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Anemia - still a major health problem in many parts of the world!

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Abstract

Anemia is a major global health problem, especially in developing countries. Still this fundamental health issue has not been solved but continues to exist affecting the health, quality of life and working capacity in billions of people all over the world. This paper gives a review on the prevalence and major causes of anemia seen on a global scale. Most cases of anemia are due to iron deficiency, which often work in symphony with folate deficiency and/or vitamin B₁₂ deficiency as well as with infections. More efforts should be dedicated to tackle this massive problem - we have the tools and we know the ways. Iron fortification of appropriate food items combined with iron supplements in specific population groups has proved to be efficient. Initially, the efforts should be centered on the specific risk groups for iron deficiency anemia, i.e. young children, adolescent females, women of reproductive age as well as pregnant women and postpartum lactating mothers.

Key Words: anemia; anemia, iron deficiency; developing countries; folic acid deficiency; helminthiasis; malaria; vitamin B₁₂ deficiency

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7 **Introduction**

8 The presence of anemia is basically defined as a red blood cell count, which is below the
9 accepted lower level of the normal range [1]. However, in the daily clinical routine,
10 anemia is defined by a hemoglobin (Hb) concentration, which is below the recommended
11 lower thresholds established by epidemiological population surveys or by the local
12 laboratory. In order to perform useful comparisons between different countries it is
13 convenient to use the hemoglobin thresholds defined by the World Health Organization
14 (WHO) shown in Table 1 [2, 3].
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19 Table 1. Hemoglobin (Hb) concentration thresholds used to define anemia in subjects
20 living at sea level according to the World Health Organization guidelines [3]
21

22

Age or gender group	Hb threshold (g/L)
Children (6 months to under 5 years)	110
Children (5 years to under 12 years)	115
Children (12 years to under 15 years)	120
Non-pregnant women (15 years and over)	120
Pregnant women	110
Men (15 years and over)	130

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34 These threshold values apparently do not overestimate the prevalence of anemia. In
35 Denmark, epidemiological surveys on presumably healthy subject without iron deficiency
36 have shown that the 5th percentile for men is 134 g/L, for women of reproductive age 124
37 g/L [4, 5] and for pregnant women 110 g/L in the 1st, 105 g/L in the 2nd and 110 g/L in
38 the 3rd trimester [6].
39

40 The World Health Organization estimates that anemia affects nearly 2 billion people all
41 over the world, what is nearly one third of the rapidly growing world population of
42 approximately 7 billion people [7]. These figures indicate that in many countries, anemia
43 constitutes a serious health problem in the population as shown in Table 2.
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52 Table 2. Public health significance of different prevalences of anemia according to the
53 World Health Organization [3]
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Prevalence of anaemia (%)	Public health significance
≤4.9	No public health problem
5.0-19.9	Mild public health problem

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20.0-39.9	Moderate public health problem
≥40	Severe public health problem

What are the causes of anemia?

There are many different causes of anemia and they often work in symphony, so in the single individual various nutritional deficiencies, different infections/infestations may all play a role. This may of course have influence on the choice of treatment for the anemia and for the planning of future prophylaxis in the population.

Iron

Iron is an essential mineral for man and an important component of metalloproteins involved in oxygen transport and metabolism. In a well-nourished individual, the body contains approximately 3-4 g of iron. Almost two thirds of the iron is found in hemoglobin, the protein in the red blood cells that carries oxygen to the body's tissues. The most common nutrition deficiency in both developing as well as in developed countries is iron deficiency [7].

Iron is mandatory for the production of hemoglobin in the red blood cell progenitors (the erythroblasts) and if the iron supply to the bone marrow is inadequate, the hemoglobin production fails and the number of red blood cells in the circulation declines. This subsequently leads to development of iron deficiency anemia (IDA) with a low hemoglobin concentration. A characteristic feature is also that IDA can be corrected or cured by treatment with iron, either by the oral route or by intravenous iron therapy.

