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Intravenous Iron Therapy is Associated with Improved Maternal Quality of Life, Less Postnatal Depression and Longer Breastfeeding after Treatment of Iron Deficiency Anaemia in Pregnancy: A Prospective Randomised Controlled Study

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ARTICLE SUMMARY

Article focus

- **Health related quality of life assessment during and after pregnancy in 126 women with iron deficiency, who received either a single dose intravenous iron polymaltose followed by oral iron maintenance or an oral iron only.**
- **Study of postnatal depression and its association with the treatment arms and iron status**
- **Assessment of breastfeeding duration and correlation to mothers' iron status**

Key-Messages

- **Health related quality of life is improved significantly in anaemic pregnant women by repletion of their iron stores during pregnancy.**
- **About 80% of the intravenous iron group showed a maintained normal ferritin until delivery with long-term benefits such as prolongation of the breast-feeding period and less postnatal clinical depression.**
- **There were strong associations between iron status and a number of the HRQoL scales with improved general health (P=0.021), improved physical energy (P=0.016), less psychological downheartedness (P=0.005), less clinical depression (P=0.003), and overall improved mental component scale (P<0.001). The duration of breastfeeding was longer (P=0.046) in women who received intravenous iron.**

Strengths and limitations

- **This study addresses a novel finding of postnatal depression and breast- feeding period in correlation with iron status.**
- **There is very limited data regarding quality of life measurement during and after pregnancy that makes the scientific input of the current study important, albeit a relatively small number of pregnant women studied.**

ABSTRACT

Background: To date there are no data available regarding the impact of intravenous versus oral iron on the wellbeing and health-related quality of life (HRQoL) in particular postnatal depression and duration of breast- feeding during and after pregnancy.

Objective: To assess long-term effect of iron therapy on HRQoL during pregnancy and post-natal period.

Design: We conducted a randomised controlled open label trial of intravenous versus oral iron therapy for pregnancy-related iron deficiency anaemia between March 2007 and January 2009 at the Launceston General Hospital, Tasmania, Australia.

Participants and Interventions: Of the 196 pregnant Caucasian women randomised to receive oral iron or a single intravenous iron polymaltose infusion followed by oral iron maintenance, 126 women completed the HRQoL study.

Methods: The participants were followed up post-delivery for a median period of 32 months (range, 26-42) with a well-being and health-related QoL questionnaire using a modified short form 36 QoL survey and child growth charts as set by the Australasian Paediatric Endocrine Group (APEG).

Results: Patients who received intravenous iron demonstrated significantly higher Hb and serum ferritin levels ($p<0.001$). There were strong associations between iron status and a number of the HRQoL scales with improved general health ($P=0.021$), improved physical energy ($P=0.016$), less psychological downheartedness ($P=0.005$), less clinical depression ($P=0.003$), and overall improved mental component scale ($P<0.001$). The duration of breastfeeding was longer ($P=0.046$) in women who received intravenous iron. The babies born in both groups recorded similarly on APEG growth chart assessments.

Conclusion: Our data suggest that HRQoL is improved in anaemic pregnant women by repletion of their iron stores during pregnancy. About 80% of the intravenous iron polymaltose group showed a maintained normal ferritin until delivery with long-term benefits and a minimal effect on their babies. Further studies to confirm these findings are warranted.

Trial registration: Australia and New Zealand Clinical Trial Registry under: http://www.ANZCTR.org.au under ACTRN 12609000177257 and in the World Health Organization website under: www.who.int/**trial**search/**trial**.aspx?**trial**id=ACTRN12609000596202.

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Key words: Quality of life assessment, iron deficiency anaemia, oral iron, intravenous iron, pregnancy, long-term effect.

INTRODUCTION

There are no available data regarding quality of life assessment and long term effects of intravenous versus oral iron therapy during pregnancy. In addition to the physical impact of iron deficiency anaemia (IDA) on pregnant women,[1-3] IDA is a potential risk factor for preterm delivery and subsequent low birth weight and may be associated with inferior neonatal health.[3-4] Infants born to women with IDA are more likely to become anaemic themselves, which in turn is known to have a potential effect on an infant's mental and motor development.[5-9] Although iron supplementation during pregnancy is a widely practiced public health measure, there are some concerns regarding iron replacement therapy and its long-term effect, especially the intravenous form.[10,11] However, pregnant women do not always respond adequately to oral iron therapy due to difficulties associated with ingestion of the tablets and their side effects, impacting negatively on their compliance.[3,10,11] Side effects include gastrointestinal disturbances characterized by colicky pain, nausea, vomiting, diarrhoea and/or constipation, and occur in up to 28% of patients taking oral iron preparations.[10,11] Furthermore, the presence of chronic bowel disease can affect the absorption of iron, minimising the benefit received from oral iron therapy.[11]

In the past, intravenous iron had been associated with undesirable and sometimes serious side-effects limiting its use.[12] Recently, new type II iron complexes have been developed with the potential to reverse iron deficiency with less side effects than their predecessors.[12-14] Despite increasing evidence for the safety of the newer preparations in both pregnant and general populations, intravenous iron continues to be underutilised.[15]

An initial randomized controlled trial showed that intravenous iron polymaltose leads to improved efficacy and iron stores compared to oral iron alone in pregnancy-related IDA (p=0.001) without major side effects.[14] The objectives of the current follow-up study were to assess wellbeing and quality of life in these women during and after both treatments, as measured by a modified SF36

questionnaire, the effect of iron therapy on breastfeeding rates and on the general wellbeing of the babies born to these women as measured by child growth charts set by the Australasian Paediatric Endocrine Group (APEG).

PATIENTS AND METHODS

The initial prospective randomised-controlled trial was conducted between March 2007 and January 2009 at the Launceston General Hospital (LGH), a tertiary referral centre for Northern Tasmania, Australia. This follow-up study took place between January 2010 and January 2011. An informed consent form was obtained from all participants according to the Code of Ethics. The trial was approved by the Tasmanian Human Research Ethics Committee and registered in the Australia New Zealand Clinical Trials Registry under trial No**:** ACTRN12609000177257 with web addresses of the trial as follow: http://www.ANZCTR.org.au/ACTRN12609000177257.aspx and the World Health Organization website under: www.who.int/**trial**search/**trial**.aspx?**trial**id=ACTRN12609000596202.

Participants

Pregnant women aged 18 years or above who presented to the LGH with IDA between 2007 and 2009 were invited to participate. In the original study, two hundred Caucasian pregnant women aged 18 years or above were identified with moderate IDA, defined as Hb ≤115 g/L (reference range (RR) 120-160 g/L) and low iron stores based on a serum ferritin level <30 µg/L (RR 30-440 µg/L).

Of the original 196 pregnant Caucasian women randomised to receive oral iron or a single intravenous iron polymaltose infusion, 126 women completed the QoL follow-up study. The median age was 29 years at enrolment (range, 21 to 43); and the median follow up period was 32 months (range, 26 to 42) post-delivery.

Randomisation and interventions: Informed consent was obtained by a research midwife. Treatment arm was randomised in blocks of 10 and assignment was performed by the LGH Pharmacy Department in order to avoid possible bias. The oral-only treatment arm comprised iron sulphate 250 mg tablets, (elemental iron 80 mg, Abbott, Australasia Pty Ltd) to be taken daily within two days after booking until delivery. The IV arm required a single intravenous infusion of iron polymaltose (Ferrosig, Sigma Pharmaceuticals, Australia) within 1 week after booking followed by oral iron identical to the other arm. Pre-enrolment, there were no significant differences in the dietary iron intake or supplement intake between the two groups based on a specially-designed questionnaire addressing these issues. Patients assigned to IV iron polymaltose received a 100 mg test-dose dissolved in 50 ml normal saline infused over 30 minutes. Clinical observation and vital signs were assessed initially and every 15 min from the start of the infusion. After the test-dose was tolerated, the remainder of iron polymaltose dose was infused. The total dose of IV iron polymaltose was calculated according to the patient's body weight at their first antenatal visit and entry Hb level according to the product guidelines; iron dose in mg (50 mg per 1 ml) = body weight (maximum 90) in kg x target Hb (120 g/L) - actual Hb in g/L) x constant factor (0.24) + iron depot (500).[14]

Outcome measurement: Two Health-Related Quality of Life (HRQoL) questionnaires were administered during the initial and follow-up studies: Firstly, a clinical questionnaire was completed prospectively by trained midwives at 4 weeks after initiation of treatment, at 28 and 34 weeks gestation, and then post delivery. This questionnaire assessed four aspects of energy levels, activity, tolerance and side effects of treatment, and was used to guide individual patient clinical decision-making as well as providing a safety audit of the trial treatments.[14] Secondly, a retrospective survey was conducted between June and October 2010 by trained research personnel via phone interview using a modified version of the SF-36 questionnaire.[16,17] These modifications included: (1) use of eleven of the 36 questions (Table 1); and (2) the women were asked to recall their response to each of

the questions for four time points, pre-trial prior to commencement of iron therapy during the pregnancy, four weeks after starting iron therapy, one week after delivery, and the last four weeks prior to the telephone questionnaire contact (Table 1). In order to validate the retrospective use of the modified SF-36 to assess the women's HRQoL during and after pregnancy, the associations of the physical activity component of the prospective monitoring questionnaire following entry into the trial with the Physical Component Scales values of the modified SF-36 at each of the time points were estimated. We hypothesized that the association would be greatest at 4 weeks compared to trial entry, time of delivery or at the time of questionnaire completion. In addition, data regarding breastfeeding and the health of the woman's child were collected from the baby growth booklet. This included breastfeeding duration, baby gender, age, weight, and previous hospitalization, if any, in addition to the baby's sleep quality since birth and specific growth data for the children as set by the Australasian Paediatric Endocrine Group (APEG). Haemoglobin and ferritin levels for participants at delivery were available for all participants, however no further testing was performed during the follow up. The principal investigators including the statistician evaluated the questionnaire results data.

Statistical methods

The HRQoL scores that form the raw data for this analysis are rank-order in nature. Means and standard deviations of the scores were estimated using generalized estimating equations for illustrative purposes only. Physical and mental composite scores were calculated in the modified SF36 according to the SF-12 scoring guidelines.[16,17] Group comparison and covariate effect size calculation, odds ratios (OR with 95% confidence intervals and P values) were estimated using repeated measures of ordinal logistic regression, with covariates selected for inclusion by backward stepwise regression (P for exclusion 0.22) from maternal age, haemoglobin, ferritin, Socio-Economic Indexes for Areas (SEIFA; based on the Collector District of residence of mothers), quality of sleep, use and duration of breast-feeding, hospitalization of baby, baby gender and mode of delivery. When iron status was

selected for inclusion in the model, the association between iron status (ferritin) and HRQoL was reported independently of trial treatment group. P values were corrected for multiple comparisons where necessary by the Holm method. The effect of IV iron versus oral iron on time of cessation of breastfeeding was compared by estimation of hazard ratio (HR; 95% confidence intervals and P-values) by Cox proportional hazards regression adjusted for covariates selected for inclusion by backward stepwise regression (P for exclusion 0.22). Neonatal growth in the treatment groups was compared by multivariate third-order polynomial regression as an approximation to APEG growth assessment. All HRQoL statistical analyses were performed using Stata SE for Windows 11.1 (StataCorp, College Station, Tx USA).

