

## Routine iron supplementation during pregnancy

Mahomed K

**Date of most recent substantive amendment : 20 November 1996**

**Objectives:** *To assess the effect of routine iron supplementation on pre-specified haematological and biochemical parameters, and on maternal and fetal measures of pregnancy outcome.*

**Search strategy:** *The search strategy developed by the Pregnancy and Childbirth Group has been used.*

**Selection criteria:** *All acceptably controlled trials evaluating the role of routine iron supplementation to pregnant women were eligible. There is one study [Finland 1991] that compares routine versus selective iron supplementation only when the haemoglobin concentration fell below 10g/dl.*

**Data collection and analysis:** *Data from published trials were used. Principal authors were contacted whenever clarification was required.*

**Main results:** *Routine iron supplementation raises or maintains the serum ferritin above 10ug/l, and results in a substantial reduction in the proportion of women with a haemoglobin level below 10 or 10.5g/dl in late pregnancy. Routine supplementation, however, had no detectable effect on any substantive measures of either maternal or fetal outcome. The one trial of routine versus selective supplementation [Finland 1991] showed a reduced likelihood of Caesarean section and post partum blood transfusion, but more dead infants in the routinely supplemented group. The results from a single trial should, however, be interpreted with caution.*

**Conclusions:** *The available data from controlled trials clearly demonstrate the positive effect of routine iron supplementation in preventing low haemoglobin at delivery or at 6 weeks post partum. There is very little information on effect, beneficial or harmful, on measurable effects of pregnancy outcome both for mother and newborn. There is therefore no strong evidence to advise for or against a policy of routine iron supplementation in pregnancy. There are few data derived from communities in which iron deficiency is common and anaemia is a serious clinical problem. Trials are needed in these populations to establish the most appropriate strategies for preventing and treating iron deficiency, and these studies should be large enough to detect important effects on maternal and fetal outcomes.*

### Background

As pregnancy proceeds, most women show haematological changes suggesting iron deficiency; the haemoglobin and serum iron concentrations fall and the total iron binding capacity rises; the mean corpuscular haemoglobin concentration may remain constant or may fall.

In developing countries, the amount of available iron from dietary sources may not meet the additional demands placed on maternal iron stores by the growing fetus, placenta and the increased maternal red cell mass even though the increased demands are partially off set by the amenorrhoea and increased absorption of iron during pregnancy. Anaemia in pregnancy is a major health problem in many developing countries where in addition to nutrition, other factors such as malaria and helminthic infections contribute to the increased maternal and perinatal mortality and morbidity.

In developed countries, the decrease in blood values is rarely of a magnitude sufficient to be serious especially in women receiving adequate diet, yet it has been almost universal practice that all pregnant women routinely receive iron supplementation during pregnancy. In fact it has been suggested that iron supplementation in these women may increase blood viscosity and thus possibly impair placental circulation and fetal growth (Koller 1982).

### Objectives

To evaluate the effect of routine iron supplementation to pregnant women with normal levels of haemoglobin.

255

The following hypotheses were to be tested:

- a) Routine iron supplementation would have no measurable effect on pre-specified haematological and biochemical parameters.
- b) Routine iron supplementation would have no effect on maternal and perinatal mortality and morbidity.
- c) Selective iron supplementation (ie only when there is laboratory evidence of anaemia) would have no effect on maternal and perinatal mortality and morbidity.

## **Criteria for considering studies for this review**

### **Types of participants**

Pregnant women prior to 28 weeks' gestation and usually recruited at the first antenatal clinic visit. Women were recruited if the initial haemoglobin level was >10g/dl except in one trial [Indonesia 1993] in which the cut off level for entry was a haemoglobin level >8g/dl.

### **Types of intervention**

In most trials, around 100mg elemental iron was supplemented orally. The control groups received a placebo tablet or no iron. It is not clear from many of the trial reports whether iron was given to any participant if their haemoglobin levels fell below a certain value. Many trials assessed the use of iron and folate combined in a single preparation but comparisons in this review are with respect to iron or no iron and these trials were only included if the groups were comparable in respect to other forms of supplementation ie control group women received folic acid.

