suggested that this deficiency was likely and could not be excluded on clinical grounds, or where the distinction between folate and vitamin B<sub>12</sub> deficiency could not be reasonably made without precipitating neurological damage. Therapy was amended if necessary once the red cell folate and vitamin B<sub>12</sub> concentrations were available. FBC and differential and reticulocyte counts were repeated on days 2 - 4, 5 - 6, 7, 14 and at 1 month in order to document the response to treatment. Serum electrolytes (in particular potassium concentrations) were monitored during the recovery period.

### Statistical analysis

Clinical and laboratory information was collected on information and result flow sheets. Each item of information

was coded and entered onto a database with the aid of a computer program. The database was sorted and statistically analysed using frequency tables, univariate analysis, contingency tables and Kruskal-Wallis analysis.

### Ethical clearance

Ethical clearance for this study was obtained from the Ethics Committee for Research on Human Subjects, University of the Witwatersrand, Johannesburg.

## RESULTS

### Total patients with megaloblastic anaemia

During the 1-year period, 104 (82 female and 22 male) black patients presented to Chris Hani Baragwanath Hospital with megaloblastic anaemia (Table I). There were two main groups of patients, those with a definite (34%) or suspected (16%) diagnosis of pernicious anaemia, and those with pregnancy- or lactation-related folate deficiency (32% of the patients).

### Pregnancy- and lactation-related folate deficiency

Twenty-eight patients presented with megaloblastic anaemia between 2 weeks and 24 months after the birth of their last infant. Five patients were in the immediate puerperal period, 16 patients presented during the first year after delivery and a further 7 patients presented 12 - 24 months after delivery. A further 4 patients were pregnant; of these 2 were still breast-feeding at 34 weeks' gestation, 1 was receiving treatment for pulmonary tuberculosis, and 1 was pregnant with twins. The remaining patient presented following a spontaneous abortion. The youngest patient was 15 years of age. Only 2 patients were over 40 years of age; 1 was 48 years old and postpartum after her 7th pregnancy; the other was 42 years old, pregnant for the 6th time and still breast-feeding her last child aged 2 years (Fig. 1). The duration of lactation of postpartum patients ranged

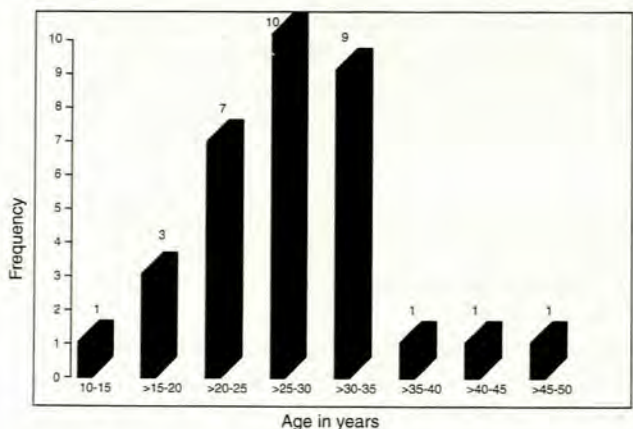


Fig. 1. Age distribution of 33 South African women with pregnancy- or lactation-related folate-deficiency megaloblastic anaemia.





