MJA
The Medical Journal of Australia

# Supporting Information

## Supplementary tables and figures

**This appendix was part of the submitted manuscript and has been peer reviewed.**
**It is posted as supplied by the authors.**

Appendix to: Qassim A, Grivell RM, Henry A, et al. Intravenous or oral iron for treating iron deficiency anaemia during pregnancy: systematic review and meta-analysis. *Med J Aust* 2019; doi: 10.5694/mja2.50308.

**Table 1. Search strategy for systematic review**

**MEDLINE**

1. *Pregnancy.mp OR pregnancy/*
2. *Obstetric$.mp OR obstetrics/*
3. *Prenatal care.mp OR prenatal care/*
4. *1 OR 2 OR 3*
5. *Iron dextran.mp OR iron-dextran OR Iron-dextran complex/*
6. *Iron sucrose.mp*
7. *Sodium ferric gluconate.mp*
8. *Ferumoxytol.mp*
9. *Ferric carboxymaltose.mp OR FCM.mp*
10. *Iron isomaltoside.mp*
11. *Iron polymaltose.mp*
12. *Iron saccharate.mp*
13. *Ferric compounds.mp OR exp ferric compounds/*
14. *Ferrous compounds.mp OR exp ferrous compounds/*
15. *Iron.mp OR exp iron/*
16. *5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12*
17. *IV.mp OR Intravenous.mp OR exp injections, intravenous/ OR exp administration, intravenous/ OR exp infusions, intravenous/*
18. *4 AND 16 AND 17*

*mp = default search; ie, search within all search fields combined (eg, title, abstract, keywords)*

*exp = This command explodes the term entered in the command line such that the subject heading and all narrower terms are included in the search.*

**EMBASE**

1. *'Obstetrics'/exp OR 'obstetric*' OR 'prenatal period' OR 'pregnancy'/exp OR 'pregnancy' AND [embase]/lim*
2. *'Iron polymaltose'/exp OR 'iron polymaltose' OR 'ferric carboxymaltose' OR 'iron saccharate' OR 'iron sucrose' OR 'sodium ferric gluconate' OR 'ferumoxytol' OR 'iron isomaltoside' OR 'iron dextran' OR 'iron-dextran' AND [embase]/lim*
3. *'Intravenous drug administration'/exp OR 'intravenous drug administration' OR 'IV' OR 'intravenous'/exp OR 'intravenous' AND [embase]/lim*
4. *#1 AND #2 AND #3*

*exp = This command explodes the term entered in the command line such that the subject heading and all narrower terms are included in the search.*

*lim = limits the search according to the descriptor specified.*

**Scopus**

1. *(“pregnancy” OR “obstetric*” OR “prenatal care” OR “antenatal”)*
2. *("iron polymaltose" OR "ferric carboxymaltose" OR "iron saccharate" OR “iron sucrose” OR “iron dextran” OR “iron-dextran” OR “sodium ferric gluconate” OR “ferumoxytol” OR “iron isomaltoside”)*
3. *(“intravenous” OR “IV” OR “infusion”)*
4. *1 AND 2 AND 3*

**Cochrane Central Register of Controlled Trials**

*(“pregnancy” OR “obstetric*” OR “prenatal care” OR “antenatal”) AND ("iron polymaltose" OR "ferric carboxymaltose" OR "iron saccharate" OR “iron sucrose” OR “iron dextran” OR “iron-dextran” OR “sodium ferric gluconate” OR “ferumoxytol” OR “iron isomaltoside”) AND (“intravenous” OR “IV” OR “infusion”)*

**Web of Science**

TI=(pregnancy OR obstetric* OR prenatal care OR antenatal) AND TI=("iron polymaltose" OR "ferric carboxymaltose" OR "iron saccharate" OR iron sucrose OR iron dextran OR iron-dextran OR sodium ferric gluconate OR ferumoxytol OR iron isomaltoside) AND TI=(intravenous OR IV)

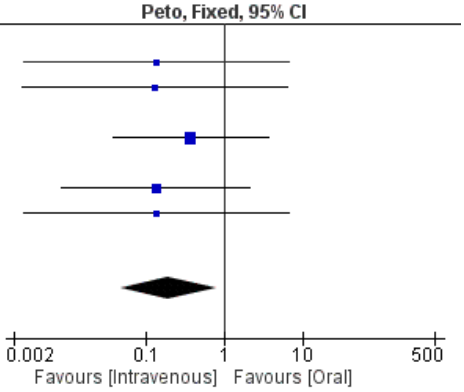
*TI = restrict search to titles*

**Figure 1. Forest plots for primary (A) and secondary perinatal outcomes (B–F), and for maternal and neonatal haematological outcomes (G–J)**

**A. Blood transfusion**

| Study or Subgroup | Intravenous Events | Intravenous Total | Oral Events | Oral Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Aggarwal 2012 | 0 | 25 | 0 | 25 | | Not estimable |
| Al 2005 | 0 | 45 | 1 | 45 | 12.7% | 0.14 [0.00, 6.82] |
| Bayoumeu 2002 | 0 | 24 | 1 | 23 | 12.7% | 0.13 [0.00, 6.54] |
| Dubey 2013 | 0 | 100 | 0 | 100 | | Not estimable |
| Froessler 2013 | 1 | 69 | 2 | 51 | 36.6% | 0.37 [0.04, 3.68] |
| Gupta 2014 | 0 | 50 | 0 | 50 | | Not estimable |
| Khalafallah 2010 | 0 | 92 | 2 | 91 | 25.3% | 0.13 [0.01, 2.13] |
| Kochhar 2013 | 0 | 50 | 1 | 50 | 12.7% | 0.14 [0.00, 6.82] |
| Sarmishta 2017 | 0 | 100 | 0 | 100 | | Not estimable |
| **Total (95% CI)** | | **555** | | **535** | **100.0%** | **0.19 [0.05, 0.78]** |
| Total events | 1 | | 7 | | | |

