TRANSFUSION MEDICINE
Official Journal of the British Blood Transfusion Society
British Blood Transfusion Society
Transfusion Medicine | REVIEW ARTICLE

Iron deficiency among blood donors: experience from the Danish Blood Donor Study and from the Copenhagen ferritin monitoring scheme

A. S. Rigas,[1] O. B. Pedersen,[2] K. Magnussen,[3] C. Erikstrup[4] & H. Ullum[1]

[1]*Department of Clinical Immunology, Copenhagen University Hospital, Copenhagen, Denmark,* [2]*Department of Clinical Immunology, Næstved Hospital, Næstved, Denmark,* [3]*Department of Clinical Immunology, Hvidovre Hospital, Hvidovre, Denmark, and* [4]*Department of Clinical Immunology, Aarhus University Hospital, Aarhus, Denmark*

Received 16 December 2016; accepted for publication 31 August 2017

SUMMARY

Blood components collected from blood donors are an invaluable part of modern-day medicine. A healthy blood donor population is therefore of paramount importance. The results from the Danish Blood Donor Study (DBDS) indicate that gender, number of previous donations, time since last donation and menopausal status are the strongest predictors of iron deficiency. Only little information on the health effects of iron deficiency in blood donors exits. Possibly, after a standard full blood donation, a temporarily reduced physical performance for women is observed. However, iron deficiency among blood donors is not reflected in a reduced self-perceived mental and physical health. In general, the high proportion of iron-deficient donors can be alleviated either by extending the inter-donation intervals or by guided iron supplementation. The experience from Copenhagen, the Capital Region of Denmark, is that routine ferritin measurements and iron supplementation are feasible and effective ways of reducing the proportion of donors with low haemoglobin levels.

Key words: donor, iron deficiency, iron supplementation.

Iron deficiency among blood donors has been recognised as a serious problem within the blood-banking community. Numerous studies have showed that blood donors are at an increased risk of developing iron deficiency and consequently iron deficiency anaemia, which may lead to donor deferral. In addition, not only iron is pivotal to the development of erythrocytes, but it also impacts the other aspects of human physiology. Several screening tests for iron stores have been conducted, and different ways of mitigating the risk of iron deficiency in blood donors have been constructed. In this review, we provide an overview of the causes and consequences of iron deficiency and the ways to detect iron deficiency in blood donors and introduce a possible way of managing iron deficiency in blood donors through guided iron supplementation as illustrated by the Copenhagen ferritin monitoring scheme.

Correspondence: Henrik Ullum, MD, PhD, Professor, Department of Clinical Immunology, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark.
Tel.: +45 35453545; Fax: +45 35390038; e-mail: henrik.ullum@regionh.dk

BLOOD DONATION AND IRON DEFICIENCY

An estimation by the World Health Organization (WHO) shows that blood is donated around 112·5 million times globally every year from various types of blood donors (voluntary unpaid, family/replacement and paid) (factsheet, 2016). The blood components collected from these donors after processing are an invaluable part of modern-day medicine.

The safety and health of blood donors are therefore of paramount importance. To optimise the general health of the donor population, a better understanding of the health implications of blood donation is needed, especially with regard to the effects of blood donation on the iron homeostasis.

Blood donation is associated with the loss of iron during full blood donations and, to a lesser extent, plasmapheresis because of blood drawn for laboratory analyses (Bier-Ulrich *et al.*, 2003) and blood loss during the harness and cell separation procedure (Page *et al.*, 2010). The exact loss of iron associated with a donation of 450–500 mL whole blood is dependent on the Hb concentration of the donor and has been estimated to be in the range of 200–250 mg (Brittenham, 2011). Accordingly, high prevalence rates of iron deficiency among blood donors have been reported. Among the frequent donors in the United States, 27·1% of women and 16·4% of men had iron deficiency with a ferritin level below 12 ng mL^{-1} (Cable *et al.*, 2011). In the Danish Blood Donor Study (DBDS), we reported that among high-frequency donors, 39, 22 and 9% of pre-menopausal women, post-menopausal women and men, respectively, had

doi: 10.1111/tme.12477

iron deficiency with a ferritin level less than 15 ng mL^{-1} (Rigas *et al.*, 2014).

Number of previous donations, time since last donation, sex and menopausal status are the strongest predictors of iron deficiency in a blood donor population (Rigas *et al.*, 2014).