RESULTS

Of the original 196 patients randomised to receive the trial medications (98 received IV plus oral iron; 98 received oral iron only), 183 patients completed the trial by the collection of blood for iron status estimation at the time of delivery. Data of HRQoL were collected from 126 women, representing 69% of the cohort who completed the trial, while 31% of patients were uncontactable or did not respond to the researcher messages (see Figure 1 for description of patient flow). Basic demographic data of those patients included in the follow-up study showed that the median age was 29 years at enrolment (range, 21 to 43); and the median follow up was 32 months (range, 26 to 42) post-delivery. There were no significant differences in demographic or iron status measurements between any of the groups of women recruited to the trial.

As reported in the original study, at delivery the proportion of women with lower than normal ferritin levels was 79% for women who were treated with oral iron as compared to 4.5% for women who received IV iron ($p<0.001$).[14] Furthermore, the percentage of women at delivery with Hb level <116 g/L was 29% in the oral iron group versus 16% in the IV iron group ($p=0.04$).[14] This indicates that the

IV iron application was associated with a significantly higher percentage of treated women with normal ferritin levels and accordingly Hb. The HRQoL Physical Component Scale (OR 1.84; 95% CI 1.03 to 3.30; P=0.041) and General Health (OR 2.71; 95% CI 1.37 to 5.37; P=0.021) responses were improved in the IV compared to the oral iron group, but these differences became less apparent at subsequent assessment time points (Figure 2a and b).

Furthermore, there were strong associations between the level of iron status, independent of how that iron status was achieved, and a number of the HRQoL scales (Figure 2): notably improved General Health (OR 1.49; 95% CI 1.09 to 2.03; P=0.021), improved Physical Energy (OR 1.36; 95% CI 1.06 to 1.74; P=0.016), less Psychological Downheartedness (OR 1.57; 95% CI 1.14 to 2.15; P=0.005), less Clinical Depression (OR 2.05; 95% CI 1.27 to 3.32; P=0.003), and overall improved Mental Component Scale (OR 1.55; 95% CI 1.23 to 1.97; P<0.001). In addition, there was a mild trend towards a positive association between higher socioeconomic status and improved Mental Component Scale scores (p=0.17).

There was an increased duration of breastfeeding (HR for cessation was 0.70; 95% CI 0.50 to 0.99; p=0.046) in women in the IV iron group (Figure 3) where older women were more likely to breast feed longer (OR 0.76; 95% CI 1.00 to 1.52; P=0.006) (Table 2). Earlier cessation of breastfeeding was associated with downheartedness (OR 1.23; 95% CI 1.00 to 1.52; P=0.06). There was no difference between the oral iron or IV plus oral iron groups in the weight of the baby at birth (p=0.64), and no difference in the rate of weight gain (p=0.90).

The association between the physical symptom questions index from the clinical monitoring questionnaire and the Physical Component Scale of the HRQoL for the four time periods is shown in Table 3. There was significant association between the physical symptom questions index at 4 weeks after trial entry and each of the HRQoL recall time points, and that the association was strongest for the 4 weeks recall (OR 3.18; 2.14 to 4.74; P<0.001). An unanticipated finding of this study was an

association between male gender babies and an unfavourable mental health component outcome for participant women across the two groups. Of the seven component questions, two showed a significant association, with women who had male babies less likely to be calm and peaceful (OR=0.55, 0.32-0.97, p=0.039) and more likely to have accomplished less than they would have liked to as a result of their emotional state (OR=1.33, 1.05-1.69, p=0.018).

DISCUSSION

We report on 126 patients in a follow up study of the effect of IV iron versus oral iron therapy during pregnancy on long-term HRQoL. There are no data available studying the effects of both IV and oral iron on post-delivery psychological and physical welfare of the mother, the quality of the bonding to her baby and the rate of developmental progress of the baby. Our study demonstrates that there was an improvement in the self-assessed feeling of general health in both treatment groups from the pre-labour period to all subsequent periods. Although the improvement was significantly greater in the IV iron group 4 weeks after commencement of trial treatment (p=0.02), at subsequent measurement periods the difference persisted at a lesser magnitude that did not achieve a statistical significance.

Regardless of treatment and regardless of which period was being considered, higher haemoglobin and higher ferritin levels were associated with better baby sleep quality and the mother breastfeeding as well as higher assessment of general health.

The HRQoL questionnaire includes many useful relevant aspects regarding general health, activities, level of energy and depression. There was a substantial improvement of iron status in women who received IV iron as demonstrated during the trial analysis. Criticism may arise due to the modified questionnaire being a retrospective HR-QoL evaluation which should ideally have been conducted within a shorter period of time, even though the opportunity for a prospective evaluation had been missed in our study. Therefore in order to overcome a possible recall bias, the number of retrospective questions would be needed to be abbreviated, since the women were asked to recall their responses to

each question at four different time points, so the full SF-36 was impractical and may be judged to be an excessive burden on the women. Thus, we attempted to provide a retrospective form of validation by showing that the clinical HR-QoL questions in the physical domain, recorded prospectively at week 4 after trial, were most strongly associated with the Physical Component Scales of the recall of modified SF-36 at week 4 compared to the other time points. This indicates that the retrospective methodology was able to provide an acceptable degree of accuracy in the differentiation of HR-QoL levels at different time points despite the concerns that may have arisen with this issue. The assumption being made is that the way those patients will judge their physical and mental condition will be relatively stable over time,[18] an assumption with which we agree that may occur in patients with chronic diseases. However, this assumption may not hold for women during and after pregnancy. The expectations by the woman about how she should be feeling at the different stages of pregnancy, around the time of delivery, and when she is caring for one or more young infant and child may differ substantially at those different time points. At least in our analysis the judgment the woman is making about how to answer the questions is likely to be the same for each time point, since she had made that judgment at one point in time: the repeated measures analysis compares each woman with herself, thus substantially reducing the impact of variation between women in this judgment. Thus, for the purpose of generating a hypothesis concerning iron status and quality of life, we believe that our methodology has been adequate. Despite of the relative small number of women studied, it is worthwhile publishing our study due to lack of researches that address HRQoL during and after pregnancy, particularly, in view of the emerging novel association between iron status and postnatal clinical depression as well as breastfeeding duration in our cohort of patients.

Regarding the incidental findings of unfavourable mental health component outcomes for women with male babies, there is only a single report in the literature addressing this issue with similar findings.[19] Perhaps this may be explained with the observation that male babies are usually more active and this

may be associated with post natal depression.[19] However, due to lack of data, this issue should be addressed separately and studied thoroughly in future research.

In summary, there was a significant improvement in the general health of women who received IV iron (p=0.02), but this effect was found directly after the IV iron treatment. The duration of breast-feeding was longer (p=0.04) in those women who had received IV iron. Women with better iron status were less downhearted (p=0.005) and less likely to develop postnatal clinical depression (p=0.003). Our results would indicate that it is worthwhile considering Hb and iron status as a surrogate marker for assessment of women's wellbeing, not only during pregnancy, but also during the postnatal period.

Further studies are warranted to confirm and extend our findings, and to determine outcomes in different populations with IDA in order to improve the estimates of the magnitude of the benefits of intravenous iron for the management of iron deficiency anaemia.

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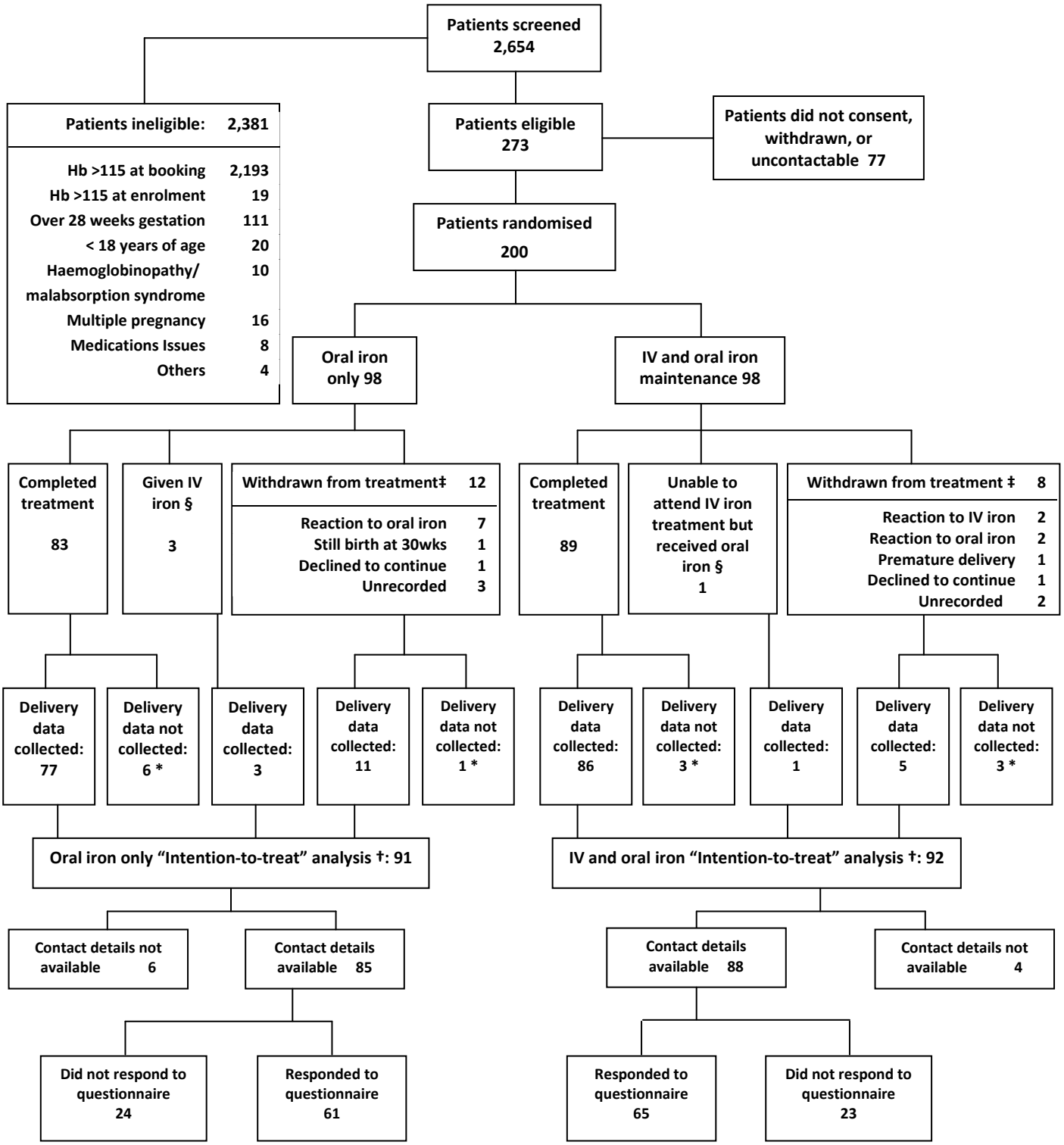
Figure 1. Trial flow diagram: disposition of study participants by treatment assignment.



Footnotes to Figure 1. Patients Flow Chart.