In the spectrum of anemia, iron deficiency anemia (IDA) is by far the most important, causing approximately 75-80% of the total burden of anemias [1-3]. Typically, the anemia is microcytic with a low mean red blood cell volume (MCV) and hypochromic with a low hemoglobin content in the red blood cells, i.e. low mean corpuscular hemoglobin (MCH) and low mean corpuscular hemoglobin concentration (MCHC). Basically iron deficiency may arise due to an insufficient dietary iron intake. Dietary surveys have shown that even in developed countries, dietary iron intake is too low in some population groups [8]. For example, Danish women of reproductive age women have a mean dietary iron intake of 9 mg/day [8], which means that more than 90% of the women have an intake below the recommended daily allowance of ~18 mg/day [9].

Dietary iron consists of heme iron and non-heme iron. Heme iron has a good bioavailability leading to a favorable gastrointestinal iron absorption, whereas non-heme iron has a poor bioavailability indicating a low iron absorption.

Heme iron is present in food products of animal origin (meat, poultry, fish), while non-heme iron predominantly is found in food products of plant origin (vegetables, cereals, grains, legumes). In addition, meat contains the so called "meat factor" which enhances absorption of non-heme iron. Therefore, individuals who regularly consume foods of animal origin, are at a lower risk of iron deficiency than individuals who exclusively consume foods of plant origin.

Ongoing, continuing blood losses predominantly from the gastrointestinal tract due to infections, intestinal parasites and/or inflammatory bowel disease may contribute to IDA in many parts of the world.

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4 Furthermore, women with heavy blood losses at their menstrual periods or by recurrent
5 uterine bleeding due to gynecological disease have a highly increased risk of developing
6 IDA.
7

8 9 *Vitamin deficiencies*

10 A number of vitamin deficiencies are associated with the development of anemia such as
11 vitamin A deficiency [10] and vitamin D deficiency [11]. Vitamin C deficiency may
12 contribute to iron deficiency and IDA due to impaired iron absorption and profuse
13 bleeding from the gastrointestinal tract [12].
14

15 16 *Folate*

17 The most common vitamin deficiency producing anemia is folate deficiency [13, 14]. So
18 far, folate status in various populations has not been as intensively investigated as iron
19 deficiency and IDA, so further studies are needed before we shall have a more clear
20 picture of the prevalence of folate deficiency in many populations. Folate deficiency
21 causes a specific form of anemia termed megaloblastic anemia with high MCV. It has
22 been estimated that in developing countries, folate deficiency occurs in as many as 25 to
23 72% of women of reproductive age [13, 14].
24

25 In the fetus and newborn baby, folate deficiency is associated with a high risk of neural
26 tube defects as well as other defects [13].
27

28 Folate is present in food of plant origin, e.g. green leafy vegetables, grains ect.
29 However, the problem is that food preparation procedures (cooking, frying, milling,
30 baking) actually destroy a high percentage of the folate content in the food.
31
32

33 34 *Vitamin B₁₂*

35 Vitamin B₁₂ deficiency is probably the second most common vitamin deficiency causing
36 anemia, which is a megaloblastic anemia with high MCV and typical morphological
37 features such as hyperlobulation of the nuclei of the granulocytes [1]. In developing
38 countries, vitamin B₁₂ deficiency constitutes a significant problem [13] and studies from
39 Lebanon and Turkey have revealed that ~40% of women of reproductive age have
40 vitamin B₁₂ deficiency [14,15] which in addition to insufficient dietary vitamin B₁₂
41 intake, may be due to the food cobalamin malabsorption syndrome or pernicious anemia
42 [14].
43

44 In addition to anaemia, vitamin B₁₂ deficiency causes neuropathy with pronounced
45 neurological symptoms. In the fetus and newborn baby, vitamin B₁₂ deficiency has been
46 associated with an increased risk of neural tube defects [16].
47

48 Vitamin B₁₂ is present in food of animal origin, which means that subjects consuming a
49 food of predominantly plant origin, e.g. vegetarians are not getting enough vitamin B₁₂
50 and therefore are at high risk of deficiency.
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53 54 *Infection/infestations*