A single trial [Finland 1991] has been published comparing routine iron supplementation versus selective iron only when haemoglobin levels fell below 10g/dl. This study is included in the review but the outcome variables are presented within a secondary comparison of routine versus selective iron, the control group being selective iron.

### **Types of outcome measures**

There are two types of outcomes:

- a) Haematological and biochemical parameters - haemoglobin and measures of iron status.
- b) Substantive clinical measures of pregnancy outcome and other clinical information.

### **Types of studies**

All acceptably randomised controlled trials of routine iron supplementation versus no iron or placebo, or versus selective supplementation, for approximately 16 weeks' duration.

### **Search strategy for identification of studies**

See: [Collaborative Review Group search strategy](#)

This review has drawn on the search strategy developed for the Pregnancy and Childbirth Group as a whole.

Relevant trials were identified in the Group's Specialised Register of Controlled Trials.

Additional data were obtained whenever necessary and possible by contacting the principal author.

### **Methods of the review**

Trials under consideration were evaluated for methodological quality and appropriateness for inclusion without consideration of their results.

Included trial data were processed as described in: *Materials and methods used in synthesizing evidence to evaluate the effects of care during pregnancy and childbirth*. In: Chalmers I, Enkin MW, Kierse MJNC, (eds), *Effective Care in Pregnancy and Childbirth*, Oxford: Oxford University Press 1989;pp39-65.

### **Description of studies**

See Characteristics of Included Studies.

All trials included routine iron versus no iron or placebo except the Finland 1991 trial that compared routine iron with selective iron only if the haemoglobin value fell below 10g/dl.

### **Methodological qualities of included studies**

Possible selection bias was difficult to elucidate as authors often stated

that women were 'randomly allocated' without describing the technique. Some authors used less robust methods of allocation including the day of the week, clinic attendance or hospital number. Studies in which >25% of participants were excluded from the final analysis have not been included in the review.

Many of the studies were however double blind, and so outcome assessment was good.

Studies in which the only outcome variables were in the form of mean values with no standard deviation have also been excluded.

## **Results**

Routine iron supplementation raises or maintains the serum ferritin above 10ug/l, and results in a substantial reduction in the proportion of women with a haemoglobin level below 10 or 10.5g/dl in late pregnancy.

However, there is very little information regarding the effect if any on any substantive measures of either maternal or fetal outcome: data on outcomes such as pregnancy hypertension, maternal infection, preterm or post term delivery, Caesarean section, low birthweight, small for dates babies, low Apgar scores, need for admission to neonatal unit and congenital malformation are available from usually only a single trial.

The only possible statistically significant effects of routine supplementation, suggested by the largest trial [Finland 1991], was a reduced likelihood of Caesarean section and post partum blood transfusion and an increase in dead infants. These associations were not predicted prior to the analysis, and some were attributed by the authors to possible anxiety by midwives and obstetricians about low haematocrit values in unsupplemented group. Readers should however be cautioned from drawing any firm conclusions from results of single trials.

## **Summary of analyses**

MetaView: Tables and Figures

## **Discussion**

See Conclusions.

## **Conclusions**

### **Implications for practice**

The available data from controlled trials provide clear evidence of an improvement in haematological indices in women receiving routine iron supplementation. No conclusions can be drawn in terms of any effects, beneficial or harmful, on outcomes for mother and baby as data are available from often single trials.

The results of the largest trial suggests that routine iron supplementation may reduce the use of post partum blood transfusion. This needs to be confirmed as it would have major health implications in areas where HIV infection is prevalent with resultant need to avoid blood transfusions.

At present therefore there is no evidence to advise against a policy of routine iron supplementation in pregnancy. Routine supplementation could be warranted in populations in which iron deficiency is common.