* Fourteen patients were admitted late in labour, and no blood samples were taken before delivery

† The primary hypothesis examined the change in haemoglobin levels between the time of booking and immediately prior to delivery; an "intention-to-treat" analysis was performed according to original randomization group on those patients who had blood samples taken before delivery, whether or not the treatment was completed as per protocol

‡ Twenty one patients withdrew from the trial treatments, and all but one of these patients agreed to continued collection of haematological and other trial data; eight patients gave no reason for withdrawal

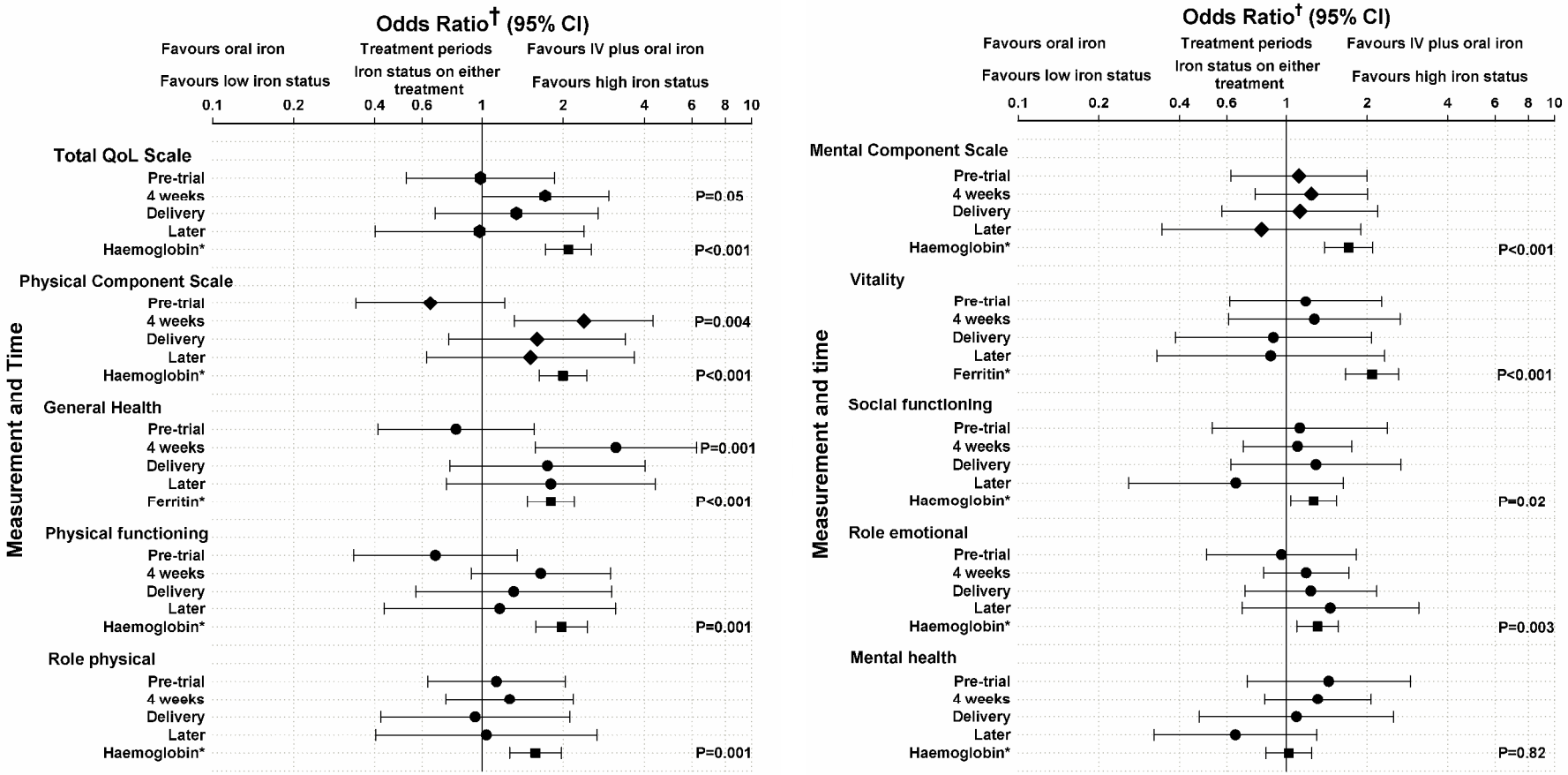
§ Five patients did not complete the intended treatments, but did not themselves choose to withdraw; three patients in the oral iron group were treated with IV iron when their haemoglobin was judged not to have responded adequately to oral iron, whilst one patient was unable to attend for IV iron treatment

Table 1. Comparison of the questions in the SF-36 and the abbreviated HRQoL questionnaire used in this study.

*Questionnaires	Original SF-36	Modified short-HRQoL
Time specified for subject response	Either in at the time of analysis or in past 4 weeks	Evaluated at four time periods: before treatment; after 4 weeks of treatment; after delivery; and during the past 4 weeks
Question: stem and detailed item	**Response and Question number:**	**Response and Question number:**
In general, would you say your health is:	Excellent; Very good; Good; Fair; Poor Q1	Same response Q1
The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	Yes, limited a lot Yes, limited a little No, not limited at all	Same response
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	Q3b	Q2a
Climbing several flights of stairs	Q3d	Q2b
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	Same response
Accomplished less than you would like	Q4b	Q3a
Were limited in the kind of work or other activities	Q4c	Q3b
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	Same response
Accomplished less than you would like	Q5b	Q6a
Did work or other activities less carefully than usual	Q5c	Q6b
Have you felt calm and peaceful?	Q9d	Q4a
Did you have a lot of energy?	Q9e	Q4b
Have you felt downhearted and depressed?	Q9f	Q4c
Have you been diagnosed with or treated for depression or postnatal depression since the birth of your baby?	Not included	Diagnosed: Yes/No Treated: Yes/No Q4d
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	All of the time; Most of the time; Some of the time; A little of the time; None of the time Q10	Same response Q5
During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all; A little bit; Moderately; Quite a bit; Extremely Q8	Not included

* Not all SF-36 questions are included in this list.

Figure 1. Comparison of physical component scale of HRQoL scores in the IV plus oral iron versus the oral iron group, and separate association with iron status



† Comparison of the effect of IV plus oral iron versus oral iron on physical and mental components of the HRQoL scores at different time periods (before starting iron, 4 weeks after starting iron, at delivery and when the mother responded to questionnaire), estimated using ordinal logistic regression adjusted for significant demographic confounders but not including iron status, corrected for repeated measures and multiple comparisons (Holm method).

* The effect of iron status on PCS and MCS scores was estimated separately without including treatment group in the analysis.

Table 2. Effect of IV iron versus oral iron on rate of cessation of breast feeding

	HR[1]	95% CI	P-value
IV plus oral	0.70	(0.50 to 0.99)	0.046
Maternal age	0.76	(0.63 to 0.92)	0.006
Downheartedness	1.23	(1.00 to 1.52)	0.055
Current alcohol intake	1.34	(0.88 to 2.03)	0.18
Mode of delivery:			
NVD	1.00		
LSCS	1.24	(0.84 to 1.82)	0.29
Forceps	1.39	(0.85 to 2.27)	0.19

[1] Hazards ratio (HR) less than 1.00 indicates a slower rate of cessation of breast-feeding, whilst an HR greater than 1.00 indicates a faster rate of ceasing breast-feeding.

[2] Abbreviations: NVD – normal vaginal delivery; LSCS – lower segment caesarean section

Table 3. Association between the physical symptom questions[3] in from the prospective clinical monitoring questionnaire and the Physical Component Scale of the retrospective HRQoL for the four time periods.

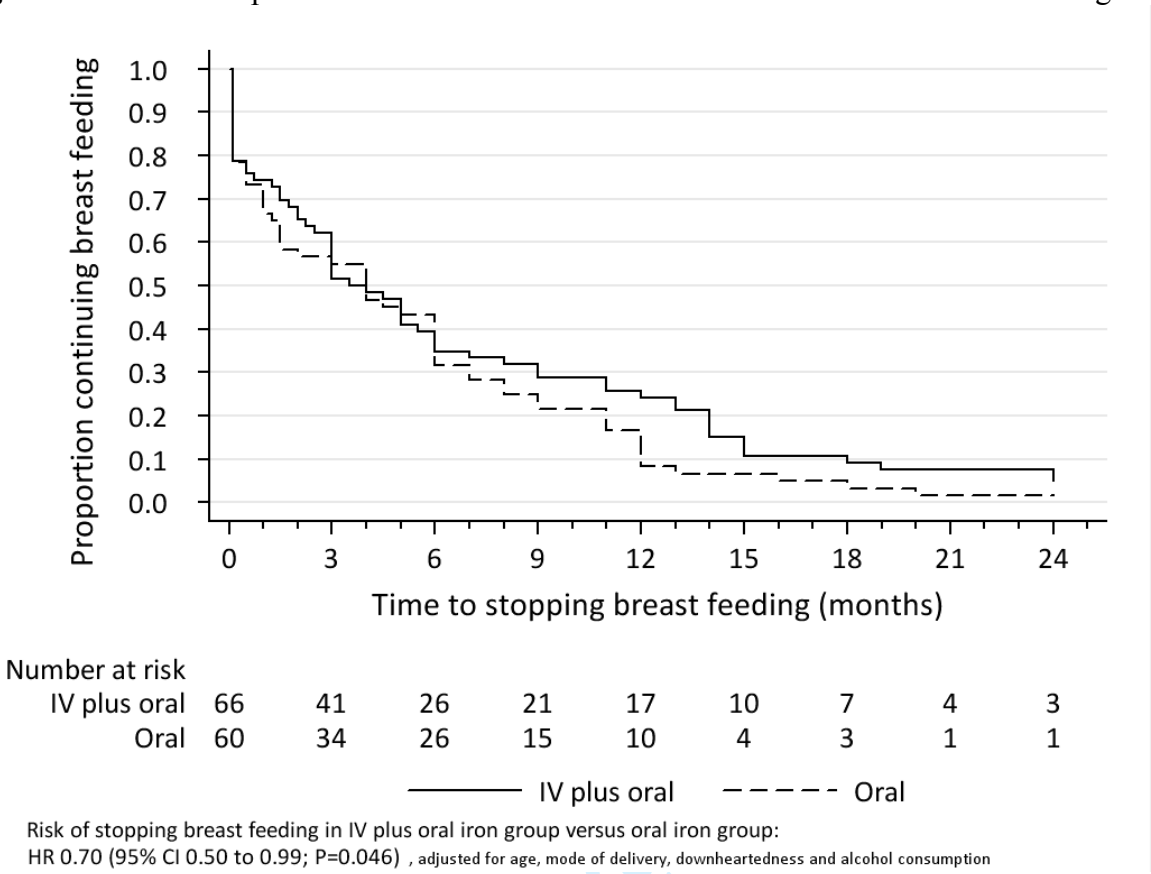
Time	Slope (SD)[1]	OR[2a]	95%CI	P-value	OR[2b]	95%CI	P-value
Pre-trial	2.67 (13.0) [1]	1.46	(1.01 to 2.11)	0.043	1.00		
4 weeks	8.07 (18.6)	3.18	(2.11 to 4.80)	<0.001	2.18	(1.44 to 3.28)	<0.001
Delivery	4.91 (12.2)	2.14	(1.37 to 3.35)	<0.001	1.46	(0.94 to 2.29)	0.10
Later	4.31 (14.1)	1.98	(1.28 to 3.08)	<0.001	1.36	(0.88 to 2.10)	0.17

[1] The slope (standard deviation) of the association between the physical symptom questions in from the clinical monitoring questionnaire and the Physical Component Scale of the HRQoL for the four time periods was estimated by repeated measures general linear modeling for illustrative purposes only (mean index score at pre-trial was 74.3 of 100).