55 Both acute and chronic infections/infestations are associated with anemia [1]. Intestinal
56 parasites, including hookworms, which are prevalent in many tropical/subtropical regions
57 play a major cause in the high prevalence of anemia in many countries [17]. Anemia
58 caused by intestinal parasites is mainly due to iron deficiency but is often combined with
59 vitamin B₁₂ deficiency as well as folate deficiency.
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4 In areas where malaria is endemic, anemia is quite common and antimalarial
5 programmes have proven to be effective in reducing the prevalence of anemia [18].
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8 *Hemoglobinopathies*

9 In many tropical and subtropical countries, the high prevalence of genetic
10 hemoglobinopathies, e.g. thalassemia, sickle cell disorders, ect. plays a significant role in
11 the prevalence of anemia. Geographically the thalassemia belt includes the Mediterranean
12 passing through West and Central Asian countries like Turkey, Iran, Afghanistan onto
13 Pakistan and India and passes on to the South East Asian countries like Indonesia, Burma
14 and Thailand, Vietnam and Cambodia. This makes it most common in African, Greek,
15 Italian, Middle Eastern and Southern Asian populations. In some of these regions as
16 many as 30% may be carriers of the gene defect [19, 20]. For example, in Southern
17 Thailand, 27% of women of reproductive age are carriers of the thalassemia trait [21].
18

19 Anemia caused by thalassemia is a purely genetic disorder/disease, but may of course
20 be associated and thus aggravated by anemia due to nutritional deficiencies and/or
21 infections/infestations (see above).
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26 **Who are the major risk groups for anemia?**

27 It appears from many surveys that the major risk groups for IDA are young children and
28 after childhood individuals of female gender, i.e. adolescent females who grow rapidly
29 and in addition have their first menstruations with iron losses, women of reproductive age
30 who lose iron with their menstrual periods, pregnant women with an increased need for
31 iron and lactating women (Table 3, Table 4).
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42 Table 3. Global prevalence of anemia and estimated number of individuals affected [3]
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45 Gender or age group	46 Anemia* (%)	47 Population affected (millions)
48 Children, preschool-age	47	293
49 Children, school-age	25	305
50 Men	13	260
51 Non-pregnant women	30	468
52 Pregnant women	42	56
53 Elderly men and women	24	164

54 *) According to hemoglobin thresholds in Table 1
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4 Anemia in apparently healthy well-nourished individuals is not very frequent [4, 5]. In
5 Denmark, epidemiological population surveys have shown that the frequency of anemia
6 in men 30 to 60 years of age is ~1% [4] and in women of reproductive age ~4% [5].
7 Denmark has a balanced social welfare structure, which gives all residents almost equal
8 access to obtain good nutrition and health services. Consequently, the high prevalence of
9 anemia on a global scale is predominantly due to the extremely high frequency in
10 developing countries as well as in developed countries with large social differences
11 between population groups, for example as in USA [22].
12
13

14 In both developing and developed countries, the prevalence of anemia has a social
15 imbalance. It is more prevalent in the lower social strata, in the lower income groups and
16 in the least educated fraction of a population [7]. This is an important point when it
17 comes to treatment and prophylaxis of anemia.
18
19

20 *Newborn infants and young children*

21 It appears from Table 3 that children 0.5-5 years of age on a global scale actually have
22 the highest estimated prevalence of anemia, i.e. 47%. In Europe the prevalence of anemia
23 is estimated to be 17% [3] which indicates that the prevalence must be extremely high in
24 other regions, such as Africa, which unfortunately is on the top of the list with a
25 prevalence of anemia of 65% [3].
26
27

28 Overall, the fetus' and newborn infant's iron status depend on the iron status of the
29 pregnant woman and therefore, iron deficiency in the mother-to-be means that the
30 growing fetus probably will be iron deficient as well. Iron is an element, which is
31 essential for normal growth and development of most organs in the fetus, especially for
32 the hematopoietic organs and what is very important, also for the normal development of
33 the brain. Studies have shown that infants and children born to iron deficient mothers
34 have a poorer cognitive development of the brain functions and a lower intelligence
35 quotient than infants and children born to iron replete mothers. These findings may have
36 profound implications for the later development and social functions of the growing
37 child. If iron deficiency is very prevalent in the female population, it may therefore affect
38 the health profile as well as the social structure of the society in a negative direction.
39
40