Iron deficiency is not only a problem within the blood-banking community. Globally, iron deficiency is the leading nutritional deficiency. Anaemia is a common manifestation of iron deficiency, and it can therefore be used to approximate the prevalence of iron deficiency. Specifically, it may be assumed that roughly 50% of all cases of anaemia are caused by iron deficiency ((WHO), 2007) and that these cases represent 40% of the total iron-deficient population. It has been estimated that up to 25–30% of the world's population, 7·3 billion are anaemic (McLean *et al.*, 2009), suggesting that the number of iron-deficient individuals is in the order of 2·7 billion individuals.

Because iron deficiency among blood donors is a result of repeated donations and not part of general nutritional deficiency, blood donors are feasible subjects to study the causes of iron deficiency. Also, since repeated blood donors return to the blood bank at regular intervals, this population is easily assessable in order to study the health effects of iron deficiency.

CONSEQUENCES OF IRON DEFICIENCY

Iron is important for numerous physiological processes (Pantopoulos *et al.*, 2012), and consequently, the manifestations of iron deficiency may be many and diverse. Anaemia is the most severe consequence of iron deficiency. In addition, iron deficiency manifested as anaemia in pregnancy has been associated with negative perinatal outcomes, such as low birthweight (Murphy *et al.*, 1986; Scholl *et al.*, 1992; Zhou *et al.*, 1998), premature birth (Murphy *et al.*, 1986; Klebanoff *et al.*, 1991; Scholl *et al.*, 1992; Zhou *et al.*, 1998) and perinatal death (Murphy *et al.*, 1986). Furthermore, studies indicate that children with iron deficiency anaemia exhibit poorer scholastic achievements even after therapeutic iron supplementation (Lozoff *et al.*, 2000). In iron-deficient but non-anaemic adolescent women, iron supplements may improve fatigue (Krayenbuehl *et al.*, 2011; Vaucher *et al.*, 2012). Iron deficiency may additionally compromise both the innate and the specific immune systems through decreased neutrophil function and bactericidal activity, depression of T lymphocyte function, thymic atrophy and impaired natural killer cell activity (Oppenheimer, 2001; Bergman *et al.*, 2004; Ekiz *et al.*, 2005). However, clinically relevant immunological outcome has yet to be determined.

In a blood donor population, little is known about the clinical consequences apart from potential anaemia of the phlebotomy-induced iron deficiency. In DBDS, we found that iron deficiency evaluated as a ferritin level below 15 ng mL^{-1} predicts 0·25 mmol L^{-1} (95% CI: 0·22–0·28) and 0·35 mmol L^{-1} (95% CI: 0·28–0·42) as lower values of current haemoglobin (Hb) levels for women and men, respectively. In addition, a ferritin level below 15 ng mL^{-1} predicted a 1·81- and 2·20-fold increased risk of a drop in Hb level of more than 0·5 mmol L^{-1} at subsequent donations for women and men, respectively (Kotze *et al.*, 2015). However, in DBDS, we found neither any association between a low Hb level and the risk of a subsequent infection nor any decline in Hb levels and risk of infections (Kotze *et al.*, 2016). Iron is an important element for bacteria and depriving invading bacteria of iron is an established part of the innate host defence (Cassat & Skaar, 2013). These opposite directed effects of iron on the immune system may explain the lack of association between low Hb levels and risks associated with subsequent infections.

Iron supplementation for iron-deficient non-anaemic individuals has shown significant effect on endurance, athletic performance and fatigue (Krayenbuehl *et al.*, 2011; Vaucher *et al.*, 2012; Waldvogel-Abramovski *et al.*, 2013). Even within a blood donor population, a standard blood donation of 450 mL may temporarily impair physical performance (Stangerup *et al.*, 2017). However, iron deficiency without anaemia is not associated with reduced self-perceived health-related quality of life (Rigas *et al.*, 2015).

HOW TO SCREEN DONORS FOR IRON DEFICIENCY

For evaluating iron stores, various methods, such as ferritin, zinc protoporphyrin (ZPP) and soluble transferrin receptor measurements, exist. Although these methods describe different aspects of the iron homeostasis, they all give an indication whether iron stores are absent or replete. Iron stores may be viewed as a continuum ranging from replete over low tissue iron storage to functional iron deficiency resulting in anaemia.

The majority of blood banks screen for iron deficiency only indirectly by means of applying an Hb cut-off for eligible donors. However, a high proportion of blood donors are iron-deficient despite the eligible Hb levels of blood donation (Baart *et al.*, 2013). Therefore, using Hb levels as the only screening method is insufficient and will fail to identify the large number of iron-deficient donors.