### **Implications for research**

The effect of iron supplementation on the major haematological indices is so well established that no further trials are needed to prove that iron is a haematinic (although it might be noted that the use of serum ferritin as an ultimate criterion of iron deficiency in pregnancy has not been established).

There are few data derived from communities in which iron deficiency is common and anaemia a serious clinical problem. Trials are needed in these populations to establish the most appropriate strategies for preventing and treating iron deficiency, and these studies should be large enough to detect important effects on maternal and fetal outcome.

Whether routine iron supplementation causes any harm in well nourished communities is still unclear and will not be clarified without further large scale, scrupulously conducted randomised trials.

## **Conflict of interest**

None.

## Acknowledgements

We are grateful to the numerous authors who responded to our queries.

## Characteristics of included studies

Table: Characteristics of included studies

## Characteristics of excluded studies

### Study : Denmark 1991a

Study compares high versus low dose of iron.

### Study : France 1983

203 women initially recruited. Although the authors state it was placebo controlled data were only available in 154 women and reliability of these data was unclear.

### Study : India 1970

Allocation was by random assignment and although 800 women recruited, only 35% included in final analysis.

### Study : Italy 1989

Data only reported as normal iron balance predelivery.

### Study : Netherlands 1983

There were no data for more than 50% of the women pre delivery. No further information was available from the authors.

### Study : South Africa 1983

Too many exclusions from trial with unclear allocation method. Data not available in 16 out of 73 treatment and 25 out of 73 control group.

### Study : UK 1956

Haemoglobin levels expressed as improvement in mean haemoglobin. No further information from authors.

### Study : UK 1958

Results reported as rise in haemoglobin levels and although the study was exceptionally good in terms of concealment of allocation the results not usable as no standard deviations available.

### Study : UK 1965

Only means without standard deviations available. Data therefore not included.

### Study : UK 1977

Mean haemoglobin and iron levels reported without standard deviation. No further information available from authors.

### Study : USA 1960

Too many exclusions in the final analysis in the control group. Data from 24 out of 25 in treatment group but only 12 out of 25 in control group.

### Study : USA 1987

Data from >25% of participants unavailable.

## References

### References to studies included in this review

#### Australia 1961

*Morgan EH. Plasma-iron and haemoglobin levels in pregnancy. Lancet 1961;1:9-12. [229]*

#### Australia 1963

*Hankin ME. The value of iron supplementation during pregnancy. Aust NZ J Obstet Gynaecol 1963;3:111-118. [323]*

#### Burma 1976

*Batu AT, Toe T, Pe H, Nyunt KK. A prophylactic trial of iron and folic acid supplements in pregnant Burmese women. Isr J Med Sci 1976;12:1410-1417. [1104]*

#### Canada 1971

Cantlie GSD, De Leeuw NKM, Lowenstein L. Iron and folate nutrition in a group of private obstetrical patients. *Am J Clin Nutr* 1971;24:637-641. [668]

**Denmark 1991b**

Milman N, Agger AO, Nielson OJ. Iron supplementation during pregnancy. Effect on iron status markers, serum erythropoietin and human placental lactogen. A placebo controlled study in 207 Danish women. *Danish Med Bull* 1991;38/6:471-476. [7291]

**Denmark 1994**

Milma N, Agger AO, Nielson OJ. Iron status markers and serum erythropoietin in 120 mothers and newborn infants: effect of iron supplementation in normal pregnancy. *Acta Obstet Gynecol Scand* 1994;73:200-204. [8300]

**Equador 1989**

Freire WB. Hemoglobin as predictor of response to iron therapy and its use in screening and prevalence estimates. *Am J Clin Nutr* 1989;50:1442-1449. [5316]

**Finland 1980**

Puolakka J, Janne O, Pakarinen A, Jarvinen PA, Vihko R. Serum ferritin as a measure of iron stores during and after normal pregnancy with and without iron supplement. *Acta Obstet Gynecol Scand* 1980;95:43-51. [1793]