[2] The strength of that [a)] absolute association at each time point, and [b)] the relative association at the other time points was compared to the pre-trial time point and was estimated using repeated measures ordered logistic regression, expressed as odds ratios (OR; 95% confidence intervals; P-values).

[3] The scores for four questions were combined as a single index: Do you have energy? Do you feel fatigued or sleepy? Do you feel light-headed (dizzy)? Do you feel short of breath? Responses: Not at all; A little of the time; Sometimes; Most of the time; Always.

Figure 3. Effect of IV plus oral iron versus oral iron on rate of cessation of breast-feeding



Risk of stopping breast feeding in IV plus oral iron group versus oral iron group:
HR 0.70 (95% CI 0.50 to 0.99; P=0.046) , adjusted for age, mode of delivery, downheartedness and alcohol consumption

The difference arises in those women whose breast feeding duration is in the top 30% (70-80th centiles who breast-feed for at least 12 months, about 2 months longer {75th centile difference 2.25 months; 95% CI -2.79 to 7.30; P=0.38}), and particularly in the top 10% (who breast-feed for at least 15 months, about 6 months longer {90th percentile difference 6.22 months; 95% CI 0.36 to 12.1; P=0.038}).

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Intravenous Iron Therapy is Associated with Improved Maternal Quality of Life, Less Postnatal Depression and Longer Breastfeeding after Treatment of Iron Deficiency Anaemia in Pregnancy: A Follow-up Study

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Intravenous Iron Therapy is Associated with Improved Maternal Quality of Life, Less Postnatal Depression and Longer Breastfeeding after Treatment of Iron Deficiency Anaemia in Pregnancy: A Follow-up Study

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ARTICLE SUMMARY

Article focus

- Health related quality of life assessment during and after pregnancy in 126 women with iron deficiency, who received either a single dose intravenous iron polymaltose followed by oral iron maintenance or an oral iron only.
- Study of postnatal depression and its association with the treatment arms and iron status
- Assessment of breastfeeding duration and correlation to mothers' iron status

Key-Messages

- Health related quality of life is improved significantly in anaemic pregnant women by repletion of their iron stores during pregnancy.
- About 80% of the intravenous iron group showed a maintained normal ferritin until delivery with long-term benefits such as prolongation of the breast-feeding period and less postnatal clinical depression.
- There were strong associations between iron status and a number of the HRQoL scales with improved general health (P=0.021), improved physical energy (P=0.016), less psychological downheartedness (P=0.005), less clinical depression (P=0.003), and overall improved mental component scale (P<0.001). The duration of breastfeeding was longer (P=0.046) in women who received intravenous iron.

Strengths and limitations

- This study addresses a novel finding of postnatal depression and breast- feeding period in correlation with iron status.
- There is very limited data regarding quality of life measurement during and after pregnancy that makes the scientific input of the current study important, albeit a relatively small number of pregnant women studied.
- Limitations of our study include the modified questionnaire being in part a retrospective HRQoL evaluation which should ideally have been conducted within a shorter period of time.
- Further limitation is the relatively small number of women studied.

ABSTRACT

Background: To date there are no data available regarding the impact of intravenous versus oral iron on the wellbeing and health-related quality of life (HRQoL) in particular postnatal depression and duration of breast- feeding during and after pregnancy.

Objective: To assess long-term effect of iron therapy on HRQoL during pregnancy and in the post-natal period.

Design: We conducted a prospective, randomised-controlled, open-label trial of intravenous versus oral iron therapy for pregnancy-related iron deficiency anaemia between March 2007 and January 2009 at the Launceston General Hospital, Tasmania, Australia. The follow up study was conducted between January 2010 and January 2011 using a modified version of the SF-36 questionnaire together with the original prospective HRQoL data collected during 2nd and 3rd trimesters of pregnancy as well as 6-8 weeks post delivery.

Participants and Interventions: Of the original evaluable 183 pregnant Caucasian women randomised to receive oral iron or a single intravenous iron polymaltose infusion followed by oral iron maintenance, 126 women completed the follow up HRQoL study.

Methods: The participants were followed up post-delivery for a median period of 32 months (range, 26-42) with a well-being and health-related QoL questionnaire using a modified short form 36 QoL survey and child growth charts as set by the Australasian Paediatric Endocrine Group (APEG).

Results: Patients who received intravenous iron demonstrated significantly higher Hb and serum ferritin levels ($p<0.001$). There were strong associations between iron status and a number of the HRQoL scales with improved general health ($P<0.001$), improved vitality (physical energy) ($P<0.001$), less psychological downheartedness ($P=0.005$), less clinical depression ($P=0.003$), and overall improved mental component scale ($P<0.001$). The duration of breastfeeding was longer ($P=0.046$) in women who received intravenous iron. The babies born in both groups recorded similarly on APEG growth chart assessments.

Conclusion: Our data suggest that HRQoL is improved in anaemic pregnant women by repletion of their iron stores during pregnancy. About 80% of the intravenous iron polymaltose group showed a maintained normal ferritin until delivery with long-term benefits and a minimal effect on their babies. Further studies to confirm these findings are warranted.

Trial registration: Australia and New Zealand Clinical Trial Registry under: http://www.ANZCTR.org.au under ACTRN 12609000177257 and in the World Health Organization website under: www.who.int/**trial**search/**trial**.aspx?**trial**id=ACTRN12609000596202.

Funding: This research received a grant from the Clifford Craig Medical Research Trust, Launceston, Tasmania, Australia.

Key words: Quality of life assessment, iron deficiency anaemia, oral iron, intravenous iron, pregnancy, long-term effect.

INTRODUCTION

There are no available data regarding quality of life assessment and long term effects of intravenous versus oral iron therapy during pregnancy. In addition to the physical impact of iron deficiency anaemia (IDA) on pregnant women,[1-3] IDA is a potential risk factor for preterm delivery and subsequent low birth weight and may be associated with inferior neonatal health.[3-4] Infants born to women with IDA are more likely to become anaemic themselves, which in turn is known to have a potential effect on an infant's mental and motor development.[5-9] Although iron supplementation during pregnancy is a widely practiced public health measure, there are some concerns regarding iron replacement therapy and its long-term effect, especially the intravenous form.[10,11] However, pregnant women do not always respond adequately to oral iron therapy due to difficulties associated with ingestion of the tablets and their side effects, impacting negatively on their compliance.[3,10,11] Side effects include gastrointestinal disturbances characterized by colicky pain, nausea, vomiting, diarrhoea and/or constipation, and occur in up to 28% of patients taking oral iron preparations.[10,11] Furthermore, the presence of chronic bowel disease can affect the absorption of iron, minimising the benefit received from oral iron therapy.[11]

In the past, intravenous iron had been associated with undesirable and sometimes serious side-effects limiting its use.[12] Recently, new type II iron complexes have been developed with the potential to reverse iron deficiency with less side effects than their predecessors.[12-14] Despite increasing evidence for the safety of the newer preparations in both pregnant and general populations, intravenous iron continues to be underutilised.[15]

The initial randomized controlled trial showed that intravenous iron polymaltose leads to improved efficacy and iron stores compared to oral iron alone in pregnancy-related IDA treatments **(effect size for haemoglobin 6.6g/L {95% CI 3.4-9.8, p<0.001}; for ferritin 108 mg/L {95% CI 43-209, p<0.001})**. In the follow up trial of the same cohort of patients, we studied the effect of both iron

therapies on the perceived health-related quality of life (HRQoL) as measured by a modified SF36 questionnaire as well as the effect of iron therapy on breastfeeding rates and on the general wellbeing of the babies born to these women as measured by child growth charts set by the Australasian Paediatric Endocrine Group (APEG).

Rationale and objectives

We analysed HRQoL for our cohort of pregnant women prospectively during the original study at the baseline; prior to treatment in the second trimester, 4 weeks after initiation of treatment and in the third trimester pre delivery, as well as at 6-8 weeks post delivery. In the follow-up study, HRQoL questionnaire is conducted incorporating the original questionnaire in addition to additional parameters such as length of breastfeeding period and occurrence of postnatal depression as well as child growth data. This was performed at a median of 32 months post intervention in order to assess the long-term effect of both iron therapies on mothers' HRQoL in correlation to previous prospective data. This questionnaire, although performed prospectively, it has a retrospective component by asking the participated mothers the same questions that they have previously answered prospectively about their QoL during and after pregnancy compared to the current questionnaire. These data were analysed against the mothers' original prospective QoL data for validation purposes.

PATIENTS AND METHODS

The initial prospective randomised-controlled trial was conducted between March 2007 and January 2009 at the Launceston General Hospital (LGH), a tertiary referral centre for Northern Tasmania, Australia. This follow-up study took place between January 2010 and January 2011. An informed consent form was obtained from all participants according to the Code of Ethics. The original and the follow-up studies were approved by the Tasmanian Human Research Ethics Committee and registered

in the Australia New Zealand Clinical Trials Registry under trial No**:** ACTRN12609000177257 with web addresses of the trial as follow: http://www.ANZCTR.org.au/ACTRN12609000177257.aspx and the World Health Organization website under: www.who.int/**trial**search/**trial**.aspx?**trial**id=ACTRN12609000596202.

Participants

Pregnant women aged 18 years or above who presented to the LGH with IDA between 2007 and 2009 were invited to participate. In the original study, two hundred Caucasian pregnant women aged 18 years or above were identified with moderate IDA, defined as Hb ≤115 g/L (reference range (RR) 120-160 g/L) and low iron stores based on a serum ferritin level <30 µg/L (RR 30-440 µg/L).

Of the original evaluable 183 pregnant Caucasian women randomised to receive oral iron or a single intravenous iron polymaltose infusion, 126 women completed the QoL follow-up study (Table 1). The median age was 29 years at enrolment (range, 21 to 43); and the median follow up period was 32 months (range, 26 to 42) post-delivery.