Likewise, conventional red blood cell indices, such as mean corpuscular volume (MCV) and mean corpuscular haemoglobin concentration (MCHC), will be reduced in the later stages of functional iron deficiency. However, these two measures are insufficient for the identification of blood donors with low iron stores (Kiss, 2015). Similarly, with increasing functional iron deficiency, zinc becomes an alternative substrate for ferrochelatase, resulting in increased amounts of ZPP (Labbe *et al.*, 1999). A previous study indicated that ZPP may perform better when predicting future deferrals compared with ferritin (Kiss, 2015). However, in another study, the predictive effect of ZPP on future deferrals could not be confirmed (Kiss, 2015).

The measurement of soluble transferrin receptor, which reflects functional iron deficiency, is also a valid method for measuring iron stores. The ratio of soluble transferrin receptor to ferritin may aid in discriminating between functional iron deficiency erythropoiesis and iron store depletion (Kiss, 2015).

Ferritin remains a good and well-studied single marker of iron stores in blood donors (O'Meara *et al.,* 2011). Generally, a ferritin level of less than 15 ng mL^{-1} is indicative of iron deficiency, and in the absence of a co-occurring infection/inflammation as is the case in healthy blood donors, a ferritin level above 100 ng mL^{-1} strongly suggests sufficient iron stores. Ferritin levels between 30 and 100 ng mL^{-1} should be interpreted cautiously since ferritin levels may rise during infection/inflammation (WHO, 2001; (WHO), 2007). Therefore, the measurement of another acute-phase reactant, such as C-reactive protein (CRP), may be useful when evaluating the iron status with ferritin. However, in a European blood donor population, the association between CRP and ferritin levels is weak and ferritin levels can be interpreted without additional markers of inflammation (Rigas *et al.*, 2015).

Ideally, good prediction/risk analysis of which blood donors are most likely to develop iron deficiency or be deferred because of low Hb levels is needed. Genetic screening may be part of predictive algorithms for iron deficiency in the future. However, current data on the DBDS indicate that single-nucleotide polymorphisms (within the iron homeostasis) only have a minor impact on ferritin levels (Sorensen *et al.*, 2016). Likewise, a larger genome-wide association study found that genetic polymorphisms only explained a small fraction of ferritin variation (Benyamin *et al.*, 2014). Therefore, more research on the causes of iron deficiency in blood donors is warranted.

MANAGING IRON DEFICIENCY IN BLOOD DONORS

In general, two different ways are used to deal with iron deficiency in blood donors: either guided iron supplementation or extending the inter-donation intervals. With regard to guided iron supplementation, a screening method needs to be implemented. Previous studies support the use of circulating ferritin levels as a marker of iron stores (O'Meara *et al.,* 2011). It is shown that ferritin is stable in whole blood stored at 4 °C for up to 5 days (Stone *et al.*, 2016), adding to the feasibility of ferritin measurement for monitoring iron stores in blood donors. Afterwards, iron tablets may be distributed to donors by direct handling, by mail or through collection at pharmacies. The preferred practical and economical approach needs to be decided by each blood collection organisation. Whether the costs of ferritin measurements and routine iron supplementation for blood donors with low iron stores are recouped in terms of a lower rate of blood donors being deferred cannot be determined without economic analyses (Gorlin *et al.*, 2016).

Extending the inter-donation interval will probably reduce the risk of iron deficiency in blood donors. The REDS-II/RISE study found that women with an inter-donation interval of less than 19 weeks were at risk of iron deficiency compared with women who donated blood at an interval of 26 weeks or more (Cable *et al.*, 2012). Accordingly, in DBDS, we found that time since last donation was one of the strongest predictors of iron stores (Rigas *et al.*, 2014), indicating that adjusting the inter-donation interval may be a feasible approach for the prevention of iron deficiency among blood donors. Results obtained from the INTERVAL trial evaluating the effect of different inter-donation intervals will be of great interest (Moore *et al.*, 2014).