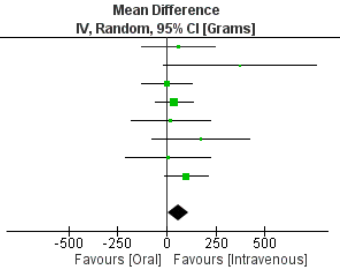
Heterogeneity: Chi² = 0.47, df = 4 (P = 0.98); I² = 0%
Test for overall effect: Z = 2.31 (P = 0.02)




**B. Birthweight**

| Study or Subgroup | Intravenous Mean [Grams] | Intravenous SD [Grams] | Intravenous Total | Oral Mean [Grams] | Oral SD [Grams] | Oral Total | Weight | Mean Difference IV, Random, 95% CI [Grams] |
|---|---|---|---|---|---|---|---|---|
| Al 2005 | 3,498 | 452 | 45 | 3,439 | 451 | 45 | 8.4% | 59.00 [-127.56, 245.56] |
| Bayoumeu 2002 | 3,595 | 785 | 24 | 3,220 | 570 | 23 | 1.9% | 375.00 [-16.02, 766.02] |
| Breymann 2017 | 3,400 | 500 | 112 | 3,400 | 500 | 109 | 16.8% | 0.00 [-131.85, 131.85] |
| Gupta 2014 | 2,607 | 252 | 50 | 2,568 | 244 | 50 | 30.8% | 39.00 [-58.23, 136.23] |
| Khalafallah 2010 | 3,440 | 693 | 92 | 3,420 | 693 | 91 | 7.2% | 20.00 [-180.81, 220.81] |
| Kochhar 2013 | 2,870 | 456 | 49 | 2,695 | 765 | 49 | 4.7% | 175.00 [-74.36, 424.36] |
| Ruangvutilert 2017 | 3,066 | 328 | 25 | 3,060 | 455 | 25 | 6.0% | 6.00 [-213.87, 225.87] |
| Rudra 2016 | 2,784 | 428 | 100 | 2,684 | 362 | 100 | 24.2% | 100.00 [-9.87, 209.87] |
| **Total (95% CI)** | | | **497** | | | **492** | **100.0%** | **58.29 [4.29, 112.28]** |

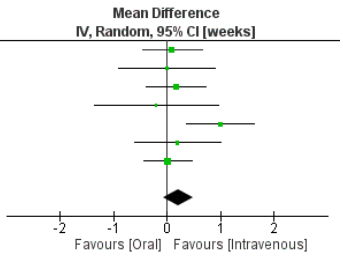
Heterogeneity: Tau² = 0.00; Chi² = 5.17, df = 7 (P = 0.64); I² = 0%
Test for overall effect: Z = 2.12 (P = 0.03)




**C. Gestation at birth**

| Study or Subgroup | Intravenous Mean [weeks] | Intravenous SD [weeks] | Intravenous Total | Oral Mean [weeks] | Oral SD [weeks] | Oral Total | Weight | Mean Difference IV, Random, 95% CI [weeks] |
|---|---|---|---|---|---|---|---|---|
| Al 2005 | 39.2 | 1.5 | 45 | 39.1 | 1.2 | 45 | 18.1% | 0.10 [-0.46, 0.66] |
| Bayoumeu 2002 | 37 | 2 | 24 | 37 | 1 | 23 | 8.4% | 0.00 [-0.90, 0.90] |
| Gupta 2014 | 38.48 | 1.36 | 50 | 38.31 | 1.47 | 50 | 18.4% | 0.17 [-0.39, 0.73] |
| Khalafallah 2010 | 38.9 | 4 | 92 | 39.1 | 4 | 91 | 5.3% | -0.20 [-1.36, 0.96] |
| Kochhar 2013 | 38 | 1 | 49 | 37 | 2 | 49 | 15.3% | 1.00 [0.37, 1.63] |
| Ruangvutilert 2017 | 39.2 | 1.6 | 25 | 39 | 1.3 | 25 | 10.1% | 0.20 [-0.61, 1.01] |
| Rudra 2016 | 38.24 | 1.67 | 100 | 38.22 | 1.59 | 100 | 24.3% | 0.02 [-0.43, 0.47] |
| **Total (95% CI)** | | | **385** | | | **383** | **100.0%** | **0.22 [-0.06, 0.50]** |

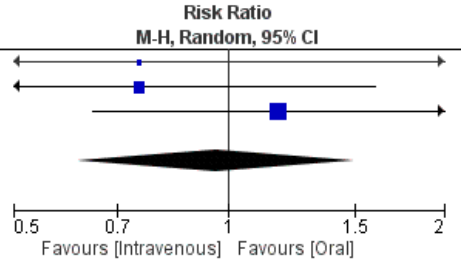
Heterogeneity: Tau² = 0.03; Chi² = 7.65, df = 6 (P = 0.26); I² = 22%
Test for overall effect: Z = 1.52 (P = 0.13)




**D. Caesarean delivery**

| Study or Subgroup | Intravenous Events | Intravenous Total | Oral Events | Oral Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Abhilashini 2014 | 3 | 50 | 4 | 50 | 9.6% | 0.75 [0.18, 3.18] |
| Al 2005 | 9 | 45 | 12 | 45 | 34.7% | 0.75 [0.35, 1.60] |
| Khalafallah 2010 | 19 | 92 | 16 | 91 | 55.8% | 1.17 [0.65, 2.14] |
| **Total (95% CI)** | | **187** | | **186** | **100.0%** | **0.96 [0.62, 1.51]** |
| Total events | 31 | | 32 | | | |

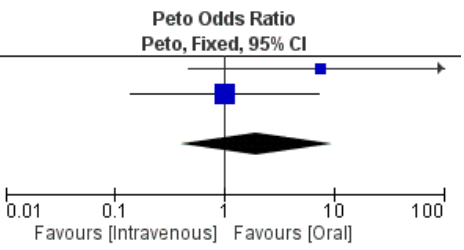
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)




**E. Hypertensive disorders of pregnancy**

| Study or Subgroup | Intravenous Events | Intravenous Total | Oral Events | Oral Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Al 2005 | 2 | 45 | 0 | 45 | 33.4% | 7.56 [0.47, 122.76] |
| Dubey 2013 | 2 | 100 | 2 | 100 | 66.6% | 1.00 [0.14, 7.21] |
| **Total (95% CI)** | | **145** | | **145** | **100.0%** | **1.97 [0.39, 9.85]** |
| Total events | 4 | | 2 | | | |