**Table I. Classification of 104 consecutive South African black patients with megaloblastic anaemia**

Group	Cause of megaloblastic anaemia	Males	Females	Total	%
1a	Pernicious anaemia (based on Schilling test and IF Ab test)	11	25	36	34
1b	Vitamin B <sub>12</sub> deficiency suggestive of PA (IF Ab positive, no Schilling test result)	3	3	6	6
1c	Vitamin B <sub>12</sub> deficiency, no further investigation: clinically suggestive of PA	2	8	10	10
1d	Vitamin B <sub>12</sub> deficiency, IF Ab positive and normal Schilling (1 with abnormal food-bound Schilling test)	0	2	2	2
2	Pregnancy-related folate deficiency				
	<i>Post partum</i>	-	28	33	32
	Post spontaneous abortion	-	1		
	Pregnant	-	4		
3	Miscellaneous cause of folate deficiency				
	Malnourished and underlying malignancy	1	-		
	Associated with TB	1	1	9	9
	Associated with AIDS + pneumocytosis	1	-		
	Associated with AIDS + TB	-	1		
	Malnourished and poor socio-economic conditions	-	2		
	Malnourished + ethanol	1	-		
	Mental retardation	-	1		
4	Miscellaneous cause of vitamin B <sub>12</sub> deficiency				
	Bowel excision	-	1		
	TB/malabsorption	-	2	5	4
	Malabsorption associated with typhoid/chronic diarrhoea	-	1		
	Gastric surgery	1	-		
5	No vitamin B <sub>12</sub> or folate assays available	1	2	3	3
	Total	22	82	104	100

AIDS = acquired immunodeficiency syndrome; IF Ab = intrinsic factor antibodies; PA = pernicious anaemia; TB = tuberculosis.

from 1 to 36 months and the number of pregnancies (gravidity) ranged from 1 to 7.

### Socio-economic and general demographic data

The majority of patients were of low socio-economic status. All pregnant patients were from the more rural areas in Northern Province (previously Northern Transvaal) or KwaZulu-Natal. The majority of patients from the postpartum lactation-related folate deficiency group were resident in urban or informal settlements within the Gauteng area. At least 25% of these patients gave a history of previously being resident within a rural area.

### Dietary history

Fifty-eight per cent of patients gave a history of adequate diet with regard to yellow/green vegetable intake. Intake included cabbage that had been fried, or *morogo*, a type of wild spinach, which had been cooked in porridge for a prolonged period of time. The majority of patients (64%) claimed to be consuming a diet adequate in protein.

### Obstetric history

Two patients gave a history of previous spontaneous abortions.

No history of antepartum haemorrhages was obtained, but 1 patient had had a postpartum haemorrhage. Only 1 patient gave a history of giving birth to an abnormal child, who was mentally handicapped following prolonged labour.

### History of previous haematinics

Although 14 patients had previously received haematinics, haematological responses had not been satisfactory. Most patients presented to prenatal clinics after 28 weeks' gestation and would therefore have received supplements for a short time only. Three patients reported intolerance in the form of vomiting, and many patients reported poor compliance. Thirteen of the 28 postpartum patients denied that they had been given supplements during pregnancy.

### Clinical data

The most common presenting symptoms were generalised weakness (88%), dizziness (42%), symptoms of infection (15%) (e.g. fever, cough, burning on micturition), vomiting (12%), abdominal pain (24%), loss of weight (6%), loss of appetite (12%), generalised body pains (18%), confusion (3%), diarrhoea (6%), headaches (6%), palpitations (6%) and bleeding (3%). Five patients had serious or chronic medical problems: 1 patient had





severe large-vessel arteritis, diagnosed as Takayasu's disease; 3 patients had tuberculosis at various stages; and the 5th patient presented 2 weeks after delivery with an 'acute megaloblastic arrest' of erythropoiesis, retained products of conception, septicaemia and a disseminated intravascular coagulopathy. None of the patients had significant neurological abnormality.

### Laboratory parameters

On presentation 19 patients had an Hb of < 5.0 g/dl; 14 patients had a platelet count (Plt) of < 100 x 10<sup>9</sup>/l, of whom 5 had a Plt of < 50 x 10<sup>9</sup>/l; and 5 patients had a white cell count (WCC) of < 2.0 x 10<sup>9</sup>/l (Table II). Fourteen patients had pancytopenia (Hb < 11.0 g/dl, WCC < 3.5 x 10<sup>9</sup>/l and Plt < 140 x 10<sup>9</sup>/l). Macrocytosis (mean cell volume (MCV) > 100 fl) was present in 13 patients; none had a MCV > 120 fl (Table II).