EXPERIENCE OF IRON SUPPLEMENTATION IN THE CAPITAL REGION OF DENMARK

In Copenhagen, ferritin measurements and targeted iron supplementation to blood donors at regular intervals were introduced in 2012. However, the problem with low Hb levels among blood donors possibly due to iron deficiency had been recognised many years earlier. In 2004 to 2006, the number of blood donors who were offered iron supplementation rose from 3 to 14% (Magnussen *et al.*, 2008). The donors who were offered iron supplementation at the blood collection sites in these years probably had either low Hb levels below the limit for donation or a drop in Hb$\geq$2 g dL^{-1} between donations. Of course, the increase in iron-supplemented donors was not a reflection of an increase in the proportion of iron-deficient donors in Copenhagen but rather an increased awareness of the potential problem with iron deficiency among blood donors. Between 1 July 2005 and 13 March 2006, 879 blood donors with Hb levels below or at the accepted level for donation were enrolled in the iron supplementation study in the Capital Region of Copenhagen. The donors in this study were offered 50 tablets of either 100 mg of elemental iron (JernC) or, in the case of abdominal discomfort, iron bisglycinate chelate (25 mg of elemental iron; Ferrochel, Albion Laboratories, Clearfield, UT). At all future donations, 20 tablets were offered if plasma ferritin level at the initial investigation was less than 50 ng mL^{-1}. The donors also received a leaflet on dietary enhancers and inhibitors of iron and general information about iron deficiency (Magnussen *et al.*, 2008). Donors with unexplained anaemia (based on the medical history and ferritin levels) were referred to their general practitioner. The study found that with guided iron supplementation, ferritin and Hb levels naturally improved without extending the donation intervals that remained at a minimum of 3 months between full blood donations. Furthermore, the cost-effectiveness of guided iron supplementation was deemed effective (Magnussen *et al.*, 2008). However, a formal economic analysis was not conducted. Afterwards, the Capital Region of Denmark implemented the routine measurement of ferritin levels on all first-time female donors and on those with an Hb level below the acceptance limit for donation [Hb cut-off for women: 7·8 mmol L^{-1} (12·5 g dL^{-1}) and Hb cut-off for men: 8·4 mmol L^{-1} (13·5 g dL^{-1})].

From 2012, any first-time donor donating blood in the Capital Region of Denmark was screened for iron deficiency by means of ferritin levels. If ferritin levels were in the range of 30 – 60 ng mL^{-1} (and normal Hb levels), the donor would be offered 20 iron tablets at future donations. If ferritin levels were below 30 ng mL^{-1} (and normal Hb levels), the blood bank would send 60 iron tablets by mail to the donor and offer 20 iron tablets at future donations. If Hb levels were below the acceptance level,

a medical history would be obtained from a medical practitioner and, if necessary, the donors would be referred to their general practitioner. Otherwise, if no medical condition was suspected, the donors were offered iron tablets depending on their ferritin level (Magnussen & Ladelund, 2015). A special team led by a senior medical consultant oversaw the ferritin screening programme. The possibility for the team of accumulating experience in donor care and the ferritin screening programme have led to the discovery of blood donors with early stages of cancer, which may be viewed as an extended medical donor care. After 2 years of follow-up, the iron supplementation programme concluded that the goal-directed iron supplementation led to a general increase in blood donor Hb concentration and a reduced proportion of donors with low Hb concentration (Magnussen & Ladelund, 2015).

Currently, the guided iron supplementation programme is still in place, and the other health regions in Denmark have implemented similar routine ferritin measurements. Furthermore, the AABB (www.aabb.org) recently put forward an advocacy of routine ferritin testing on female donors. From a practical point of view, handling the goal-directed iron supplementation programme in Copenhagen initially required extra resources because of the high proportion of donors having either low iron stores or low Hb levels. These donors were sent mailed-out information and iron supplementation. However, with the increased effect of the programme, the workload levelled off, and currently, approximately 30% of women and 5% of men need iron supplementation and general information (Magnussen & Ladelund, 2015). In summary, the senior medical practitioner in charge of implementing the goal-directed ferritin monitoring scheme concluded that even though the main goal was to keep donors within our limit for Hb and ferritin levels, a main benefit of the programme was to have a well-functioning programme for those who fell outside of Hb and ferritin levels.

CONCLUSION

Iron deficiency is both a global health issue and a specific problem for blood donors. In general, either guided iron supplementation with screening for iron deficiency through ferritin measurements or adjusting the inter-donation intervals may alleviate the high proportion of iron-deficient donors. The experience from Copenhagen, the Capital Region of Denmark, is that guided iron supplementation is an effective strategy for avoiding iron depletion.

ACKNOWLEDGMENTS

A. S. R. and H. U. prepared the initial draft; O. B. P., C. E. and K. M. revised the initial draft, and all authors contributed to the final draft. The DBDS was supported by the Danish Council for Independent Research (09-069412) and by the Danish Regions (02/2611).

