Why should women have lower reference limits for haemoglobin and ferritin concentrations than men?

D Hugh Rushton, Robin Dover, Anthony W Sainsbury, Michael J Norris, Jeremy J H Gilkes, Ian D Ramsay

The need to transport oxygen and remove carbon dioxide from animal tissue is a fundamental requirement of life, independent of age or sex.[1] The role of iron in humans and many other mammals is central to this process.[2 3] Haemoglobin concentration and red blood cell count are important diagnostic indicators for anaemia in humans and animals.

In prepubertal humans no major differences can be found between the sexes in red blood cell count or haemoglobin and serum ferritin concentrations.[4] Only after the onset of menstruation does a difference emerge.[4] Not until 10 years after the menopause does this situation revert in women, when the haemoglobin concentration becomes similar to that of aged matched men.[4 5] This situation is compounded by the fact that modern women have a different reproductive history from those in the past. They reach sexual maturity at an earlier age, have fewer pregnancies, and breast feed for shorter periods; as such they menstruate for more years than women in the past. Menstruation is the principal cause of iron loss in women.[6–8] Furthermore, 90% of UK females of childbearing age do not achieve the recommended daily intake of elemental iron (14.8 mg) from their diet.[9] Evaluation of the haemoglobin concentration and red blood cell count of women from Canada, Central America, China, and the United States shows that this situation is widespread.[4 10–14] Women worldwide are at risk of being in a negative iron balance, and by current criteria if their haemoglobin concentration is less than 115 g/l they are deemed to be anaemic, whereas in men the cut-off point is 130 g/l.[15]

As far as the authors are aware, of the primates only humans show a sex difference in haemoglobin concentration and red blood cell count. A survey of the haematology of mammals also failed to establish a difference.[16] Whereas most mammals, including the New World primates, do not menstruate, the Old World primates, which includes the apes, do. As with humans, Old World primates have premenses, breeding, and menopausal phases, and the frequency of menstruation is similar to humans, with a menses around every 28 days.[16–18] Unlike humans, however, no significant difference was found between the lower haemoglobin concentration (table) or red blood cell count (data not presented) of female primates and aged matched males sampled by the Zoological Society of London.[17]

Summary points

It is considered "normal" to find lower red blood cell counts and lower haemoglobin and serum ferritin concentrations in menstruating women than in age matched men

No other mammal, including the menstruating primates, exhibits such a sex difference, and neither is there a difference in humans before puberty or after menopause

Menstruation is the main cause of iron loss in women; 90% of UK women do not achieve the daily recommended intake of iron from their diet

Populations used to establish reference ranges for women contained a large proportion of those with iron deficiency, thus the lower limits are too low

This hidden deficiency has fundamental implications for women's health, particularly adolescent girls

Male reference ranges for ferritin and haematological parameters may be of more value when assessing iron status in women

Haem synthesis occurs largely in the mitochondria.[12] There is no evidence showing either a reduction in mitochondrial number or a reduced ability for haem synthesis in women of childbearing age than in men. It might therefore be argued that the hormonal environment is a possible cause for the observed sex difference in red blood cell count and haemoglobin and serum ferritin concentrations in humans. Increased serum erythropoietin concentrations occur in response to anaemia, which in turn increases iron absorption from the diet. Hallberg et al have shown that men and women of the same iron status absorb the same amounts of iron from the same diet.[19] If they are correct then there should be no difference in the erythropoietin concentrations of men and women with "normal" serum ferritin concentrations matched for

School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth PO1 2DT
D Hugh Rushton *honorary senior lecturer*
Michael J Norris *senior lecturer*

Imperial Cancer Research Fund, Lincoln's Inn Field, London WC2A 3PX
Robin Dover *clinical research officer*

Institute of Zoology, Zoological Society of London, Regents Park, London NW1 4RY
Anthony W Sainsbury *senior veterinary officer*

Lister Hospital, London SW1W 8RH
Jeremy J H Gilkes *consultant dermatologist*
Ian D Ramsay *consultant endocrinologist*

Correspondence to: D Hugh Rushton rushton@btinternet.com

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Lower and upper limits of haemoglobin concentration from various non-human primates

Species	Haemoglobin concentration (g/l) Males Lower limit	Males Upper limit	Females Lower limit	Females Upper limit
Non-menstruating primates:				
Lemurs (n=31)	143	203	140	204
Lorises and bushbabies (n=25)	124	210	120	194
Marmosets and tamarins (n=37)	125	196	125	188
New World monkeys (n=150)	119	195	123	190
Mean	128	201	127*	194*
Menstruating primates:				
Old World Monkeys (n=121)	110	175	103	151
Apes (n=166)	96	184	96	160
Means	103	180	99*	155†

*P>0.05. †P<0.01.

age and weight. Similarly no sex difference can be found for thyroxine; therefore, with the exception of iron and the sex hormones there is no evidence of lower concentrations for any other parameter involved in haem synthesis in women of childbearing age than there is in men.[20] Further, the data from menstruating Old World primates suggest that a difference in sex hormones is unlikely to be responsible for the sex difference in humans. Consequently, of all the parameters involved, iron is the only one with a measured difference.

The mean upper limit for haemoglobin concentration in primates that menstruate is significantly higher in males than it is in females, similar to humans. However, this is not the case in primates that do not menstruate (table), suggesting that menses is responsible for limiting the upper haemoglobin concentration in non-human primates that menstruate.[17] Perhaps the same may be true of humans, with an iron deficient diet significantly influencing the lower haemoglobin concentration in women.