41 It is therefore a serious and frequent problem in childhood anemia that many children
42 are born to mothers who have IDA and therefore already from their birth start out in life
43 with iron deficiency and may be even with IDA. Congenital iron deficiency may later be
44 aggravated by insufficient nutrition both qualitatively and quantitatively.
45
46

47 *Adolescent females*

48 The prepubertal growth spurt put great demands on iron nutrition both in males and
49 females. In a Danish epidemiological survey of 16-17-year-old adolescents, 0% of males
50 and 23% of females had small iron stores and 0% of males and 10% of females had iron
51 deficiency [23]. In Denmark, adolescent males have a higher intake of different kinds of
52 meat than females, who are more reluctant to consume what they often term "dead
53 animals". In addition, adolescent females have their menarche and start to lose iron by
54 their upcoming menstrual periods. The combination of these three factors, growth, iron
55 losses and dietary habits make them more vulnerable to develop iron deficiency and IDA.
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Table 4. Global prevalence of anemia in non-pregnant women and pregnant women by World Health Organization (WHO) region (data collected 1993-2005) [3]

WHO region	Non-pregnant women (%)	Pregnant women (%)
Africa	47.5 (43.4–51.6)†	57.1 (52.8–61.3)
Americas	17.8 (12.9–22.7)	24.1 (17.3–30.8)
South-East Asia	45.7 (41.9–49.4)	48.2 (43.9–52.5)
Europe	19.0 (14.7–23.3)	25.1 (18.6–31.6)
Eastern Mediterranean	32.4 (29.2–35.6)	44.2 (38.2–50.3)
Western Pacific	21.5 (20.8–22.2)	30.7 (28.8–32.7)
Global	30.2 (28.7–31.6)	41.8 (39.9–43.8)

Non-pregnant women: 15 to <50 years of age. Pregnant women no age range indicated
 †95% confidence interval

Women of reproductive age

In Europe, the prevalence of anemia among women of reproductive age is 15% [3]. In Denmark, among apparently healthy women of reproductive age, ~40 % have low iron status (serum ferritin < 30 µg/L); 10% have iron deficiency (serum ferritin <16 µg/L) and ~3% IDA [5].

Due to the regular blood and iron losses at their menstrual periods, women of reproductive age a priori face a difficult situation concerning their iron balance. The amount of iron lost by menstruation varies from woman to woman, but is quite constant in the individual women [24]. Natural mechanisms in women have not compensated for these iron losses. In general, both in developed and especially in developing countries, women of reproductive age consume a diet containing an insufficient amount of iron to cover their needs, in part due to the sedentary lifestyle and consequently lower energy intake. Furthermore, the dietary iron they consume is predominantly non-heme iron, which has a very low bioavailability. In other words – their consumption of meat, poultry and fish is inadequate.

On a world-wide scale, more than 468 millions non-pregnant women suffer from anemia; of these women ~80 millions live in Europe and the Americas and the remaining 388 millions in more or less developed regions of the world (Table 4) [3].

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6 *Pregnant women*

7 When an iron deficient woman becomes pregnant, her need for iron will increase
8 dramatically. Pregnancy is a setting where the normal physiological demands for iron
9 display an extraordinary increase of such a magnitude, which has not recognized in other
10 physiological situations [6]. When iron deficient women or women with IDA become
11 pregnant, both the prevalence and the severity of IDA may increase markedly during
12 pregnancy unless prophylaxis or treatment is brought into action.

13
14 The prevalence of anemia in pregnancy display marked variation from region to region.
15 The lowest prevalence ~25% is found in Europe and the Americas, whereas South-East
16 Asia and Africa present high prevalences of 48% and 57%, respectively [3]. In Denmark,
17 pregnant women who do not take iron supplements have a prevalence of anemia of ~25%
18 [24]; in contrast, the prevalence of anemia in women taking 40 mg ferrous iron daily is
19 below 5% [25].