Randomisation and interventions: Informed consent was obtained by a research midwife. Treatment arm was randomised in blocks of 10 and assignment was performed by the LGH Pharmacy Department in order to avoid any possible bias. The oral-only treatment arm comprised iron sulphate 250 mg tablets, (elemental iron 80 mg, Abbott, Australasia Pty Ltd) to be taken daily within two days after booking until delivery. The IV arm required a single intravenous infusion of iron polymaltose (Ferrosig, Sigma Pharmaceuticals, Australia) within 1 week after booking followed by oral iron identical to the other arm. Pre-enrolment, there were no significant differences in the dietary iron intake or supplement intake between the two groups based on a specially-designed questionnaire addressing these issues. Patients assigned to IV iron polymaltose received a 100 mg test-dose

dissolved in 50 ml normal saline infused over 30 minutes. Clinical observation and vital signs were assessed initially and every 15 min from the start of the infusion. After the test-dose was tolerated, the remainder of iron polymaltose dose was infused. The total dose of IV iron polymaltose was calculated according to the patient's body weight at their first antenatal visit and entry Hb level according to the product guidelines; iron dose in mg (50 mg per 1 ml) = body weight (maximum 90) in kg x target Hb (120 g/L) - actual Hb in g/L) x constant factor (0.24) + iron depot (500).[14]

Outcome measurement: Two Health-Related Quality of Life (HRQoL) questionnaires were administered during the initial and follow-up studies: Firstly, a clinical questionnaire was completed prospectively by trained midwives at 4 weeks after initiation of treatment, at 28 and 34 weeks gestation, and then 6-8 weeks post delivery. This questionnaire assessed four aspects of energy levels, activity, tolerance and side effects of treatment, and was used to guide individual patient clinical decision-making as well as providing a safety audit of the trial treatments.[14] Secondly, a propsective/ retrospective survey was conducted between June and October 2010 by trained research personnel via phone interview using a modified version of the SF-36 questionnaire.[16,17] These modifications included: (1) use of eleven of the 36 questions (Table 2); and (2) the women were asked to recall their response to each of the questions for four time points, pre-trial prior to commencement of iron therapy during the pregnancy, four weeks after starting iron therapy, one week after delivery, and the last four weeks prior to the telephone questionnaire contact (Table 2). This has been compared to the same questions answered prospectively by the participants. In order to validate the retrospective use of the modified SF-36 to assess the women's HRQoL during and after pregnancy, the associations of the physical activity component of the prospective monitoring questionnaire following entry into the trial with the Physical Component Scales values of the modified SF-36 at each of the time points were estimated. We hypothesized that the association would be greatest at 4 weeks compared to trial entry, time of delivery or at the time of questionnaire completion. In addition, data regarding breastfeeding

and the health of the woman's child were collected from the baby growth booklet. This included breastfeeding duration, baby gender, age, weight, and previous hospitalization, if any, in addition to the baby's sleep quality since birth and specific growth data for the children as set by the Australasian Paediatric Endocrine Group (APEG). Haemoglobin and ferritin levels for participants at delivery were available for all participants, however no further testing was performed during the follow up. The principal investigators including the statistician evaluated the questionnaire results data.

Statistical methods

The HRQoL scores that form the raw data for this analysis are rank-order in nature. Means and standard deviations of the scores were estimated using generalized estimating equations for illustrative purposes only. Physical and mental composite scores were calculated in the modified SF36 according to the SF-12 scoring guidelines.[16,17] Group comparison and covariate effect size calculation, odds ratios (OR with 95% confidence intervals and P values) were estimated using repeated measures of ordinal logistic regression, with covariates selected for inclusion by backward stepwise regression (P for exclusion 0.22) from maternal age, haemoglobin, ferritin, Socio-Economic Indexes for Areas (SEIFA; based on the Collector District of residence of mothers), quality of sleep, use and duration of breast-feeding, hospitalization of baby, baby gender and mode of delivery. **This included randomization group covariate interactions in the starting model with exclusion of those interactions using the above criteria.** When iron status was selected for inclusion in the model, the association between iron status (ferritin) and HRQoL was reported independently of trial treatment group. P values were corrected for multiple comparisons where necessary by the Holm method. The effect of IV iron versus oral iron on time of cessation of breastfeeding was compared by estimation of hazard ratio (HR; 95% confidence intervals and P-values) by Cox proportional hazards regression adjusted for covariates selected for inclusion by backward stepwise regression (P for exclusion 0.22). **The time to cessation of breast-feeding was taken from the subject's baby growth booklet for all**

participants. Neonatal growth in the treatment groups was compared by multivariate third-order polynomial regression as an approximation to APEG growth assessment. All HRQoL statistical analyses were performed using Stata SE for Windows 11.1 (StataCorp, College Station, Tx USA).

RESULTS

Of the original 196 patients randomised to receive the trial medications (98 received IV plus oral iron; 98 received oral iron only), 183 patients completed the trial by the collection of blood for iron status estimation at the time of delivery. Data of HRQoL were collected from 126 **of the 183** women who completed the original trial, representing 69% of the cohort who completed the trial, while **57** (31%) of **the 183** patients were moved away, uncontactable or did not respond to the researcher messages (see Figure 1 for description of patient flow). Basic demographic data of those patients included in the follow-up study showed that the median age was 29 years at enrolment (range, 21 to 43); and the median follow up was 32 months (range, 26 to 42) post-delivery. There were no significant differences in demographic or iron status measurements between any of the groups of women recruited to the trial.

As reported in the original study, at delivery the proportion of women with lower than normal ferritin levels was **53 of 67** (79%) for women **with analysable iron status measurements** who were treated with oral iron as compared to **3 of 66** (4.5%) for women who received IV iron **(Fisher's exact** $p<0.001$).[14] Furthermore, the percentage of women at delivery with Hb level <116 g/L was 29% **(25 of 85)** in the oral iron group versus 16% (**14 of 87)** in the IV iron group ($p=0.04$).[14] This indicates that the IV iron application was associated with a significantly higher percentage of treated women with normal ferritin levels and accordingly Hb. **The HRQoL Physical Component Scale (difference 10.3; 95% CI 3.3 to 17.2; P=0.27; OR 2.39; 95% CI 1.32 to 4.32; P=0.004) and General Health (difference 15.1; 95% CI 6.0 to 24.2; P=0.31; OR 3.14; 95% CI 1.57 to 6.26; P=0.001) responses**

were improved in the IV compared to the oral iron group, but these differences became less apparent at subsequent assessment time points (Figure 2a and b).

Furthermore, there were strong associations between the level of iron status, independent of how that iron status was achieved, and a number of the HRQoL scales (Figure 2): notably improved General Health (slope {1SD log.-ferritin} 10.0; 7.2 to 12.7; P<0.001; OR 1.49; 95% CI 1.09 to 2.03; P=0.021), improved Vitality (slope {1SD log.-ferritin} 10.0; 7.3 to 12.8; P<0.001; OR 2.09; 95% CI 1.66 to 2.62; P<0.001), less Psychological Downheartedness ({1SD haemoglobin} OR 1.57; 95% CI 1.14 to 2.15; P=0.005), less Clinical Depression ({1SD log.-ferritin} OR 2.05; 95% CI 1.27 to 3.32; P=0.003), and overall improved Mental Component Scale (slope {1SD haemoglobin} 3.8; 2.5 to 5.0; P<0.001; OR 1.71; 95% CI 1.39 to 2.10; P<0.001)(Psychological Downheartedness and Clinical Depression analysis used raw scores rather than 100-point scales).

There was an increased duration of breastfeeding (HR for cessation was 0.70; 95% CI 0.50 to 0.99; p=0.046) in women in the IV iron group (Figure 3) where older women were more likely to breast feed longer (HR 0.76; 95% CI 1.00 to 1.52; P=0.006) (Table 3). Earlier cessation of breastfeeding was associated with downheartedness (HR 1.23; 95% CI 1.00 to 1.52; P=0.06). There was no difference between the oral iron or IV plus oral iron groups in the weight of the baby at birth (p=0.64), and no difference in the rate of weight gain (p=0.90).

The association between the physical symptom questions index from the clinical monitoring questionnaire and the Physical Component Scale of the HRQoL for the four time periods is shown in Table 4. There was significant association between the physical symptom questions index at 4 weeks after trial entry and each of the HRQoL recall time points, and that the association was strongest for the 4 weeks recall (OR 3.18; 2.14 to 4.74; P<0.001).

DISCUSSION

There are no data available studying the effects of both IV and oral iron on post-delivery psychological and physical welfare of the mother, the quality of the bonding to her baby and the rate of developmental progress of the baby. We report on 126 patients in a follow up study of the effect of IV iron versus oral iron therapy on HRQoL during and after pregnancy. Our study demonstrates that there was an improvement in the self-assessed feeling of general health in both treatment groups from the pre-labour period to all subsequent periods. Although the improvement was significantly greater during pregnancy in the IV iron group 4 weeks after commencement of trial treatment ($p=0.001$), the difference persisted in the subsequent measurement periods at a lesser magnitude that did not achieve a statistical significance.

Regardless of treatment and regardless of which period was being considered, higher haemoglobin and higher ferritin levels were associated with better baby sleep quality and a longer mother breastfeeding period as well as higher assessment of general health.

The modified HRQoL questionnaire used in our study includes many useful relevant aspects regarding general health, activities, level of energy and depression. There was a substantial improvement of iron status in women who received IV iron compared to oral iron as demonstrated during the trial analysis ($p<0.001$). Limitations of our study include the modified questionnaire being in part a retrospective HRQoL evaluation which should ideally have been conducted within a shorter period of time. However, a correlation to a prospective evaluation of the studied subjects had been made in our study in order to overcome a possible recall bias. Therefore, the number of retrospective questions would be needed to be abbreviated, since the women were asked to recall their responses to each question at four different time points, so the full SF-36 was impractical and may be judged to be an excessive burden on the women. Thus, we attempted to provide a retrospective form of validation by showing that the clinical HRQoL questions in the physical domain, recorded prospectively at week 4 after trial,

were most strongly associated with the Physical Component Scales of the recall of modified SF-36 at week 4 compared to the other time points. This indicates that the retrospective methodology was able to provide an acceptable degree of accuracy in the differentiation of HRQoL levels at different time points despite the concerns that may have arisen with this issue. The assumption being made is that the way those patients will judge their physical and mental condition will be relatively stable over time,[18] an assumption with which we agree that may occur in patients with chronic diseases. However, this assumption may not hold for women during and after pregnancy. The expectations by the woman about how she should be feeling at the different stages of pregnancy, around the time of delivery, and when she is caring for one or more young infant and child may differ substantially at those different time points. At least in our analysis the judgment the woman is making about how to answer the questions is likely to be the same for each time point, since she had made that judgment at one point in time: the repeated measures analysis compares each woman with herself, thus substantially reducing the impact of variation between women in this judgment. Thus, for the purpose of generating a hypothesis concerning iron status and quality of life, we believe that our methodology has been adequate. Other limitations of our study include a relatively small number of women studied. However, it is worthwhile publishing our study due to lack of researches that address HRQoL during and after pregnancy, particularly, in view of the emerging novel association between iron status and postnatal clinical depression as well as breastfeeding duration in our cohort of patients.

Regarding the incidental findings of the trend for unfavourable mental health component outcomes for women with male babies, there is only a single report in the literature addressing this issue with similar findings.[19] Perhaps this may be explained with the observation that male babies are usually more active and this may be associated with post natal depression.[19] However, due to lack of data, this issue should be addressed separately and studied thoroughly in future research.