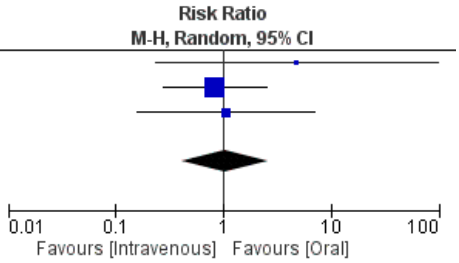
Heterogeneity: Chi² = 1.35, df = 1 (P = 0.25); I² = 26%
Test for overall effect: Z = 0.82 (P = 0.41)



**F. Pre-term birth**

| Study or Subgroup | Intravenous Events | Total | Oral Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Breymann 2017 | 2 | 121 | 0 | 115 | 9.2% | 4.75 [0.23, 97.98] |
| Gupta 2014 | 5 | 50 | 6 | 50 | 67.5% | 0.83 [0.27, 2.55] |
| Ruangvutilert 2017 | 2 | 36 | 2 | 38 | 23.3% | 1.06 [0.16, 7.10] |
| **Total (95% CI)** | | **207** | | **203** | **100.0%** | **1.03 [0.41, 2.60]** |
| Total events | 9 | | 8 | | | |

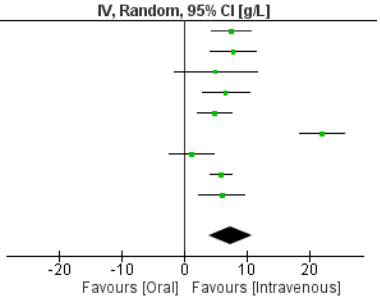
Heterogeneity: Tau² = 0.00; Chi² = 1.15, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)




**G. Maternal haemoglobin at delivery**

| Study or Subgroup | Intravenous Mean [g/L] | SD [g/L] | Total | Oral Mean [g/L] | SD [g/L] | Total | Weight | Mean Difference IV, Random, 95% CI [g/L] |
|---|---|---|---|---|---|---|---|---|
| Abhilashini 2014 | 108.4 | 9 | 50 | 100.9 | 7 | 50 | 11.5% | 7.50 [4.34, 10.66] |
| Al 2005 | 120.3 | 8 | 45 | 112.5 | 9.6 | 45 | 11.1% | 7.80 [4.15, 11.45] |
| Bayoumeu 2002 | 120 | 11 | 24 | 115 | 12 | 23 | 8.7% | 5.00 [-1.59, 11.59] |
| Gupta 2014 | 115 | 7.8 | 50 | 108.4 | 11.2 | 50 | 11.0% | 6.60 [2.82, 10.38] |
| Khalafallah 2010 | 126.6 | 9.7 | 92 | 121.8 | 8.7 | 91 | 11.8% | 4.80 [2.13, 7.47] |
| Kochhar 2013 | 134 | 9 | 50 | 112 | 9 | 50 | 11.2% | 22.00 [18.47, 25.53] |
| Neeru 2012 | 117.6 | 8 | 45 | 116.5 | 9.1 | 44 | 11.2% | 1.10 [-2.46, 4.66] |
| Rudra 2016 | 114.8 | 6.1 | 100 | 109 | 6.2 | 100 | 12.3% | 5.80 [4.10, 7.50] |
| Singh 1998 | 118 | 9.4 | 50 | 112 | 9.4 | 50 | 11.1% | 6.00 [2.32, 9.68] |
| **Total (95% CI)** | | | **506** | | | **503** | **100.0%** | **7.43 [3.94, 10.92]** |

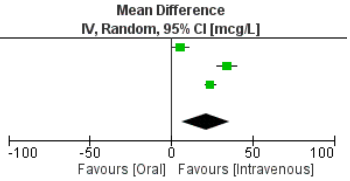
Heterogeneity: Tau² = 25.03; Chi² = 85.45, df = 8 (P < 0.00001); I² = 91%
Test for overall effect: Z = 4.17 (P < 0.0001)




**H. Maternal ferritin at delivery**

| Study or Subgroup | Intravenous Mean [mcg/L] | SD [mcg/L] | Total | Oral Mean [mcg/L] | SD [mcg/L] | Total | Weight | Mean Difference IV, Random, 95% CI [mcg/L] |
|---|---|---|---|---|---|---|---|---|
| Al 2005 | 23.7 | 13.8 | 45 | 18.1 | 11 | 45 | 33.2% | 5.60 [0.44, 10.76] |
| Kochhar 2013 | 128.8 | 15.8 | 50 | 94.6 | 14.2 | 50 | 32.8% | 34.20 [28.31, 40.09] |
| Rudra 2016 | 70.92 | 13.79 | 100 | 46.89 | 11.86 | 100 | 34.0% | 24.03 [20.47, 27.59] |
| **Total (95% CI)** | | | **195** | | | **195** | **100.0%** | **21.24 [6.54, 35.95]** |

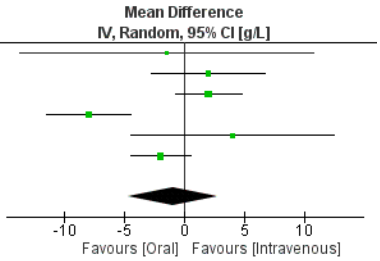
Heterogeneity: Tau² = 162.48; Chi² = 56.31, df = 2 (P < 0.00001); I² = 96%
Test for overall effect: Z = 2.83 (P = 0.005)