CONFLICT OF INTEREST

The authors have no competing interests.

REFERENCES

Baart AM, van Noord PA, Vergouwe Y, Moons KG, Swinkels DW, Wiegerinck ET, de Kort WL, Atsma F. (2013) High prevalence of subclinical iron deficiency in whole blood donors not deferred for low hemoglobin. *Transfusion*, **53**, 1670–1677.

Benyamin, B., Esko, T., Ried, J.S. *et al.* (2014) Novel loci affecting iron homeostasis and their effects in individuals at risk for hemochromatosis. *Nature Communications*, **5**, 4926.

Bergman, M., Bessler, H., Salman, H., Siomin, D., Straussberg, R. & Djaldetti, M. (2004) In vitro cytokine production in patients with iron deficiency anemia. *Clinical Immunology*, **113**, 340–344.

Bier-Ulrich, A.M., Haubelt, H., Anders, C., Nagel, D., Schneider, S., Siegler, K.E., Seiler, D. & Hellstern, P. (2003) The impact of intensive serial plasmapheresis and iron supplementation on iron metabolism and Hb concentration in menstruating women: a prospective randomized placebo-controlled double-blind study. *Transfusion*, **43**, 405–410.

Brittenham, G.M. (2011) Iron deficiency in whole blood donors. *Transfusion*, **51**, 458–461.

Cable, R.G., Glynn, S.A., Kiss, J.E. *et al.* (2011) Iron deficiency in blood donors: analysis of enrollment data from the REDS-II Donor Iron Status Evaluation (RISE) study. *Transfusion*, **51**, 511–522.

Cable, R.G., Glynn, S.A., Kiss, J.E. *et al.* (2012) Iron deficiency in blood donors: the REDS-II Donor Iron Status Evaluation (RISE) study. *Transfusion*, **52**, 702–711.

Cassat, J.E. & Skaar, E.P. (2013) Iron in infection and immunity. *Cell Host & Microbe*, **13**, 509–519.

Ekiz, C., Agaoglu, L., Karakas, Z., Gurel, N. & Yalcin, I. (2005) The effect of iron deficiency anemia on the function of the immune system. *The Hematology Journal*, **5**, 579–583.

factsheet, W. (updated 2016) Blood safety and availability. URL http://www.who.int/mediacentre/factsheets/fs279/en/. Accessed 15 September 2017

Gorlin, J., Katz, L., Elsmore, D., Kirbach, K., Erickson, Y., Hove, A., Black, C. & Walsh-Jahnke, R. (2016) Prevalence of blood donor iron deficiency and feasibility ferritin-based iron replacement: a blood collection agency-based study. *Vox Sanguinis*, **111**, 206–208.

Kiss, J.E. (2015) Laboratory and genetic assessment of iron deficiency in blood donors. *Clinics in Laboratory Medicine*, **35**, 73–91.

Klebanoff, M.A., Shiono, P.H., Selby, J.V., Trachtenberg, A.I. & Graubard, B.I. (1991) Anemia and spontaneous preterm birth. *American Journal of Obstetrics and Gynecology*, **164**, 59–63.

Kotze, S.R., Pedersen, O.B., Petersen, M.S. *et al.* (2015) Predictors of hemoglobin in Danish blood donors: results from the Danish Blood Donor Study. *Transfusion*, **55**, 1303–1311.

Kotze, S.R., Pedersen, O.B., Petersen, M.S. *et al.* (2016) Deferral for low hemoglobin is not associated with increased risk of infection in Danish blood donors. *Transfusion*, **57**, 571–577.

Krayenbuehl, P.A., Battegay, E., Breymann, C., Furrer, J. & Schulthess, G. (2011) Intravenous iron for the treatment of fatigue in nonanemic, premenopausal women with low serum ferritin concentration. *Blood*, **118**, 3222–3227.

Labbe, R.F., Vreman, H.J. & Stevenson, D.K. (1999) Zinc protoporphyrin: a metabolite with a mission. *Clinical Chemistry*, **45**, 2060–2072.

Lozoff, B., Jimenez, E., Hagen, J., Mollen, E. & Wolf, A.W. (2000) Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics*, **105**, E51.

Magnussen, K., Bork, N. & Asmussen, L. (2008) The effect of a standardized protocol for iron supplementation to blood donors low in hemoglobin concentration. *Transfusion*, **48**, 749–754.