20
21 In general, more than 56 millions pregnant women all over the world suffer from
22 anemia; of these women ~7 millions live in Europe and the Americas and the remaining
23 49 millions in more or less developed countries [3].

24
25 IDA has severe implications both for the mother-to-be and for the growing fetus and
26 newborn infant. The women may have general symptoms of anemia including fatigue,
27 weakness, dizziness, headache, palpitations, reduced physical working capacity, feeling
28 of poor health and in addition specific symptoms of iron deficiency such as reduced
29 cognitive abilities, emotional instability, depression and restless legs.

30
31 Experiences from developing countries and the lower social classes in USA have
32 furthermore shown that IDA in pregnant women has a significant negative influence of
33 the outcome of pregnancy. It causes a higher risk of complications at delivery, a higher
34 risk of early and preterm deliveries and a higher risk of delivering premature children and
35 children with a low birth weight for their gestational age [22].

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37
38 *Postpartum lactating women*

39 There is a direct link from IDA in pregnant women to IDA postpartum. If left untreated,
40 anemia in late pregnancy will inevitably continue after delivery into postpartum anemia,
41 which will even be aggravated due to the blood losses at delivery. Therefore preventing
42 postpartum anemia means definitely preventing or treating prepartum anemia.

43
44 The lactating mother needs to have good nutrition and an adequate intake of vitamins
45 and minerals in order to be physically fit to take proper care of her newborn baby and in
46 order to produce breastmilk of a good quality. Breastmilk is the main nutritional source
47 for the baby for several months, and the quality and quantity of the breastmilk rely on a
48 proper nutritional status of the mother.

49
50 The prevalence of postpartum anemia has not been studied as extensively as prepartum
51 anemia. However, we may extrapolate from the prevalence of anemia in pregnant women
52 (see above) to the prevalence in postpartum women, assuming that the figures may be
53 even higher postpartum due to blood losses at delivery. Therefore, in many regions of
54 the world, postpartum anemia is undoubtedly a very significant, but partly unrecognized
55 problem.

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59 **How can we reduce the prevalence of anemia?**

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6 *Iron deficiency*

7 How can we approach the widespread endemic of iron deficiency? There are a number of
8 options, which can be brought into action and it is important to emphasize that these
9 options may vary from region to region and from country to country. Within a specific
10 country, prophylactic options could even vary between different population subgroups.

11 Prophylactic measures should aim at restoring and maintaining an adequate iron status
12 in the groups at highest risk of iron deficiency, i.e. preschool children, adolescent
13 females, women of reproductive age, pregnant women and postpartum lactating women.
14
15

16 *Dietary measures*

17 Ideally, the most natural way of getting enough iron is through a diet with an adequate
18 iron content and a good bioavailability of the iron. However, even in Northern Europe,
19 including Denmark, dietary iron intake in women of reproductive age is too low to
20 maintain a good iron status in ~40% of the women and in ~80% of pregnant women [6].
21 In contrast, Danish men have an adequate iron and even a high prevalence of slight to
22 moderate iron overload [4].
23
24

25 In general, women consume less food of animal origin than men [8]. Furthermore, due
26 to our sedentary lifestyle in the Western countries, energy intake is relatively low and we
27 know that the total dietary iron intake is dependent on the energy intake [8]. The mean
28 dietary iron intake in Danish women of reproductive age is 9 mg/day with a
29 bioavailability of 15-20% [8]. This is well below the recommended food iron intake of 18
30 mg/day [9].
31

32 Women do not to a significant extent change their dietary habits once they become
33 pregnant and their needs for food iron increase to ~27 mg/day in order to maintain an
34 adequate iron status [6].
35

36 In many developing countries, the diet is composed mainly of foods of plant origin,
37 which per se has a low iron content, consisting of non-heme iron. Furthermore, this non-
38 heme iron has a low bioavailability and diets rich in cereal grains also contain strong
39 inhibitors of iron absorption including phytates. The widespread consumption in some
40 regions of the world of various kinds of teas, which is even taken at meals, will likewise
41 contribute to an impaired iron absorption.
42