Due to paucity of data regarding HRQoL during and after pregnancy, there are only very few literatures available. Jansen et al studied the effect of delivery and postpartum on the HRQoL.[20] A cohort of 141 pregnant women were included in this study. HRQoL questionnaires were measuring the immediate effect of delivery on HRQoL. The were conducted less than 1 day after vaginal delivery and less than two days after caesarean sections in a comparison to 3-6 weeks post delivery questionnaires for both groups.[20] The study focused on patients HRQoL recovery after both delivery interventions. In this study[20], the different time-points of conduction of the questionnaire may not necessary reflect the HRQoL during pregnancy and also after the postpartum period. Furthermore, the immediate questionnaire after delivery and 3-6 weeks time during the post-partum period may be at least, in theory, influenced by the event of delivery, in particular if complications occur, as well as the possible emotional and hormonal fluctuations during this period. It is worthwhile noting that the same study did not show association with Hb and QoL, however it did not investigate a possible effect of iron status on perceived HRQoL in conjunction with breastfeeding. This highlights our novel finding of the correlation between iron status and improved HRQoL during and after pregnancy.

In summary, there was a significant improvement in the general health of women who received IV iron ($p<0.001$), but this effect was found prominently 4 weeks after the IV iron treatment. The duration of breast-feeding was longer ($p=0.04$) in those women who had received IV iron. Women with better iron status were less downhearted ($p=0.005$) and less likely to develop postnatal clinical depression ($p=0.003$).

Our results would indicate that it is worthwhile considering Hb and iron status as a surrogate marker for assessment of women's wellbeing, not only during pregnancy, but also during the postnatal period.

Further studies are warranted to confirm and extend our findings, and to determine outcomes in different populations with IDA in order to improve the estimates of the magnitude of the benefits of intravenous iron for the management of iron deficiency anaemia.

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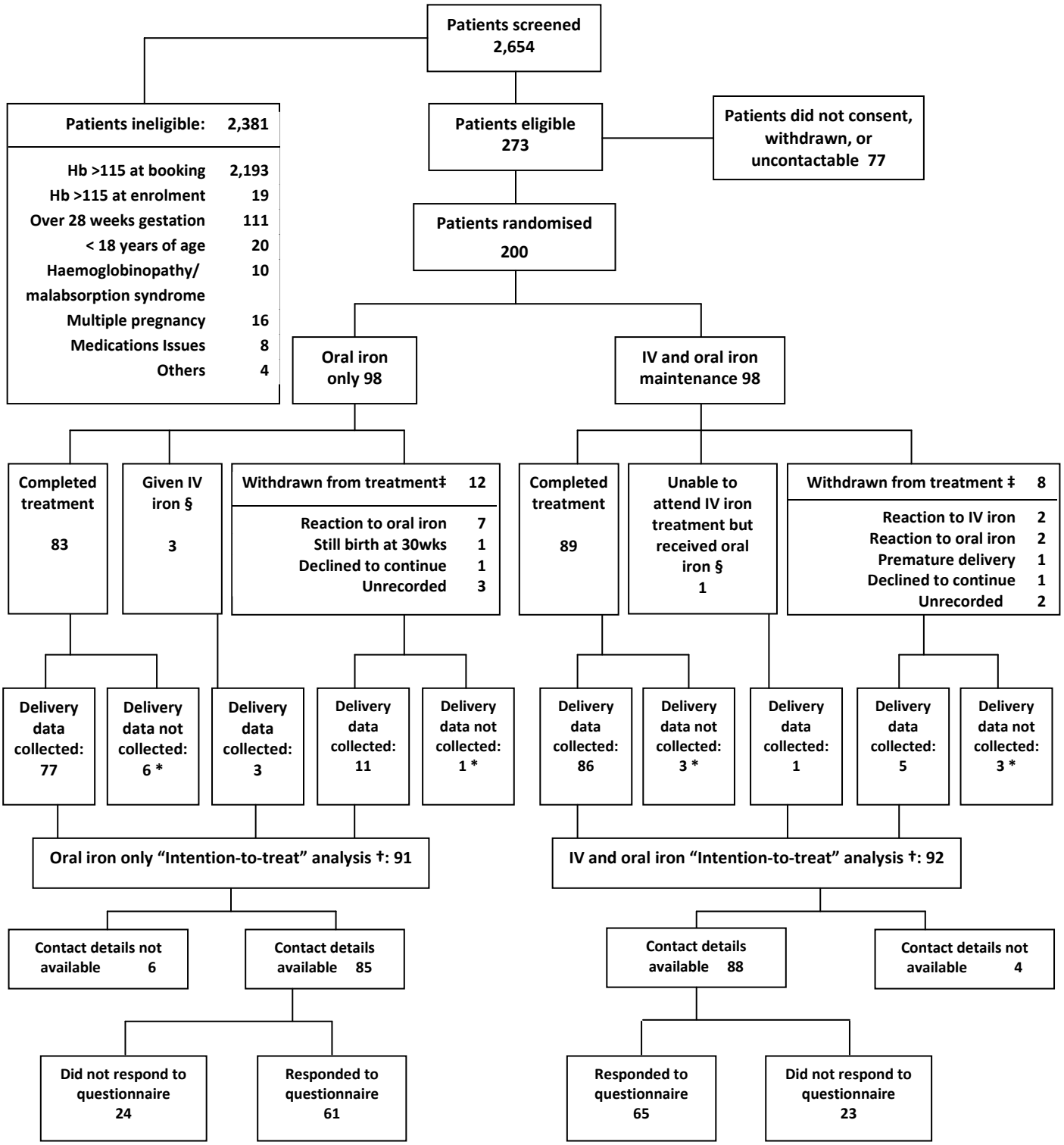
Figure 1. Trial flow diagram: disposition of study participants by treatment assignment.



Footnotes to Figure 1. Patients Flow Chart.

* Fourteen patients were admitted late in labour, and no blood samples were taken before delivery

† The primary hypothesis examined the change in haemoglobin levels between the time of booking and immediately prior to delivery; an "intention-to-treat" analysis was performed according to original randomization group on those patients who had blood samples taken before delivery, whether or not the treatment was completed as per protocol

‡ Twenty one patients withdrew from the trial treatments, and all but one of these patients agreed to continued collection of haematological and other trial data; eight patients gave no reason for withdrawal

§ Five patients did not complete the intended treatments, but did not themselves choose to withdraw; three patients in the oral iron group were treated with IV iron when their haemoglobin was judged not to have responded adequately to oral iron, whilst one patient was unable to attend for IV iron treatment

Table 1. Patients Characteristics

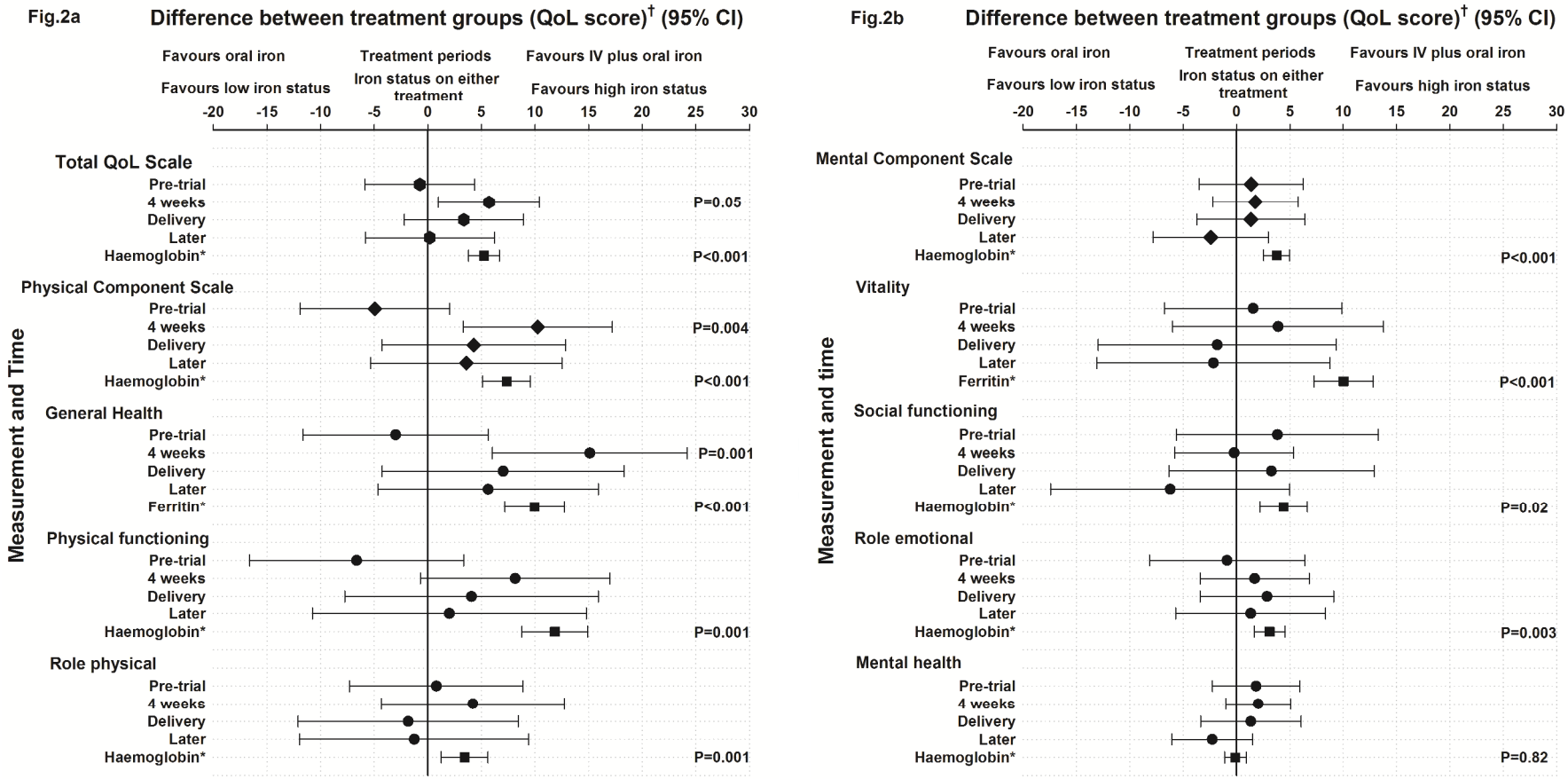
	IV iron group	**Oral iron group**
No of patients	64	62
Vaginal delivery	45	46
Caesarean section	19	16
Median age in years	28 years (range; 21-43)	28.5 years (Range; 22-42)
Mean age in years	27.5 years	28
Median time between trial intervention and delivery in months	2.7 months (range; 2.6-6)	2.8 months (range; 2.2-5.3)
Median time of follow-up in months	28 months	29 months
Baby birth weight in grams	Median 3523 g(range; 1315-4920)	Median 3480g (range; 1330-4928)
Median Initial Hb	105 g/L	108 g/L
Median Hb after intervention and prior to delivery	128 g/L	118 g/L
Median Hb post-delivery	118 g/L (range; 86-146)	112 g/L (range; 78-137)
Blood transfusion requirement	None	Two patients

Table 2. Comparison of the questions in the SF-36 and the abbreviated HRQoL questionnaire used in this study.