**I. Neonatal haemoglobin at delivery**

| Study or Subgroup | Intravenous Mean [g/L] | SD [g/L] | Total | Oral Mean [g/L] | SD [g/L] | Total | Weight | Mean Difference IV, Random, 95% CI [g/L] |
|---|---|---|---|---|---|---|---|---|
| Bayoumeu 2002 | 151.5 | 21 | 24 | 153 | 21.7 | 23 | 6.8% | -1.50 [-13.72, 10.72] |
| Breymann 2017 | 148 | 19 | 112 | 146 | 17 | 109 | 17.7% | 2.00 [-2.75, 6.75] |
| Gupta 2014 | 158 | 7 | 50 | 156 | 7 | 50 | 21.9% | 2.00 [-0.74, 4.74] |
| Khalafallah 2010 | 157 | 14.1 | 92 | 165 | 9.6 | 91 | 20.4% | -8.00 [-11.49, -4.51] |
| Kochhar 2013 | 163 | 21 | 49 | 159 | 22 | 49 | 10.9% | 4.00 [-4.52, 12.52] |
| Rudra 2016 | 156 | 9 | 100 | 158 | 9 | 100 | 22.3% | -2.00 [-4.49, 0.49] |
| **Total (95% CI)** | | | **427** | | | **422** | **100.0%** | **-0.95 [-4.71, 2.81]** |

Heterogeneity: Tau² = 14.86; Chi² = 23.35, df = 5 (P = 0.0003); I² = 79%
Test for overall effect: Z = 0.50 (P = 0.62)




**J. Neonatal ferritin at delivery**

| Study or Subgroup | Intravenous Mean [mcg/L] | SD [mcg/L] | Total | Oral Mean [mcg/L] | SD [mcg/L] | Total | Weight | Mean Difference IV, Random, 95% CI [mcg/L] |
|---|---|---|---|---|---|---|---|---|
| Bayoumeu 2002 | 132 | 104 | 24 | 134 | 107 | 23 | 4.2% | -2.00 [-62.36, 58.36] |
| Breymann 2017 | 256 | 187 | 112 | 237 | 136 | 109 | 7.6% | 19.00 [-24.03, 62.03] |
| Gupta 2014 | 156 | 46 | 50 | 148 | 39 | 50 | 27.4% | 8.00 [-8.72, 24.72] |
| Khalafallah 2010 | 185 | 101 | 92 | 142 | 86 | 91 | 15.6% | 43.00 [15.83, 70.17] |
| Kochhar 2013 | 141 | 101 | 49 | 138 | 98 | 49 | 8.8% | 3.00 [-36.40, 42.40] |
| Rudra 2016 | 158 | 40 | 100 | 156 | 42 | 100 | 36.4% | 2.00 [-9.37, 13.37] |
| **Total (95% CI)** | | | **427** | | | **422** | **100.0%** | **11.24 [-1.63, 24.11]** |

Heterogeneity: Tau² = 84.69; Chi² = 7.86, df = 5 (P = 0.16); I² = 36%
Test for overall effect: Z = 1.71 (P = 0.09)

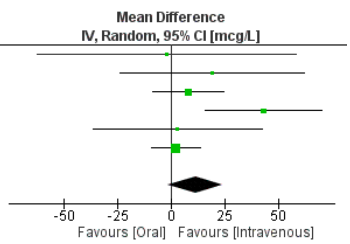


**Table 2. Pooled analyses of the effects of intravenous iron compared to oral iron for the treatment of iron deficiency anaemia in pregnancy on perinatal outcomes in single studies**

| Perinatal outcomes | Number of participants | Effect | | Quality of evidence (GRADE)* |
|---|---|---|---|---|
| | | Relative (95% CI) | Absolute (95% CI) | |
| Blood loss at delivery | 120[10] | — | MD, –9.0 mL (–96.3 to +78.3 mL) | C: low†,‡ |
| Postpartum haemorrhage | 100[11] | Peto OR, 0.14 (0.00–6.82) | –17 fewer per 1000 (–20 to +116 per 1000) | D: very low§,¶ |
| Birth length | 221[14] | — | MD, +0.10 cm (–0.64 to +0.84 cm) | C: low‡,¶ |
| Birth weight-to-length ratio (g/cm) | 221[14] | — | MD, 0 (all 0) | C: low‡,¶ |
| Stillbirth | 196[4] | Peto OR, 0.14 (0.00–6.82) | 9 fewer per 1000 (–10 to +58 per 1000) | D: very low§,** |
| Breastfeeding cessation by 24 months | 126[5] | HR, 0.70 (0.50–0.99) | 40 fewer per 1000 (–112 to –1 per 1000) | D: very low†,††,‡‡ |

CI = confidence interval; HR = hazard ratio; MD = mean difference; OR = odds ratio.

* For detailed summary of GRADE assessments and justification for each outcome, table 4.

† Downgraded one level: risk of attrition bias (high loss to follow-up [> 10%]).

‡ Downgraded one level: imprecision (small sample size, large CI including benefit and harms).

§ Downgraded two levels: imprecision (rare outcome, and large CI including significant risk of harm or benefit).

¶ Downgraded one level: risk of bias (potential selection or observer bias).

** Downgraded one level: indirectness (intervention included administration of both intravenous and oral iron, inconsistent with clinical practice recommendations. Most patients also had mild anaemia with a high mean haemoglobin level).

†† Downgraded one level: imprecision (small sample size, large CI).

‡‡ Downgraded one level: other source of bias (risk estimate was adjusted for potential intermediate factors in causal pathway).

**Table 3. Risk of bias evaluations for the fifteen included studies (sixteen publications) that compared the effectiveness of intravenous and oral iron for treating women with iron deficiency anaemia during pregnancy***