No evidence supports a view that women of reproductive age have a lower biological requirement for any haem parameters than do aged matched men. The data from humans point to the possibility that the current lower reference levels for red blood cell count and haemoglobin and serum ferritin concentrations in women have been derived from sampling populations that are deficient in iron. Consequently, it would seem that a large number of women spend a major part of their lives with a negative iron balance arising from a dietary imbalance. Iron deficiency is the most important nutritional problem affecting humans around the world.[21] The presence of haem iron in the diet of humans enhances the absorption of non-haem iron, and the trend towards diets with a lower haem iron content may add to the problem of dietary insufficiency.[22] In addition, the typical UK diet contains many common products that can limit iron absorption—for example, dairy produce, cereals, and tannin[21]—thereby compounding the situation.

The deleterious effects of iron deficiency and iron deficient anaemia are due partly to impaired delivery of oxygen to the tissues and partly to a deficiency of iron containing compounds, especially enzymes, in various tissues.[2] Restlessness and irritability in children who are deficient in iron has been related to increased concentrations of catecholamines, which return to normal after treatment with iron.[22] Lower IQ scores have been found in UK and American adolescent girls who are deficient in iron.[23 24] Abnormalities in response to infection have been shown in people who are deficient in iron, where decreased neutrophil function and impaired T cell proliferation occurs.[3] Studies in humans have confirmed the findings from animals of reduced work capacity and poor work performance in iron deficient anaemia.[25] Reduced thermoregulation has also been confirmed in people who are iron deficient where norepinephrine concentration was increased, and differences were found in concentrations of epinephrine, dopamine, triiodothyronine, and thyroxine. Normal concentrations for these parameters were restored after iron supplementation.[25] Hair loss has been reported in women with iron deficiency, which responded to iron supplementation.[26 27] The quantity of non-haem iron in the brain is to a large extent independent of the iron stores in the body.[20] Overall, 10% of the iron complement of the adult brain is present at birth, and by the age of 10 this has reached 50%; however, not until the early 20s is the full adult complement achieved.[22] Although most of the deleterious effects of iron deficiency can be reversed by appropriate iron supplementation, of concern is the possibility that if during the adolescent years a shortfall exists, then, as in rats, humans may not be able to make up the deficiency by iron supplementation, and adolescent girls may enter adult life with a compromised complement of iron in the brain.[20–25]

We propose that the current "normal" values for red blood cell count and haemoglobin and serum ferritin concentration cited by laboratories were obtained from sampling populations that contained a large proportion of women with iron deficiency. We suggest using reference ranges for men for these parameters when assessing the haematological and iron status of women. By current criteria, iron deficiency is the commonest cause of anaemia in the world, with more than half a billion people experiencing adverse effects.[28] If this hypothesis is accepted then noticeably more women will be classified as being iron deficient or anaemic. Reclassification of red blood cell count and haemoglobin and serum ferritin concentrations to normal values for men would be expected to have fundamental and positive implications for women's health and welfare.

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Measuring quality of life

Are quality of life measures patient centred?

Alison J Carr, Irene J Higginson

This is the third in a series of five articles

Academic Rheumatology, University of Nottingham, Nottingham City Hospital, Nottingham NG3 5DE
Alison J Carr
ARC senior lecturer in epidemiology

Department of Palliative Care and Policy, King's College London, New Medical School, London SE5 9PJ
Irene J Higginson
professor

Correspondence to: A J Carr
alison.carr@nottingham.ac.uk

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Quality of life measures are increasingly used to supplement objective clinical or biological measures of disease to assess the quality of service, the need for health care, the effectiveness of interventions, and in cost utility analyses. Their use reflects a growing appreciation of the importance of how patients feel and how satisfied they are with treatment in addition to the traditional focus on disease outcomes. In this respect, quality of life measures capture patients' perspectives of their disease and treatment, their perceived need for health care, and their preferences for treatment and outcomes. They are hailed as being patient centred. But the challenge in measuring quality of life lies in its uniqueness to individuals. Many of the existing measures of quality of life fail to take account of this by imposing standardised models of quality of life and preselected domains; they are thus measures of general health status rather than quality of life.

Questions arise as to whether such measures are truly patient centred and to what extent they actually represent the quality of life of individual patients or groups of patients. Do they simply describe a patient's health in terms of what health professionals or society believe constitutes quality of life for people who are ill, something that may include factors that have little relevance to or importance for patients?

This paper explores the extent to which standardised quality of life measures accurately quantify an individual patient's quality of life. It debates whether newer, individualised approaches, which allow patients to define their quality of life in relation to their goals and expectations, are more appropriate.

Summary points

Quality of life is an individual construct and measures should take account of this

Many widely used measures are not patient centred because of the ways in which items were generated, because a questionnaire may restrict a patient's choice, and because of the weighting system used

These limitations compromise their accuracy and usefulness because they do not measure what constitutes quality of life for all patients

It is possible to measure quality of life in a patient centred way using individualised measures

Some of the newer standardised measures may be more patient centred than their predecessors but further research is required

The individual nature of quality of life

Although there is no single agreed definition of health related quality of life, it is usually regarded as existing relative to individual or cultural expectations and goals (box). The first paper in this series proposed a model of quality of life that accounted for the interaction between expectations and experience.[1] While it seems reasonable to assume that there are some aspects of life that are of universal relevance to quality of life, the specific weights that individuals attach to these will differ between and in different cultures. Other aspects may be important only to the individual. For example, the first paper in this series considered how the variations in expectations of health that exist between groups and individuals will have an impact on measuring quality of life. The interactions between all these aspects (generic and individual) will also vary between individuals.[2] Moreover, these factors and their interrelationships are unlikely to remain static over time.[3] Values and priorities change in response to life circumstances, such as a life threatening illness, and experience, such as ageing or adapting to a chronic illness. Viewed in