*Questionnaires	Original SF-36	Modified short-HRQoL
Time specified for subject response	Either in at the time of analysis or in past 4 weeks	Evaluated at four time periods: before treatment; after 4 weeks of treatment; after delivery; and during the past 4 weeks
Question: stem and detailed item	**Response and Question number:**	**Response and Question number:**
In general, would you say your health is:	Excellent; Very good; Good; Fair; Poor Q1	Same response Q1
The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	Yes, limited a lot Yes, limited a little No, not limited at all	Same response
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	Q3b	Q2a
Climbing several flights of stairs	Q3d	Q2b
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	Same response
Accomplished less than you would like	Q4b	Q3a
Were limited in the kind of work or other activities	Q4c	Q3b
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	Same response
Accomplished less than you would like	Q5b	Q6a
Did work or other activities less carefully than usual	Q5c	Q6b
Have you felt calm and peaceful?	Q9d	Q4a
Did you have a lot of energy?	Q9e	Q4b
Have you felt downhearted and depressed?	Q9f	Q4c
Have you been diagnosed with or treated for depression or postnatal depression since the birth of your baby?	Not included	Diagnosed: Yes/No Treated: Yes/No Q4d
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	All of the time; Most of the time; Some of the time; A little of the time; None of the time Q10	Same response Q5
During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all; A little bit; Moderately; Quite a bit; Extremely Q8	Not included

*** Not all of the original SF-36 questions are included in this list. All the questions shown in this list, except for the last original SF-36 question about pain, were included in the questionnaire administered in this study. Where the questionnaire response was the same this is indicated, and where the response differed from the original SF-36 wording the new responses were shown. The order in which the questions (e.g. Q1 as first question, or Q5b as question subset 5 second question) were administered in the original and modified questionnaires is shown.**

Figure 2a and b. Comparison of physical component scale of HRQoL scores in the IV plus oral iron versus the oral iron group, and separate association with iron status



† Comparison of the effect of IV plus oral iron versus oral iron on physical **(graph A on the left)** and mental **(graph B on the right)** components of the HRQoL scores at different time periods (before starting iron, 4 weeks after starting iron, at delivery and when the mother responded to questionnaire), estimated using ordinal logistic regression adjusted for significant demographic confounders but not including iron status, corrected for repeated measures and multiple comparisons (Holm method).

* The effect of iron status on PCS and MCS scores was estimated separately without including treatment group in the analysis.

Table 3. Effect of IV iron versus oral iron on rate of cessation of breast feeding

	HR[1]	95% CI	P-value
IV plus oral	0.70	(0.50 to 0.99)	0.046
Maternal age	0.76	(0.63 to 0.92)	0.006
Downheartedness	1.23	(1.00 to 1.52)	0.055
Current alcohol intake	1.34	(0.88 to 2.03)	0.18
Mode of delivery:			
NVD	1.00		
LSCS	1.24	(0.84 to 1.82)	0.29
Forceps	1.39	(0.85 to 2.27)	0.19

[1] **The likelihood of cessation of breast feeding in the IV plus oral iron group was compared with that of the oral iron only group: estimated using Cox proportional hazards regression corrected for repeated-measures and adjusted for the covariates shown, expressed as hazards ratios (95% confidence intervals; P-values). Covariates included in the final multivariate model were selected by stepwise regression. The standardized normal transformation of maternal age was used ({mother's age – group mean age}/ group standard deviation of age): mean age 28.1 ± 5.6 years.** Hazards ratio (HR) less than 1.00 indicates a slower rate of cessation of breast-feeding, whilst an HR greater than 1.00 indicates a faster rate of ceasing breast-feeding.

[2] Abbreviations: NVD – normal vaginal delivery; LSCS – lower segment caesarean section

Table 4. Association between the physical symptom questions[3] in from the prospective clinical monitoring questionnaire and the Physical Component Scale of the retrospective HRQoL for the four time periods.

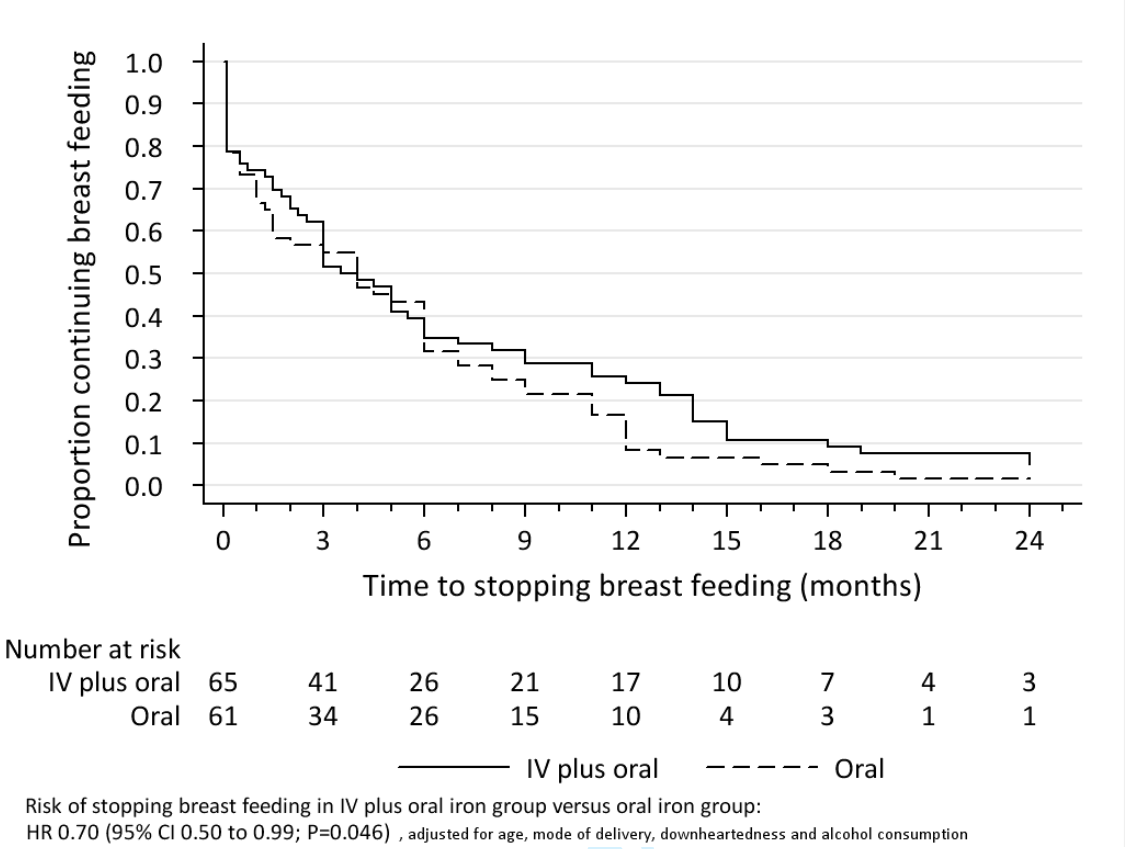
Time	Slope (SD)[1]	OR[2a]	95%CI	P-value	OR[2b]	95%CI	P-value
Pre-trial	2.67 (13.0) [1]	1.46	(1.01 to 2.11)	0.043	1.00		
4 weeks	8.07 (18.6)	3.18	(2.11 to 4.80)	<0.001	2.18	(1.44 to 3.28)	<0.001
Delivery	4.91 (12.2)	2.14	(1.37 to 3.35)	<0.001	1.46	(0.94 to 2.29)	0.10
Later	4.31 (14.1)	1.98	(1.28 to 3.08)	<0.001	1.36	(0.88 to 2.10)	0.17

1 The slope (standard deviation) of the association between the physical symptom questions in from the clinical monitoring questionnaire and the Physical Component Scale of the HRQoL for the four time periods was estimated by repeated measures general linear modeling for illustrative purposes only (mean index score at pre-trial was 74.3 of 100).

2 The strength of that [a)] absolute association at each time point, and [b)] the relative association at the other time points was compared to the pre-trial time point and was estimated using repeated measures ordered logistic regression, expressed as odds ratios (OR; 95% confidence intervals; P-values).

3 The scores for four questions were combined as a single index: Do you have energy? Do you feel fatigued or sleepy? Do you feel light-headed (dizzy)? Do you feel short of breath? Responses: Not at all; A little of the time; Sometimes; Most of the time; Always.

Figure 3. Effect of IV plus oral iron versus oral iron on rate of cessation of breast-feeding



Risk of stopping breast feeding in IV plus oral iron group versus oral iron group:
HR 0.70 (95% CI 0.50 to 0.99; P=0.046) , adjusted for age, mode of delivery, downheartedness and alcohol consumption

The difference arises in those women whose breast feeding duration is in the top 30% (70-80th centiles who breast-feed for at least 12 months, about 2 months longer {75th centile difference 2.25 months; 95% CI -2.79 to 7.30; P=0.38}), and particularly in the top 10% (who breast-feed for at least 15 months, about 6 months longer {90th percentile difference 6.22 months; 95% CI 0.36 to 12.1; P=0.038}).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page
Title and abstract	1	(*a*) The title is informative regarding the study design	1
		(*b*) Abstract was formulated as background and aims of the study, Patients and methods, results and conclusion.	3
Introduction			
Background/rationale	2	Scientific background and the rationale for the study were stated	5,6
Objectives	3	Aims and objective were mentioned	6
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	The setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	The outcomes, exposures, predictors, potential confounders, and effect modifiers are clearly mentioned.	8
Data sources/ measurement	8*	Each variable of interest data and details of methods of measurement was given. Comparability of assessment methods were explained	7,8
Bias	9	The authors declare no conflict of interest in relation with this study	1
Study size	10	The study size was explained	9
Quantitative variables	11	Variables were explained in the analyses	8,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Numbers of individuals at each stage of study were mentioned	9,10

		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10,11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-11
Discussion			
Key results	18	Key results with reference to study objectives were summarised	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**:1453-7

BMJ open

Three-year Follow-up of a Randomized-Controlled Study of Intravenous versus Oral Iron Therapy for Pregnancy Anaemia demonstrating that Intravenous Iron is Associated with Improved Maternal Quality of Life, Less Postnatal Depression and Longer Breastfeeding

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Secondary Subject Heading:	Haematology (incl blood transfusion), Public health, Qualitative research
Keywords:	Anaemia < HAEMATOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Maternal medicine < OBSTETRICS, QUALITATIVE RESEARCH

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Suppl_Tables.docm

Three-year Follow-up of a Randomized-Controlled Study of Intravenous versus Oral Iron Therapy for Pregnancy Anaemia demonstrating that Intravenous Iron is Associated with Improved Maternal Quality of Life, Less Postnatal Depression and Longer Breastfeeding

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Disclaimer: The authors declare no conflict of interest in relation to this research. There are non-financial associations that may be relevant or seen as relevant to the submitted manuscript.

ARTICLE SUMMARY

Article focus

- Health related quality of life assessment during and after pregnancy in 126 women with iron deficiency, who received either a single infusion of intravenous iron polymaltose followed by oral iron maintenance or oral iron only.
- Study of postnatal depression and its association with the treatment arms and iron status
- Assessment of breastfeeding duration and correlation to mothers' iron status

Key-Messages

- Health related quality of life is improved significantly in anaemic pregnant women by repletion of their iron stores during pregnancy.
- About 80% of the intravenous iron group showed a maintained normal ferritin until delivery with long-term benefits such as prolongation of the breast-feeding period and less postnatal clinical depression.
- There were strong associations between iron status and a number of the HRQoL scales with improved general health (P=0.021), improved physical energy (P=0.016), less psychological downheartedness (P=0.005), less clinical depression (P=0.003), and overall improved mental component scale (P<0.001). The duration of breastfeeding was longer (P=0.046) in women who received intravenous iron.