| Study | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|---|---|---|---|---|---|---|---|
| Singh 1998[1] | Unclear<br>Randomisation process not described | Unclear<br>Allocation concealment not described | High<br>Open label study | Unclear<br>No reporting of blinding of outcome assessment | Low<br>Follow-up complete | Low<br>Data provided on expected outcomes | Low<br>Intention to treat analysis |
| Bayoumeu 2002[2] | Low<br>Use of randomisation table | Unclear<br>Allocation concealment not described | High<br>Open label study | Unclear<br>No reporting of blinding of outcome assessment | Unclear<br>Delivery data available for 45 of 50 women<br>Data on one macrosomic infant in oral arm excluded from analysis | Low<br>Data provided on expected outcomes | High<br>Oral iron only administered for 4 weeks |
| Al 2005[3] | Low<br>Computer-generated randomisation table | Low<br>Consecutively numbered opaque envelopes | High<br>Open label study | Unclear<br>No reporting of blinding of outcome assessment | Low<br>Follow-up complete | Low<br>Data provided on expected outcomes | Low<br>Intention to treat analysis |
| Khalafallah 2010[4] | Low<br>Randomised in block size of 10 | Low<br>Assignment undertaken by pharmacy department | High<br>Open label study | Unclear<br>No reporting of blinding of outcome assessment | Low<br>Outcome data available for 183 or 200 women | Low<br>Data provided on expected outcomes | Low<br>Intention to treat analysis |
| Khalafallah 2012[5] | Low<br>Randomised in block size of 10 | Low<br>Assignment undertaken by pharmacy department | High<br>Open label study | Unclear<br>No reporting of blinding of outcome assessment | High<br>Outcome data only available for 126 of 196 women | Low<br>Data provided on expected outcomes | Low<br>Intention to treat analysis |
| Aggarwal 2012[6] | Unclear<br>Randomisation not described | Unclear<br>Allocation concealment not described | High<br>Open label study | Unclear<br>No reporting of blinding of outcome assessment | Low<br>Follow-up complete | Low<br>Data provided on expected outcomes | High<br>Oral iron only administered for 4 weeks |
| Neeru 2012[7] | Low<br>Block randomisation technique | Unclear<br>Allocation concealment not described | High<br>Open label study | Unclear<br>No reporting of blinding of outcome assessment | High<br>Outcome data only available for 89 of 100 women | Unclear<br>Blood transfusions only reported for IV treatment arm | High<br>Five women crossed over from oral to IV iron; five women in IV arm received blood transfusions |
| Dubey 2013[8] | Low<br>Computer-generated randomisation table | Low<br>Consecutively numbered opaque envelopes | High<br>Open label study | Unclear<br>No reporting of blinding of outcome assessment | Low<br>Outcome data available for 198 of 200 women | Low<br>Data provided on expected outcomes | Low<br>Intention to treat analysis |

| Study | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|---|---|---|---|---|---|---|---|
| Kochhar 2013[9] | Low<br>Use of randomisation table | Unclear<br>Allocation concealment not described | High<br>Open label study | Unclear<br>No reporting of blinding of outcome assessment | Unclear<br>Outcome data available for 98 of 100 women<br>Post-randomisation exclusion in IV arm | Low<br>Data provided on expected outcomes | High<br>Oral iron only administered for 4 weeks |
| Froessler 2013[10] | Low<br>Telephone randomisation service | Low<br>Use of telephone randomisation service | High<br>Open label study | Unclear<br>Blinding of outcome assessment not reported<br>Data analysed by statistician blinded to treatment allocation | High<br>Greater than 10% lost to follow-up | Low<br>Data provided on expected outcomes | High<br>Analysis not intention to treat |
| Gupta 2014[11] | Low<br>Computer-geerated randomisation table | Low<br>Consecutively numbered opaque envelopes | High<br>Open label study | Unclear<br>No reporting of blinding of outcome assessment | Low<br>Follow-up complete | Low<br>Data provided on expected outcomes | High<br>Oral iron only administered for 4 weeks |
| Abhilashini 2014[12] | Low<br>Computer-generated randomization table | Unclear<br>Allocation concealment not described | High<br>Open label study | Unclear<br>No reporting of blinding of outcome assessment | Low<br>Follow-up complete | Low<br>Data provided on expected outcomes | Low<br>Intention to treat analysis |
| Rudra 2016[13] | Low<br>Computer generated randomization | Unclear<br>Allocation concealment not described | High<br>Open label study | Unclear<br>No reporting of blinding of outcome assessment | Low<br>Follow-up complete | Low<br>Data provided on expected outcomes | Low<br>Intention to treat analysis |
| Breymann 2017[14] | Unclear<br>Randomised but process not described | Unclear<br>Allocation concealment not described | High<br>Open label study | Unclear<br>No reporting of blinding of outcome assessment | High<br>Outcome data available for 221 of 252 women | Low<br>Data provided on expected outcomes | Low<br>Intention to treat analysis |
| Ruangvutilert 2017[15] | Low<br>Computer generated randomization | Low<br>Consecutively numbered opaque envelopes | High<br>Open label study | Unclear<br>No reporting of blinding of outcome assessment | High<br>Outcome data only available for 50 of 80 women | Low<br>Data provided on expected outcomes | High<br>Analysis not intention to treat<br>Those who took < 80% of oral tablets excluded from trial |
| Sarmishta 2017[16] | Unclear<br>Randomisation process not described | Unclear<br>Allocation concealment not described | High<br>Open label study | Unclear<br>No reporting of blinding of outcome assessment | Low<br>Follow-up complete | Low<br>Data provided on expected outcomes | High<br>Oral iron only administered for 4 weeks |

* Assessed using the Cochrane Collaboration tool for assessing risk of bias. IV = intravenous.

**Table 4. GRADE evidence summary and detailed commentary for each outcome (intravenous *v* oral iron for treating iron deficiency anaemia during pregnancy)**