**Table II. Presenting laboratory parameters of 33 South African women with pregnancy- or lactation-related folate-deficiency megaloblastic anaemia**

Parameter	Med.	Mean	Range	Reference range
Hb (g/dl)	3.9	4.5	1.5 - 8.8	11.0 - 15.5
MCV (fl)	96	95	76 - 115	82.0 - 100
WCC (x 10 <sup>9</sup> /l)	3.4	4.3	1.3 - 18.4	4.0 - 11.0
Platelets (x 10 <sup>9</sup> /l)	108	126	21 - 422	140 - 400
Potassium (mmol/l)	3.4	3.5	2.2 - 4.5	3.3 - 5.0
Bilirubin, total (μmol/l)	21	18.5	5.0 - 48.0	4 - 21
Bilirubin, direct (μmol/l)	8.0	7.4	3.0 - 13.0	2 - 6
Bilirubin, indirect (μmol/l)	12.0	11.1	2.0 - 36.0	2 - 15
LDH (U/l)	5 079	7 031	1 592 - 15 260	210 - 430

Hb = haemoglobin; LDH = lactate dehydrogenase; MCV = mean cell volume, WCC = white cell count.

### Follow-up

Treatment was followed by reticulocytosis preceding a return to normal values of Hb, WCC and Plt (Table III); no patient developed significant hypokalaemia. Only 1 patient, who had AIDS and tuberculosis, showed no response to therapy.

## 2 DISCUSSION

Over half of the 104 consecutive patients attending Chris Hani Baragwanath Hospital with megaloblastic anaemia over a 1-year period had proven or probable Addisonian pernicious anaemia (Table I). This observation confirms the similar observation from Harare, Zimbabwe,<sup>14</sup> and contradicts the widely held belief that pernicious anaemia is not seen among

**Table III. Haematological and serum potassium values of 33 South African women with pregnancy- or lactation-related folate-deficiency megaloblastic anaemia following appropriate treatment**

	Days 2-4	Days 5-6	Day 7	Day 14	Day 21	One month
<b>Reticulocytes (%)</b>						
Mean	10	15	13	7	5	2
Med.	8	16	11	4	5	2
Min.	< 1	< 1	4	3	< 1	< 1
Max.	26	31	25	13	10	6
<b>Haemoglobin (g/dl)</b>						
Mean	6.2	6.8	6.9	9.3	9.9	10.7
Med.	6.6	6.7	6.8	9.4	9.6	11.0
Min.	3.2	2.9	4.5	7.2	8.8	8.1
Max.	9.7	9.8	10.3	10.9	12.3	12.4
<b>WCC (x 10<sup>9</sup>/l)</b>						
Mean	7	10.2	8.3	8.9	7.5	7.0
Med.	6.4	5.9	6.7	7.8	7.0	4.9
Min.	2.5	2.2	2.9	3.2	3.8	4
Max.	14.9	31.7	23	20.3	13.3	12.9
<b>Platelets (x 10<sup>9</sup>/l)</b>						
Mean	126	174	368	418	450	337
Med.	109	138	276	396	409	321
Min.	32	40	145	110	250	175
Max.	354	532	714	888	940	639
<b>Serum potassium (mmol/l)</b>						
Mean	3.3		4.1			
Med.	3.2		4.0			
Min.	2.7		3.4			
Max.	4.6		5.0			

WCC = white cell count.

Africans in non-tropical sub-Saharan Africa. It remains true, however, that pernicious anaemia is rare in tropical Africa.<sup>15</sup>

The second largest group of patients (32%) were those with folate deficiency related to lactation and pregnancy. Folate deficiency was seen predominantly among lactating women, which was an unexpected finding. Twenty-eight lactating women were seen compared with only 4 women seen during pregnancy, and 1 post-abortion (Table I). Five lactating women were in the immediate puerperium, so their deficiency was likely to have been induced primarily by the demands of pregnancy. The remaining patients presented between 6 weeks and 24 months after delivery with no causative factors detected other than nutritional inadequacy and lactation.