43 It is therefore apparent that nutritional measures against iron deficiency in the risk
44 groups would imply drastic and unrealistic changes in dietary habits, which most likely
45 cannot be implemented in the populations.
46
47

48 *Iron fortification of foods*

49 Many Western countries have previously used iron fortification of bread flour. In
50 Denmark flour was for many years fortified with 30 mg carbonyl iron per kg flour. This
51 fortification was stopped in 1987 according to the regulations of the European Union. A
52 follow-up analysis of iron status in the Danish population was performed 10 years after
53 the abolition of the food iron fortification. The results showed that women of
54 reproductive age had unchanged iron status [5], whereas iron status had increased
55 significantly in men, despite the absence of iron fortification! [4]. It has been discussed
56 whether iron fortification should be reintroduced, due to the high prevalence of low iron
57 status in women of reproductive age. However, a general food iron fortification would
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4 probably increase the prevalence of the already established iron overload in the male
5 population. In addition, it may have deleterious effect on subjects with genetic iron
6 overload, i.e. the hereditary forms of hemochromatosis, especially *HFE*
7 hemochromatosis, which is quite frequent in populations of Northern European descent
8 [27, 28]. Subjects with hereditary hemochromatosis have an abnormally high intestinal
9 iron absorption and certainly do not need extra iron in their diet [28].

10
11 Therefore, in the Western countries, we should not rely on food iron fortification but on
12 specific iron prophylaxis in the risk groups.
13

14 However, the situation is different in other parts of the world. In South-East Asia as
15 many as 46% of women of reproductive age have anemia, mainly IDA, which indicates
16 that probably at least 90% of the this female population are iron deficient. Furthermore,
17 genetic iron overload is infrequent in this region. In such a setting, iron fortification of
18 appropriate food items seems justified.
19

20 In South-East Asian countries, regular consumption of NaFeEDTA-fortified fish sauce
21 improves iron status and reduces the prevalence of anemia in anemic women [29].
22 Furthermore, several South-East Asian countries are planning to introduce iron fortified
23 flour.
24

25 In Africa, where the prevalence of anemia is 48% in women of reproductive age, food
26 iron fortification should be balanced against the prevalence of infections, especially
27 malaria, which possibly may be aggravated by the presence of ample iron [30]. However,
28 prospective controlled human studies on the interaction between iron status and malaria
29 have not yet been performed, but a Cochrane review on oral iron supplementation for
30 anemia in children in malaria-endemic areas did not demonstrate any significant change
31 in the prevalence of malaria in iron supplemented children [31].
32
33

34 35 *Iron supplementation*

36 In the Western countries with easy access to the health care system, it is easy to identify
37 persons with iron deficiency and IDA by analyzing hemoglobin and serum ferritin.
38 According to the outcome, adequate treatment or prophylaxis with oral iron can be
39 instituted.
40

41 In developing countries where the health care is less efficient, especially in the rural
42 districts, hemoglobin is often analyzed with a hemoglobinometer, e.g. Hemocue® but
43 there are no facilities for the analysis of ferritin. In regions with a high prevalence of
44 anemia, there is a definite need to establish the ferritin analysis on a broader scale and to
45 use it routinely in association with the analysis of hemoglobin. There is also a need for a
46 simple ferritin analysis, which can be performed under field conditions.
47

48 Even if ferritin cannot be analyzed, in regions with a high prevalence of IDA, the
49 finding of anemia should imply generous use of oral iron supplementation in order to
50 benefit the risk groups.
51
52

53 *Iron prophylaxis in pregnancy*

54 Due to the drastic increase in the need for iron during pregnancy, the majority of pregnant
55 women have a definite need for iron supplements [6]. This goes both for Western
56 countries and developing countries. Ideally the iron supplement should be tailored to the
57 individual woman according to her iron status, i.e. serum ferritin concentration [32]. But
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4 so far, a general iron prophylaxis regime including all pregnant women is used in most
5 countries.