| Outcomes | Quality of the evidence (GRADE) | Comment |
|---|---|---|
| **Perinatal outcomes** | | |
| Maternal blood transfusion | C: low | Downgraded one level for risk of bias: no studies applied treatment blinding or pre-defined blood transfusion thresholds.<br>Downgraded one level for imprecision: transfusion was a rare outcome; and large confidence interval for risk estimate. Further, sensitivity analyses for pooled effect estimate identified significant variability (Supporting Information, table 5). |
| Birthweight (g) | C: low | Downgraded one level for risk of bias: four of eight studies at unclear risk of allocation bias; four of eight studies at high risk of bias; three studies at risk of comparator bias as oral iron (control arm) only administered for 4 weeks; one study at risk of attrition bias (38% lost to follow-up). Sensitivity analyses found differences in treatment effect according to risk of bias.<br>Downgraded one level for imprecision: large confidence interval including clinically non-significant treatment effect. |
| Gestation at birth (weeks) | C: low | Downgraded one level for risk of bias: three of seven studies at unclear risk of allocation bias; four of eight studies at high risk of bias; three studies at risk of comparator bias as oral iron (control arm) only administered for 4 weeks; one study at risk of attrition bias (38% lost to follow-up). Sensitivity analyses found differences in treatment effect according to risk of bias.<br>Downgraded one level for imprecision: large confidence interval including clinically non-significant treatment effect. |
| Caesarean delivery | C: low | Downgraded two levels for imprecision: large confidence interval that includes significant risk of harm or benefit. |
| Hypertensive disorders of pregnancy | D: very low | Downgraded one level for risk of bias: two studies at unclear risk of observer bias.<br>Downgraded two levels for imprecision: large confidence interval that includes significant risk of harm or benefit. |
| Pre-term birth | D: very low | Downgraded one level for risk of bias: one of three studies at unclear risk of attrition bias; all three studies at high risk of bias; one study at risk of comparator bias as oral iron (control arm) only administered for 4 weeks; two studies at risk of attrition bias (losses to follow-up of 12% and 38%).<br>Downgraded two levels for imprecision: large confidence interval that includes significant risk of harm or benefit. |
| Blood loss at delivery (mL) | C: low | Downgraded one level for risk of attrition bias (high loss to follow-up [> 10%]).<br>Downgraded one level for imprecision: small sample size and large confidence interval including benefit and harms. |
| Post partum haemorrhage | D: very low | Downgraded two levels for imprecision: rare outcome; large confidence interval including significant risk of harm or benefit.<br>Downgraded one level for risk of bias: potential for selection bias or observer bias. |
| Birth length (cm) | C: low | Downgraded one level for imprecision: small sample size; large confidence interval including benefit and harms.<br>Downgraded one level for risk of bias: potential for selection bias or observer bias. |
| Birth weight-to-length ratio (g/cm) | C: low | Downgraded one level for imprecision: small sample size; large confidence interval including benefit and harms.<br>Downgraded one level for risk of bias: potential for selection bias or observer bias. |
| Stillbirth | D: very low | Downgraded two levels for imprecision: rare outcome; large confidence interval including significant risk of harm or benefit.<br>Downgraded one level for indirectness: intervention included administration of both intravenous and oral iron, inconsistent with clinical practice recommendations. Most patients also had mild anaemia (high mean haemoglobin level). |
| Breastfeeding ceased by 24 months | D: very low | Downgraded one level for risk of attrition bias: high loss to follow-up (> 30%).<br>Downgraded one level for imprecision: small sample size and large confidence interval.<br>Downgraded one for other source of bias: risk estimate was adjusted for potential intermediate factors in the causal pathway, including maternal mental health status post partum and mode of delivery. |

| Outcomes | Quality of the evidence (GRADE) | Comment |
|---|---|---|
| **Haematological parameters at delivery** | | |
| Maternal | | |
| Haemoglobin (g/L) | C: low | Downgraded one level for risk of bias: six of eight studies at unclear risk of allocation bias; four of eight studies at high risk of bias; three studies at risk of comparator bias as oral iron (control arm) only administered for 4 weeks; one study at risk of intervention bias (five women in intravenous iron arm received blood transfusions antenatally).<br>Downgraded one level for inconsistency: high heterogeneity ($I^2$ = 91%). |
| Ferritin (μg/L) | C: low | Downgraded one level for risk of bias: two of three studies at unclear risk of allocation bias; one study at high risk of comparator bias as oral iron (control arm) only administered for 4 weeks. Subgroup analysis found evidence of differences in estimates based on risk of bias.<br>Downgraded one level for inconsistency: high heterogeneity ($I^2$ = 96%). |
| Neonatal | | |
| Haemoglobin (g/L) | C: low | Downgraded one level for risk of bias: four of six studies at unclear risk of allocation bias; three studies at high risk of comparator bias as oral iron (control arm) only administered for 4 weeks.<br>Downgraded one level for inconsistency: high heterogeneity ($I^2$ = 79%) |
| Ferritin (μg/L) | C: low | Downgraded one level for risk of bias: four of six studies at unclear risk of allocation bias; three studies at high risk of comparator bias as oral iron (control arm) only administered for 4 weeks.<br>Downgraded one level for imprecision: large confidence interval including clinically non-significant treatment effect. |

IV = intravenous.

GRADE Working Group grades of evidence:

**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate quality:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low quality:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

**Very low quality:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

**Table 5. Sensitivity analyses for pooled effect estimate for primary outcome of blood transfusion**

| Method | Continuity correction | Studies with zero events in both arms | Pooled effect estimate (95% confidence interval) |
|---|---|---|---|
| Peto odds ratio | None | Excluded | OR, 0.19 (0.05–0.78) |
| Mantel–Haenszel | None | Excluded | RR, 0.11 (0.01–0.98) |
| Mantel–Haenszel | 0.05 | Excluded | RR, 0.13 (0.02–0.99) |
| Mantel–Haenszel | 0.05 | Included | RR, 0.16 (0.02–0.99) |
| Mantel–Haenszel | 0.5 | Excluded | RR, 0.30 (0.08–1.11) |
| Mantel–Haenszel | 0.5 | Included | RR, 0.42 (0.14–1.22) |
| Logistic regression | None | Excluded | RR, 0.12 (0.01–1.00) |
| Generalised linear mixed model | None | Excluded | RR, 0.13 (0.02–1.02) |
| Arcsine difference | None | Included | –0.068 (–0.127 to –0.009) |

OR = odds ratio; RR = risk ratio.