**Finland 1991**

Hemminki E, Rimpela U. A randomized comparison of routine vs selective iron supplementation during pregnancy. *J Am Coll Nutr* 1991;10:3-10. [6172]

Hemminki E, Rimpela U. Iron supplementation, maternal packed cell volume, and fetal growth. *Arch Dis Child* 1991;66:422-425. [7325]

Hemminki E, Rimpola U, Yla-Outinen A. Iron prophylaxis during pregnancy and infections. *Int J Vitam Nutr Res* 1991;61:370-371. [7324]

Hemminki E, Rimpela U. Iron supplementation, maternal packed cell volume, and fetal growth. *Arch Dis Child* 1991;66:422-425. [6173]

Hemminki E, Uski A, Koponen P, Rimpela U. Iron supplementation during pregnancy - experiences of a randomized trial relying on health service personnel. *Controlled Clinical Trials* 1989;10:290-298. [8291]

**France 1989**

De Benaze C, Galan P, Wainer R, Hercberg S. Prevention of iron deficient anemia during pregnancy by early iron supplementation: a controlled trial. *Rev Epidemiol Sante Publique* 1989;37:109-118. [5214]

**Gambia 1994**

Menendez C, Todd J, Alonso PL, Francis N, Lulat S, Ceasay S, M'Boge B, Greenwood BM. The effects of iron supplementation during pregnancy, given by traditional birth attendants, on the prevalence of anaemia and malaria. *Trans R Soc Trop Med Hyg* 1994;88:590-593. [8723]

**India 1962**

Menon MKK, Rajan L. Prophylaxis of anaemia in pregnancy. *J Obstet Gynaecol Br Cmmwth* 1962;12:382-389. [263]

**Indonesia 1993**

Suharno D, West CE, Karyadi D, Hautvast JGA. Supplementation with vitamin A and iron for nutritional anaemia in pregnant women in West Java, Indonesia. *Lancet* 1993;342:1325-1328. [8213]

**Nigeria 1985**

Harrison KA, Fleming AF, Briggs ND, Rossiter CE. Child-bearing, health and social priorities: a survey of 22,774 consecutive hospital births in Zaria, Northern Nigeria. 5. Growth during pregnancy in Nigerian teenage primigravidae. *Br J Obstet Gynaecol* 1985;92/5:32-39. [4036]

**Nigeria 1986**

Fleming AF, Ghatoura GBS, Harrison KA, Briggs ND, Dunn DT. The prevention of anaemia in pregnancy in primigravidae in the guinea savanna of Nigeria. *Ann Trop Med Parasitol* 1986;80:211-233. [2958]

**Norway 1983**

Romslo I, Haram K, Sagen N, Augensen K. Iron requirements in normal pregnancy as assessed by serum ferritin, serum transferrin saturation and erythrocyte protoporphyrin determinations. *Br J Obstet Gynaecol* 1983;90:101-107. [2055]

**Sweden 1975**

Svanberg B, Arvidsson B, Norrby A, Rybo G, Solvell L. Absorption of supplemental iron during pregnancy - a longitudinal study with repeated bone marrow studies and absorption measurements. *Acta Obstet Gynecol Scand* 1975;48:87-108. [1075]

**UK 1966a**

Chisholm M. A controlled clinical trial of prophylactic folic acid and iron in pregnancy. *J Obstet Gynaecol Br Cmmwth* 1966;73:191-196. [410]

**UK 1966b**

Paintin DB, Thomson AM, Hytten FE. Iron and haemoglobin level in pregnancy. *J Obstet Gynaecol Br Cmmwth* 1966;73:181-190. [440]

**UK 1966c**

Willoughby MLN, Jewell FJ. Investigation of folic acid requirements in pregnancy. *BMJ* 1966;2:1568-1571. [458]