6
7 In Denmark and USA, pregnant women are recommended oral iron supplements from
8 their first visit to the antenatal clinic at approximately 10 weeks gestation. The general
9 recommendation in Denmark is 40 mg ferrous iron and in USA 30 mg ferrous iron daily
10 taken between meals.

11
12 Some studies suggest that in order to be of optimum benefit for the outcome of
13 pregnancy, iron supplements should be started already when the woman decides to
14 become pregnant in order to establish adequate iron reserves during pregnancy and
15 postpartum. This approach is especially important in regions where iron deficiency and
16 IDA are prevalent among women of reproductive age, such as South-East Asia and
17 Africa. Furthermore, this approach is in accordance with the concept of folic acid
18 supplements, which should be started when conception is planned (see below).

19
20 In regions, where iron deficiency and IDA is highly prevalent, the dose of iron should
21 be higher than in the Western countries. An appropriate dose would be 100 mg ferrous
22 iron/day, preferably taken at bedtime or between meals [32].

23
24 Tablets, which combine iron, folic acid, vitamin B₁₂ and vitamin C will be much easier
25 for the women to administrate instead of taking the single components in separate tablets.

26 27 *Iron treatment of iron deficiency anemia*

28 IDA should initially be treated with oral ferrous iron in doses of 100-200 mg/day. It is
29 essential to check the hemoglobin concentration after 2-4 weeks to see if the treatment
30 works and induces an increase in hemoglobin. Iron should be continued for at least 6
31 months after hemoglobin concentrations have reached normal levels in order to rebuild a
32 minimum of body iron reserves. In profound IDA with hemoglobin <90 g/L intravenous
33 iron should be considered.
34
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37 *Treatment of iron deficiency anemia in pregnancy*

38 Prophylaxis is better than cure! However, some women have so severe IDA at their first
39 visit to the antenatal clinic that oral ferrous iron in prophylactic doses of 40-50 mg may
40 be inadequate in order to correct the anemia prior to delivery. The Guidelines by the
41 Swiss Society for Gynecology and Obstetrics recommend that if the woman's
42 hemoglobin is <105 g/L, first-line treatment is to increase the dose of oral iron to 200
43 mg/day. Hemoglobin should be checked after 2 weeks and if there is an increase of 10
44 g/L or more, oral iron should be continued throughout pregnancy. In women who after 2
45 weeks do not respond to oral iron by an increase in hemoglobin of 10 g/L or more,
46 intravenous iron treatment should be considered [33].
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49 For treatment of IDA in pregnancy, The Network for Advancements of Transfusion
50 Alternatives (NATA) recommends oral ferrous iron 100-200 mg/day in the 1st and 2nd
51 trimester. If there is no increase in hemoglobin after 2 weeks, intravenous iron therapy
52 should be considered. In the 3rd trimester intravenous iron is advocated as first-line
53 treatment, because oral iron, even in high doses, has too short time to work in order to
54 correct the anemia before delivery [34].
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57 Studies from the Indian subcontinent have demonstrated that intravenous iron therapy
58 can be very efficient in the correction of IDA in late pregnancy. Intravenous iron can be
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4 administered as a single dose infusion, which is convenient for the patient and reduces
5 the costs of the health care system.
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7 *Treatment of postpartum iron deficiency anemia*

8 Postpartum anemia is a poorly recognized problem. In many developed countries,
9 including Denmark, the mothers are discharged from the public birth clinics within hours
10 after delivery. So far it has not been possible to measure hemoglobin at 48 hours after
11 delivery in order to estimate the prevalence of postpartum anemia. The prevalence of
12 major maternal bleeding >500 ml in association with delivery is in the range of 5-7%.
13 The Guidelines by the Swiss Society for Gynecology and Obstetrics recommend that if
14 the woman's hemoglobin is 95-120 g/L, first-line treatment is to increase the oral iron to
15 80-200 mg/day. If hemoglobin has dropped to <95 g/L intravenous iron 500-1000 mg is
16 recommended and at hemoglobin levels <80 g/L it should be considered giving
17 recombinant human erythropoietin in addition to intravenous iron [33].
18