**Table 6. Stratified effect estimates, intravenous *v* oral iron for treating iron deficiency anaemia during pregnancy, by subgroup**

| Outcome | RCTs | Participants | Effect measure | Effect estimate | $I^2$ |
|---|---|---|---|---|---|
| **Maternal blood transfusion** | | | | | |
| Overall | 9 | 1090 | Peto OR | 0.19 (0.05–0.78) | 0 |
| Baseline Hb | | | | | |
| < 90 g/L | 5 | 650 | Peto OR | 0.14 (0.00–6.82) | 0 |
| ≥ 90g/L | 4 | 440 | Peto OR | 0.20 (0.05–0.90) | 0 |
| Mean gestation at treatment | | | | | |
| ≤ 28 weeks | 3 | 330 | Peto OR | 0.13 (0.02–0.94) | 0 |
| > 28 weeks | 6 | 760 | Peto OR | 0.28 (0.04–2.07) | 0 |
| Study setting | | | | | |
| Low or middle income | 6 | 740 | Peto OR | 0.14 (0.01–2.16) | 0 |
| High income | 3 | 350 | Peto OR | 0.22 (0.04–1.10) | 0 |
| Risk of bias | | | | | |
| High | 6 | 617 | Peto OR | 0.24 (0.04–1.42) | 0 |
| Low | 3 | 473 | Peto OR | 0.13 (0.01–1.29) | 0 |
| Iron formulation | | | | | |
| Carboxymaltose/polymaltose | 1 | 183 | Peto OR | 0.13 (0.01–2.13) | NA |
| Sucrose | 8 | 907 | Peto OR | 0.22 (0.04–1.10) | 0 |
| **Birthweight (g)** | | | | | |
| Overall | 8 | 989 | WMD | 58 (4 to 112) | 0 |
| Baseline Hb | | | | | |
| < 90 g/L | 3 | 398 | WMD | 74 (4 to 144) | 0 |
| ≥ 90g/L | 5 | 591 | WMD | 35 (–51 to 120) | 0 |
| Mean gestation at treatment | | | | | |
| ≤ 28 weeks | 4 | 528 | WMD | 108 (20 to 195) | 0 |
| > 28 weeks | 3 | 240 | WMD | 38 (–42 to 119) | 0 |
| Study setting | | | | | |
| Low or middle income | 5 | 538 | WMD | 67 (4 to 130) | 0 |
| High income | 3 | 451 | WMD | 56 (–97 to 208) | 37 |
| Risk of bias | | | | | |
| High | 4 | 295 | WMD | 78 (–29 to 184) | 19 |
| Low | 4 | 694 | WMD | 54 (–18 to 126) | 0 |
| Iron formulation | | | | | |
| Carboxymaltose/polymaltose | 2 | 404 | WMD | 6 (–104 to 116) | 0 |
| Sucrose | 6 | 585 | WMD | 75 (13 to 137) | 0 |
| **Gestational age (weeks)** | | | | | |
| Overall | 7 | 768 | WMD | 0.2 (–0.1 to 0.5) | 22 |
| Baseline Hb | | | | | |
| < 90 g/L | 3 | 398 | WMD | 0.4 (–0.2 to 0.9) | 69 |
| ≥ 90g/L | 4 | 370 | WMD | 0.1 (–0.3 to 0.5) | 0 |
| Mean gestation at treatment | | | | | |
| ≤ 28 weeks | 4 | 528 | WMD | 0.3 (–0.3 to 0.8) | 59 |
| > 28 weeks | 3 | 240 | WMD | 0.2 (–0.2 to 0.5) | |

| Outcome | RCTs | Participants | Effect measure | Effect estimate | $I^2$ |
|---|---|---|---|---|---|
| Study setting | | | | | |
| Low or middle income | 5 | 538 | WMD | 0.3 (–0.1 to 0.6) | 42 |
| High income | 2 | 230 | WMD | –0.1 (–0.8 to 0.6) | 0 |
| Risk of bias | | | | | |
| High | 4 | 295 | WMD | 0.4 (–0.1 to 0.8) | 42 |
| Low | 3 | 473 | WMD | 0.0 (–0.3 to 0.4) | 0 |
| Iron formulation | | | | | |
| Carboxymaltose/polymaltose | 1 | 183 | WMD | –0.2 (–1.4 to 1.0) | NA |
| Sucrose | 6 | 585 | WMD | 0.2 (–0.1 to 0.5) | 30 |
| **Neonatal haemoglobin (g/L)** | | | | | |
| Overall | 6 | 849 | WMD | –1.0 (–4.7 to 2.8) | 79 |
| Baseline Hb | | | | | |
| < 90 g/L | 3 | 398 | WMD | 0.5 (–3.0 to 3.9) | 63 |
| ≥ 90g/L | 3 | 451 | WMD | –2.8 (–10.6 to 5.0) | 82 |
| Mean gestation at treatment | | | | | |
| ≤ 28 weeks | 4 | 528 | WMD | –2.9 (–7.7 to 1.9) | 72 |
| > 28 weeks | 1 | 100 | WMD | 2.0 (–0.7 to 4.7) | NA |
| Study setting | | | | | |
| Low or middle income | 3 | 398 | WMD | 0.5 (–3.0 to 3.9) | 63 |
| High income | 3 | 451 | WMD | –2.8 (–10.6 to 5.0) | 82 |
| Risk of bias | | | | | |
| High | 3 | 245 | WMD | 2.0 (–0.5 to 4.6) | 0 |
| Low | 3 | 604 | WMD | –2.8 (–7.9 to 2.3) | 84 |
| Iron formulation | | | | | |
| Carboxymaltose/polymaltose | 2 | 404 | WMD | –3.1 (–12.9 to –6.7) | 91 |
| Sucrose | 4 | 445 | WMD | 0.3 (–2.7 to 3.2) | 45 |
| **Neonatal ferritin (µg/L)** | | | | | |
| Overall | 6 | 849 | WMD | 11.2 (–1.6 to 24.1) | 36 |
| Baseline Hb | | | | | |
| < 90 g/L | 3 | 398 | WMD | 3.9 (–5.3 to 13.0) | 0 |
| ≥ 90g/L | 3 | 451 | WMD | 30.3 (7.1–53.5) | 9 |
| Mean gestation at treatment | | | | | |
| ≤ 28 weeks | 4 | 528 | WMD | 13.3 (–10.1 to 36.7) | 61 |
| > 28 weeks | 1 | 100 | WMD | 8.0 (–8.7 to 24.7) | NA |
| Study setting | | | | | |
| Low or middle income | 3 | 398 | WMD | 3.9 (–5.3 to 13.0) | 0 |
| High income | 3 | 451 | WMD | 30.3 (7.1–53.5) | 9 |
| Risk of bias | | | | | |
| High | 3 | 245 | WMD | 6.7 (–8.8 to 21.6) | 0 |
| Low | 3 | 604 | WMD | 19.5 (–9.4 to 48.4) | 74 |
| Iron formulation | | | | | |
| Carboxymaltose/polymaltose | 2 | 404 | WMD | 36.2 (13.2 to 59.1) | 0 |
| Sucrose | 4 | 445 | WMD | 3.7 (–5.3 to 12.8) | 0 |