Magnussen, K. & Ladelund, S. (2015) Handling low hemoglobin and iron deficiency in a blood donor population: 2 years' experience. *Transfusion*, **55**, 2473–2478.

McLean, E., Cogswell, M., Egli, I., Wojdyla, D. & de Benoist, B. (2009) Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993–2005. *Public Health Nutrition*, **12**, 444–454.

Moore, C., Sambrook, J., Walker, M. *et al.* (2014) The INTERVAL trial to determine whether intervals between blood donations can be safely and acceptably decreased to optimise blood supply: study protocol for a randomised controlled trial. *Trials*, **15**, 363.

Murphy, J.F., O'Riordan, J., Newcombe, R.G., Coles, E.C. & Pearson, J.F. (1986) Relation of haemoglobin levels in first and second trimesters to outcome of pregnancy. *Lancet*, **1**, 992–995.

O'Meara, A., Infanti, L., Stebler, C., Ruesch, M., Sigle, J.P., Stern, M. & Buser, A. (2011) The value of routine ferritin measurement in blood donors. *Transfusion*, **51**, 2183–2188.

Oppenheimer, S.J. (2001) Iron and its relation to immunity and infectious disease. *The Journal of Nutrition*, **131**, 616S–633S discussion 633S–635S.

Page, E.A., Coppock, J.E., Harrison, J.F. (2010) Study of iron stores in regular plateletpheresis donors. *Transfusion Medicine*, **20**, 22–29.

Pantopoulos, K., Porwal, S.K., Tartakoff, A. & Devireddy, L. (2012) Mechanisms of mammalian iron homeostasis. *Biochemistry*, **51**, 5705–5724.

Rigas, A.S., Sorensen, C.J., Pedersen, O.B. *et al.* (2014) Predictors of iron levels in 14,737 Danish blood donors: results from the Danish Blood Donor Study. *Transfusion*, **54**, 789–796.

Rigas, A.S., Pedersen, O.B., Sørensen, C.J. *et al.* (2015) No association between iron status and self-reported health-related quality of life in 16,375 Danish blood donors: results from the Danish Blood Donor Study. *Transfusion*, **55**, 1752–1756.

Scholl, T.O., Hediger, M.L., Fischer, R.L. & Shearer, J.W. (1992) Anemia vs iron deficiency: increased risk of preterm delivery in a prospective study. *The American Journal of Clinical Nutrition*, **55**, 985–988.

Sorensen, E., Rigas, A.S., Thørner, L.W. *et al.* (2016) Genetic factors influencing ferritin levels in 14,126 blood donors: results from the Danish Blood Donor Study. *Transfusion*, **56**, 622–627.

Stangerup, I., Kramp, N.L., Ziegler, A.K., Dela, F., Magnussen, K. & Helge, J.W. (2017) Temporary impact of blood donation on physical performance and hematologic variables in women. *Transfusion*, **57**, 1905–1911.

Stone, M., Brambilla, D., Murcia, K., Dimapasoc, M., Cyrus, S., Cable, R.G., Kiss, J.E. & Busch, M.P. (2016) Feasibility of routine ferritin testing for donor management: validation of delayed processing and demonstration of within donor reproducibility over time. *Transfusion*, **56**, 2422–2425.

Vaucher, P., Druais, P.L., Waldvogel, S. & Favrat, B. (2012) Effect of iron supplementation on fatigue in nonanemic menstruating women with low ferritin: a randomized controlled trial. *Canadian Medical Association Journal*, **184**, 1247–1254.

Waldvogel-Abramovski, S., Waeber, G., Gassner, C., Buser, A., Frey, B.M., Favrat, B. & Tissot, J.D. (2013) Iron and transfusion medicine. *Blood Reviews*, **27**, 289–295.

WHO (2001) Iron deficiency anemia: assessment, prevention and control. A guide for programme managers. URL http://www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf. Accessed 15 September 2017

(WHO), D.o.N.f.H.a.D. (2007) Assessing the iron status of populations. 2nd edition [WWW document]. URL http://www.who.int/nutrition/publications/micronutrients/anaemia_iron_deficiency/9789241596107.pdf.

Zhou, L.M., Yang, W.W., Hua, J.Z., Deng, C.Q., Tao, X. & Stoltzfus, R.J. (1998) Relation of hemoglobin measured at different times in pregnancy to preterm birth and low birth weight in Shanghai, China. *American Journal of Epidemiology*, **148**, 998–1006.