19 The Network for Advancements of Transfusion Alternatives recommends intravenous
20 iron at hemoglobin levels 60-95 g/L and blood transfusion at hemoglobin levels <60 g/L
21 [34].
22

23 *Folate deficiency*

24 In order to prevent neural tube defects in the fetus it is important to maintain a good
25 folate status in women of reproductive age who may become pregnant as well as in
26 pregnant women. The neural tube is formed within approximately 30 days after
27 conception, so it is essential that the woman's folate status is good already prior to
28 conception. This can be obtained by a general folic acid fortification of appropriate food
29 items, usually flour [13] as well as by individual folic acid supplementation. The general
30 recommendation for supplemental folic acid is 400 µg/day [13]. The nutrition authorities
31 in USA have implemented folic acid fortification of flour, but nevertheless still
32 recommend that women of reproductive age should take additional folic acid
33 supplements of 400 µg/day [35].
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36 *Vitamin B₁₂ deficiency*

37 Although the recommended daily intake of vitamin B₁₂ is ~2.4 µg/day, many elderly
38 persons appear to require much higher supplement doses to achieve optimum vitamin B₁₂
39 status, probably due to a limited gastrointestinal absorption. In order to increase the
40 dietary intake of vitamin B₁₂, the diet should be rich in foods of animal origin. This
41 would, however, be almost impossible for the majority of people in many developing
42 countries due to the high costs of meat and poultry. If the deficiency is caused by
43 malabsorption of vitamin B₁₂, dietary measures would be insufficient and
44 prophylaxis/treatment should rely on oral supplementation of synthetic vitamin B₁₂ in
45 adequate doses. The synthetic form of vitamin B₁₂ is absorbed much better than the food
46 forms, and may in high doses bypass the "natural" absorption mechanism [13].
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49 *Infections/infestations*

50 In communities where infections/infestations are frequent and contribute significantly to
51 a high prevalence of anemia, treatment and prophylactic eradication of infections are
52 important in order to improve the situation [36].
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4 In areas with high frequencies of parasitic diseases such as malaria and intestinal
5 helminth infestations, antimalarial programmes as well as deworming programmes
6 should be effectuated [18].
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8 In Africa, ~30 million women living in malaria-endemic areas become pregnant each
9 year. For these women, malaria is a threat both to themselves and to their babies, with up
10 to 200 000 newborn deaths each year as a result of malaria in pregnancy. Pregnant
11 women are particularly vulnerable to malaria as pregnancy reduces a woman's immunity
12 to malaria, the parasites being resident in the placenta, making her more susceptible to
13 malaria infection and increasing the risk of illness, severe anemia and death. For the
14 unborn child, maternal malaria increases the risk of spontaneous abortion, stillbirth,
15 premature delivery and low birth weight – and is therefore a leading cause of child
16 mortality [37].
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20 *Hemoglobinopathies*

21 The management of the hemoglobinopathy issue relies primarily on genetic counseling in
22 order to limit or avoid the occurrence of severe disease, which demands expensive
23 treatment and is associated with a poor quality of life and a poor survival rate. Systematic
24 follow-up and case management of abnormal newborn screen for hemoglobinopathy can
25 improve the acceptance of genetic counselling [38].
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30 **Conclusion**

31 Anemia has been recognized as a major health problem in developing countries for many
32 years: Still this basic problem has not been solved but continues to exist affecting the
33 health, quality of life and working capacity in billions of people around the world. Most
34 cases of anemia are due to iron deficiency, which often work in symphony with folate
35 and/or vitamin B₁₂ deficiency as well as infections/infestations.
36

37 The World Health Organization has initiated successful campaigns against a number of
38 infectious diseases - but the battle against anemia is far from being won and more efforts
39 should be concentrated on tackling this massive problem - we have the tools and we
40 know the ways. Initially, the efforts should be centered on the risk groups for iron
41 deficiency anemia, i.e. young children, adolescent females, women of reproductive age as
42 well as pregnant women and postpartum lactating mothers.
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