| Outcome | RCTs | Participants | Effect measure | Effect estimate | $I^2$ |
|---|---|---|---|---|---|
| **Maternal haemoglobin (g/dL)** | | | | | |
| Overall | 9 | 1009 | WMD | 7.4 (3.9 to 10.9) | 91 |
| Baseline Hb | | | | | |
| < 90 g/L | 5 | 600 | WMD | 9.5 (4.0 to 15.1) | 94 |
| ≥ 90g/L | 4 | 409 | WMD | 4.6 (1.8 to 7.5) | 55 |
| Mean gestation at treatment | | | | | |
| ≤ 28 weeks | 6 | 719 | WMD | 7.5 (2.2 to 12.8) | 94 |
| > 28 weeks | 3 | 290 | WMD | 7.3 (5.3 to 9.4) | 0 |
| Study setting | | | | | |
| Low or middle income | 6 | 679 | WMD | 8.4 (3.4 to 13.4) | 94 |
| High income | 3 | 330 | WMD | 5.2 (3.1 to 7.3) | 0 |
| Risk of bias | | | | | |
| High | 4 | 336 | WMD | 8.8 (–1.4 to 18.9) | 96 |
| Low | 5 | 673 | WMD | 6.1 (4.9 to 7.2) | 0 |
| Iron formulation | | | | | |
| Carboxymaltose/polymaltose | 2 | 283 | WMD | 5.2 (3.1 to 7.4) | 0 |
| Sucrose | 7 | 726 | WMD | 8.0 (3.5 to 12.6) | 93 |
| **Maternal ferritin (µg/L)** | | | | | |
| Overall | 3 | 390 | WMD | 21.2 (6.54 to 36.0) | 96 |
| Baseline Hb | | | | | |
| < 90 g/L | 2 | 300 | WMD | 28.8 (18.9 to 38.8) | 88 |
| ≥ 90g/L | 1 | 90 | WMD | 5.6 (0.44 to 10.8) | NA |
| Mean gestation at treatment | | | | | |
| ≤ 28 weeks | 2 | 300 | WMD | 28.8 (18.9 to 38.8) | 88 |
| > 28 weeks | 1 | 90 | WMD | 5.6 (0.4 to 10.8) | NA |
| Study setting | | | | | |
| Low or middle income | 3 | 390 | WMD | 21.2 (6.5 to 36.0) | 96 |
| High income | 0 | 0 | WMD | NA | NA |
| Risk of bias | | | | | |
| High | 1 | 100 | WMD | 34.2 (28.3 to 40.1) | NA |
| Low | 2 | 290 | WMD | 14.9 (–3.2 to 33.0) | 97 |
| Iron formulation | | | | | |
| Carboxymaltose/polymaltose | 0 | 0 | NA | NA | NA |
| Sucrose | 3 | 390 | WMD | 21.2 (6.5 to 36.0) | 96 |
| **Pre-term birth** | | | | | |
| Overall | 3 | 410 | RR | 1.03 (0.41–2.60) | 0 |
| Baseline Hb | | | | | |
| < 90 g/L | 1 | 100 | RR | 0.83 (0.27–2.55) | NA |
| ≥ 90g/L | 2 | 310 | RR | 1.62 (0.32–8.12) | 0 |
| Mean gestation at treatment | | | | | |
| ≤ 28 weeks | 0 | 0 | RR | NA | NA |
| > 28 weeks | 2 | 174 | RR | 0.89 (0.34–2.33) | 0 |

| Outcome | RCTs | Participants | Effect measure | Effect estimate | $I^2$ |
|---|---|---|---|---|---|
| Study setting | | | | | |
| Low or middle income | 2 | 174 | RR | 0.89 (0.34–2.33) | 0 |
| High income | 1 | 236 | RR | 4.75 (0.23–98.0) | NA |
| Risk of bias | | | | | |
| High | 3 | 410 | RR | 1.03 (0.41–2.60) | 0 |
| Low | 0 | 0 | RR | NA | NA |
| Iron formulation | | | | | |
| Carboxymaltose/polymaltose | 1 | 236 | | 4.75 (0.23–97.98) | NA |
| Sucrose | 2 | 174 | | 0.89 (0.34–2.33) | 0 |
| **Caesarean delivery** | | | | | |
| Overall | 3 | 373 | RR | 0.96 (0.62–1.51) | 0 |
| Baseline Hb | | | | | |
| < 90 g/L | 1 | 100 | RR | 0.75 (0.18–3.18) | NA |
| ≥ 90g/L | 2 | 273 | RR | 0.99 (0.62–1.58) | 0 |
| Mean gestation at treatment | | | | | |
| ≤ 28 weeks | 1 | 183 | RR | 1.17 (0.65–2.14) | NA |
| > 28 weeks | 2 | 190 | RR | 0.75 (0.38–1.47) | 0 |
| Study setting | | | | | |
| Low or middle income | 2 | 190 | RR | 0.75 (0.38–1.47) | 0 |
| High income | 1 | 183 | RR | 1.17 (0.65–2.14) | NA |
| Risk of bias | | | | | |
| High | 0 | 0 | RR | NA | NA |
| Low | 3 | 373 | RR | 0.96 (0.62–1.51) | 0 |
| Iron formulation | | | | | |
| Carboxymaltose/polymaltose | 1 | 184 | RR | 1.17 (0.65–2.14) | NA |
| Sucrose | 2 | 190 | RR | 0.75 (0.38–1.47) | 0 |

Hb = haemoglobin; NA = not applicable; OR = odds ratio; RR = relative risk; WMD = weighted mean difference.

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