Although over half of the patients claimed to have adequate intakes of yellow/green vegetables, their accounts of their diets were likely to be inaccurate, and it is certain that any folate-rich foods were cooked for prolonged periods of time, sufficient to destroy much of the food-folate. The majority (19 patients) were aged between 25 and 35 years, were





multiparous and had been lactating for many months. Evidence from a number of sources suggests that lactation may drain maternal folate stores.<sup>5,16</sup> The folate content of breast-milk (5 µg/100 ml) equates to a loss of approximately 25 µg folic acid per day.<sup>17</sup> Red cell folate levels in lactating mothers are significantly lower than those of their infants during the first year of life.<sup>18</sup>

Megaloblastic anaemia is the most florid and obvious consequence of folate deficiency, and a high frequency implies widespread subclinical folate deficiency in the community. A minor degree of maternal folate deficiency in early pregnancy, either nutritional or due to genetically determined defects of folate metabolism, such as a thermolabile variant of 5,10-methylenetetrahydrofolate reductase, is now recognised as an important risk factor for neural tube defects in infants.<sup>19,21</sup> Lactation-induced folate deficiency in particular could lead to a high rate of folate deficiency at the time of subsequent conception. High incidences of neural tube defects have been reported in certain rural areas of South Africa where folate deficiency in pregnancy is common,<sup>9,22</sup> although research has not yet been published to directly link the two conditions.

Besides megaloblastic anaemia during infancy, childhood, pregnancy and lactation<sup>23</sup> and neural tube defects, reported adverse consequences of folate deficiency include intra-uterine growth retardation,<sup>24,25</sup> growth retardation in infancy and childhood,<sup>26</sup> immature pelvic development leading to obstructed labour in teenage pregnancies,<sup>27</sup> and hyperhomocystinaemia, possibly carrying an increased risk of arterial disease and coronary heart disease.<sup>21,28</sup> With the possible exception of arterial disease, all these conditions are of major public health importance in sub-Saharan Africa.

Prevention of folate deficiency should be given high priority in the South African community. There are three strategies: (i) supplementation for groups at risk; (ii) modification of the diet to increase natural folate intake; and (iii) fortification with folic acid of a commonly consumed and centrally prepared staple.

Supplementation has limited impact. In South Africa infrastructure is still being developed that will provide primary health care for women in the reproductive age range, as well as for children. Where clinics are established, the appropriate supplements may not always be available. Women attend prenatal clinics late or not at all, and there may be poor compliance, especially when folic acid is combined with iron in the same tablet. These factors were exemplified by the haematological histories of the subjects in this study. Preconception supplementation is even more difficult to provide effectively, as most pregnancies are unplanned and the need for supplementation is not appreciated.<sup>29</sup> It is recommended that as part of the expanding primary health care programme in South Africa, prenatal care should include the provision of a combined tablet of ferrous sulphate 200 mg and folic acid 400 µg taken daily during pregnancy and into the puerperium.

Research into fortification of a staple with folic acid was pioneered in South Africa.<sup>6,30-33</sup> However, the previous government never implemented this strategy and the present study has shown that the pattern of folate deficiency has remained unchanged for decades. Research into fortification of a staple (maize meal) equivalent to folic acid 300 µg per day produced an appropriate rise of red cell folate concentration. Recent research confirms the earlier South African observations.<sup>33-35</sup> Fortification at a target of 300 µg per day (as proposed by earlier researchers) or 400 µg per day is not likely to endanger patients with pernicious anaemia,<sup>36,37</sup> who are seen relatively frequently in all major South African ethnic groups. However, doses in excess of 1 mg/day are likely to mask underlying cobalamin deficiency and result in progressive and irreversible neurological damage.<sup>36-38</sup>

The formation of policies for folic acid fortification should be prioritised by the South African government as well as by governments of other African and Asian countries where nutritional folate deficiency is common.<sup>5,23,39,40</sup>

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