**UK 1967**

Willoughby MLN. An investigation of folic acid requirements in pregnancy. II. *Br J Haematol* 1967;13:503-509. [501]

**UK 1971**

Chanarin I, Rothman D. Further observations on the relation between iron and folate status in pregnancy. *BMJ* 1971;2:81-84. [669]

**USA 1955**

Holly RG. Anemia in pregnancy. *Obstet Gynecol* 1955;5:562-569. [86]

**USA 1958**

Pritchard JA, Hunt CF. A comparison of the hematologic responses following the routine prenatal administration of intramuscular and oral iron. *Surg Gynecol Obstet* 1958;106:516-518. [139]

**USA 1986**

Groner JA, Holtzman NA, Charney E, Mellits ED. A randomized trial of oral iron on tests of short-term memory and attention span in young pregnant women. *J Adolesc Health care* 1986;7:44-48. [1575]

**References to studies excluded from this review****Denmark 1991a**

Guildholt IS, Trolle BG, Hvidman LE. Iron supplementation during pregnancy. *Acta Obstet Gynecol Scand* 1991;70:9-12. [6616]

**France 1983**

Zittoun J, Blot I, Hill C, Zittoun R, Papiernik E, Tchernia G. Iron supplements vs placebo during pregnancy: its effects on iron and folate status on mothers and newborns. *Ann Nutr Metab* 1983;27:320-327. [2274]

#### **India 1970**

Iyengar L, Apte SV. Prophylaxis of anemia in pregnancy. *Am J Clin Nutr* 1970;23:725-730. [628]

#### **Italy 1989**

Tura S, Carezza L, Baccarani M, Bagnara M, Bocci A, Bottone P, Bresadola M, Bruzzese G, Cassano F, Coccia ME, D'Alberton A, Danesino V, Diani F, Fanin R, Gerli S, Gianni L, Grossi E, Martinelli P, Montoneri C, Papadia L, Pecorari D, Sanlorenzo O, Tannoia N, Thiella M. Therapy and iron supplements with ferritin during pregnancy. A randomized prospective study of 458 cases. *Recenti Prog Med* 1989;80:607-614. [5554]

#### **Netherlands 1983**

Buytaert G, Wallenburg HCS, Van Eijk HG, Buytaert P. Iron supplementation during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1983;15:11-16. [2392]

Wallenberg HCS and Van Eijk HG. Effect of oral iron supplementation during pregnancy on maternal and fetal iron status. *J Perinat Med* 1984;12:7-12. [2576]

#### **South Africa 1983**

Dommissie J, Bell DJH, Du Toit ED, Midgley V, Cohen M. Iron-storage deficiency and iron supplementation in pregnancy. *S Afr Med J* 1983;64:1047-1051. [2419]

#### **UK 1956**

Edgar W, Rice HM. Administration of iron in antenatal clinics. *Lancet* 1956;1:599-602. [106]

#### **UK 1958**

Kerr DNS, Davidson S. The prophylaxis of iron-deficiency anemia in pregnancy. *Lancet* 1958;2:483-488. [135]

#### **UK 1965**

Chanarin I, Rothman D, Berry V. Iron deficiency and its relation to folic acid status in pregnancy. Results of a clinical trial. *BMJ* 1965;1:480-485. [367]

#### **UK 1977**

Fenton V, Cavill I, Fisher J. Iron stores in pregnancy. *Br J Haematol* 1977;37:145-149. [1240]

#### **USA 1960**

Hood WE, Bond WL. Iron deficiency prophylaxis during pregnancy. *Obstet Gynecol* 1960;16:82-84. [181]

#### **USA 1987**

Dawson EB, McGanity WJ. Protection of maternal iron stores in pregnancy. *J Reprod Med* 1987;32/S:478-487. [3664]

#### **Additional references**

##### **Koller 1982**

Koller O. The clinical significance of haemodilution during pregnancy. *Obstet Gynecol Survey* 1982;37:649-652.

#### **Previously published versions**