Strengths and limitations

- This study addresses a novel finding of a correlation between both postnatal depression and breast- feeding period with iron status.
- There is very limited data regarding quality of life measurement during and after pregnancy which makes the scientific input of the current study important, albeit the relatively small number of pregnant women studied.
- Limitations of our study include the modified questionnaire being in part a retrospective HRQoL evaluation which should ideally have been conducted within a shorter period of time.
- Further limitation is the relatively small number of women studied.

ABSTRACT

Background: To date there are no data available regarding the impact of intravenous versus oral iron on the wellbeing and health-related quality of life (HRQoL) of the mothers in particular with regards to postnatal depression and the duration of breast-feeding.

Objective: To assess long-term effect of iron therapy on HRQoL during pregnancy and in the post-natal period.

Design: We conducted a prospective, randomised-controlled, open-label trial of **intravenous and oral iron versus only oral iron** for pregnancy-related iron deficiency anaemia between March 2007 and January 2009 at the Launceston General Hospital, Tasmania, Australia. The follow up study was conducted between January 2010 and January 2011 using a modified version of the SF-36 questionnaire together with the original prospective HRQoL data collected during 2nd and 3rd trimesters of pregnancy as well as 6-8 weeks post delivery.

Participants and Interventions: Of the original evaluable 183 pregnant Caucasian women randomised to receive oral iron or a single intravenous iron polymaltose infusion followed by oral iron maintenance, 126 women completed the follow up HRQoL study.

Methods: The participants were followed up 4 weeks after initiation of treatment and pre-delivery, as well as post-delivery for a median period of 32 months (range, 26-42) with a well-being and health-related QoL questionnaire using a modified SF36 QoL-survey and child growth charts as set by the Australasian Paediatric Endocrine Group (APEG).

Results: Patients who received intravenous iron demonstrated significantly higher Hb and serum ferritin levels ($p<0.001$). There were strong associations between iron status and a number of the HRQoL scales with improved general health ($P<0.001$), improved vitality (physical energy) ($P<0.001$), less psychological downheartedness ($P=0.005$), less clinical depression ($P=0.003$), and overall improved mental component scale ($P<0.001$). The duration of breastfeeding was longer ($P=0.046$) in intravenous iron group. The babies born in both groups recorded similarly on APEG growth chart assessments.

Conclusion: Our data suggest that HRQoL is improved in anaemic pregnant women by repletion of their iron stores. About 80% of the intravenous iron group showed a maintained normal ferritin until delivery with long-term benefits and a minimal effect on their babies. Further studies to confirm these findings are warranted.

Trial registration: Australia and New Zealand Clinical Trial Registry under: http://www.ANZCTR.org.au under ACTRN 12609000177257 and in the World Health Organization website under: www.who.int/**trial**search/**trial**.aspx?**trial**id=ACTRN12609000596202.

Funding: This research received a grant from the Clifford Craig Medical Research Trust, Launceston, Tasmania, Australia.

Key words: Quality of life assessment, iron deficiency anaemia, oral iron, intravenous iron, pregnancy, long-term effect.

INTRODUCTION

There are no available data regarding quality of life assessment and long term effects of intravenous versus oral iron therapy during pregnancy. In addition to the physical impact of iron deficiency anaemia (IDA) on pregnant women,[1-3] IDA is a potential risk factor for preterm delivery and subsequent low birth weight and may be associated with inferior neonatal health.[3-4] Infants born to women with IDA are more likely to become anaemic themselves, which in turn is known to have a potential effect on an infant's mental and motor development.[5-9] Although iron supplementation during pregnancy is a widely practiced public health measure, there are some concerns regarding iron replacement therapy and its long-term effect, especially the intravenous form.[10,11] However, pregnant women do not always respond adequately to oral iron therapy due to difficulties associated with ingestion of the tablets and their side effects, impacting negatively on their compliance.[3,10,11]

In the past, intravenous iron had been associated with undesirable and sometimes serious side-effects limiting its use.[12] Recently, new type II iron complexes have been developed with the potential to reverse iron deficiency with less side effects than their predecessors.[12-14] Despite increasing evidence for the safety of the newer preparations in both pregnant and general populations, intravenous iron continues to be underutilised.[15]

The initial randomized controlled trial **(PMID: 20546462)** showed that intravenous iron polymaltose leads to improved efficacy and iron stores compared to oral iron alone in pregnancy-related IDA treatments (effect size for haemoglobin 6.6g/L {95% CI 3.4-9.8, p<0.001}; for ferritin 108 mg/L {95% CI 43-209, p<0.001}).[14] In the follow up trial using the same cohort of patients, we studied the effect of both iron therapies on the perceived health-related quality of life (HRQoL) as measured by a modified SF36 questionnaire. The effect of iron therapy on breastfeeding rates and on the general wellbeing of the babies born to these women was measured by child growth charts set by the Australasian Paediatric Endocrine Group (APEG).

PATIENTS AND METHODS

Rationale and objectives

We analysed HRQoL for our cohort of pregnant women prospectively during the original study at the baseline; prior to treatment in the second trimester, 4 weeks after initiation of treatment and in the third trimester pre delivery, as well as at 6-8 weeks post delivery. In the follow-up study, a HRQoL questionnaire was conducted incorporating the original questionnaire in addition to other parameters such as length of breastfeeding period and occurrence of postnatal depression as well as child growth data. This was performed at a median of 32 months post intervention in order to assess the long-term effect of both iron therapies on mothers' HRQoL in correlation with previous prospective data. This questionnaire, although performed prospectively, had a retrospective component which asked the participating mothers the same questions that they had previously answered prospectively about their QoL during and after pregnancy compared to the current questionnaire. These data were analysed against the mothers' original prospective QoL data for validation purposes.

The initial prospective randomised-controlled trial was conducted between March 2007 and January 2009 at the Launceston General Hospital (LGH), a tertiary referral centre for Northern Tasmania, Australia. This follow-up study took place between January 2010 and January 2011. An informed consent form was obtained from all participants according to the Code of Ethics. The original and the follow-up studies were approved by the Tasmanian Human Research Ethics Committee and registered in the Australia New Zealand Clinical Trials Registry under trial No**:** ACTRN12609000177257 with web addresses of the trial as follow: http://www.ANZCTR.org.au/ACTRN12609000177257.aspx and

the World Health Organization website under: www.who.int/**trial**search/**trial**.aspx?**trial**id=ACTRN12609000596202.

Participants

Pregnant women aged 18 years or above who presented to the LGH with IDA between 2007 and 2009 were invited to participate. In the original study (Figure 1), two hundred Caucasian pregnant women aged 18 years or above were identified with moderate IDA, defined as Hb ≤115 g/L (reference range (RR) 120-160 g/L) and low iron stores based on a serum ferritin level <30 µg/L (RR 30-440 µg/L).

Of the original evaluable 183 pregnant Caucasian women randomised to receive oral iron or a single intravenous iron polymaltose infusion, 126 women completed the QoL follow-up study (Table 1). The median age was 29 years at enrolment (range, 21 to 43); and the median follow up period was 32 months (range, 26 to 42) with an average follow-up period of 36 months post-delivery.

Randomisation and interventions

Informed consent was obtained by a research midwife. Treatment arm was randomised in blocks of 10 and assignment was performed by the LGH Pharmacy Department in order to avoid any possible bias. The oral-only treatment arm comprised iron sulphate 250 mg tablets, (elemental iron 80 mg, Abbott, Australasia Pty Ltd) to be taken daily within two days after booking until delivery. The IV arm required a single intravenous infusion of iron polymaltose (Ferrosig, Sigma Pharmaceuticals, Australia) within 1 week after booking followed by oral iron identical to the other arm. Pre-enrolment, there were no significant differences in the dietary iron intake or supplement intake between the two groups based on a specially-designed questionnaire addressing these issues. Patients assigned to IV iron polymaltose received a 100 mg test-dose dissolved in 50 ml normal saline infused over 30 minutes. Clinical observation and vital signs were assessed initially and every 15 min from the start of

the infusion. After the test-dose was tolerated, the remaining of iron polymaltose dose was infused. The total dose of IV iron polymaltose was calculated according to the patient's body weight at their first antenatal visit and entry Hb level according to the product guidelines; iron dose in mg (50 mg per 1 ml) = body weight (maximum 90) in kg x target Hb (120 g/L) - actual Hb in g/L) x constant factor (0.24) + iron depot (500).[14]

Outcome measurement

Two Health-Related Quality of Life (HRQoL) questionnaires were administered during the initial and follow-up studies: Firstly, a clinical questionnaire was completed prospectively by trained midwives at 4 weeks after initiation of treatment, at 28 and 34 weeks gestation, and then 6-8 weeks post delivery. This questionnaire assessed four aspects; energy levels, activity, tolerance and side effects of treatment, and was used to guide individual patient clinical decision-making as well as providing a safety audit of the trial treatments.[14] Secondly, a prospective/retrospective survey was conducted between June and October 2010 by trained research personnel via phone interview using a modified version of the SF-36 questionnaire.[16,17] These modifications included: (1) use of eleven of the 36 questions (Table 2); and (2) the women were asked to recall their response to each of the questions for four time points, pre-trial prior to commencement of iron therapy during the pregnancy, four weeks after starting iron therapy, one week after delivery, and the last four weeks prior to the telephone questionnaire contact (Table 2). This has been compared in retrospect to the same questions answered prospectively by the participants at these different times. In order to validate the retrospective use of the modified SF-36 to assess the women's HRQoL during and after pregnancy, the associations of the physical activity component of the prospective monitoring questionnaire following entry into the trial with the Physical Component Scale values of the modified SF-36 at each of the time points were estimated. We hypothesized that the association would be greatest at 4 weeks compared to trial entry,

time of delivery or at the time of questionnaire completion. In addition, data regarding breastfeeding and the health of the woman's child were collected from the baby's growth booklet. This included breastfeeding duration, baby gender, age, weight, and previous hospitalization, if any, in addition to the baby's sleep quality since birth and specific growth data for the children as set by the Australasian Paediatric Endocrine Group (APEG). Haemoglobin and ferritin levels for participants at delivery were available for all participants, however no further testing was performed during the follow up. The principal investigators, including the statistician, evaluated the questionnaire results data.

Statistical methods

The HRQoL scores that form the raw data for this analysis are rank-order in nature. Means and standard deviations of the scores were estimated using generalized estimating equations for illustrative purposes only. Physical and mental composite scores were calculated in the modified SF36 according to the SF-12 scoring guidelines.[16,17] Group comparison and covariate effect size calculation, odds ratios (OR with 95% confidence intervals and P values) were estimated using repeated measures of ordinal logistic regression, with covariates selected for inclusion by backward stepwise regression (P for exclusion 0.22) from maternal age, haemoglobin, ferritin, Socio-Economic Indexes for Areas (SEIFA; based on the Collector District of residence of mothers), quality of sleep, use and duration of breast-feeding, hospitalization of baby, baby gender and mode of delivery. This included randomization group covariate interactions in the starting model with exclusion of those interactions using the above criteria. When iron status was selected for inclusion in the model, the association between iron status (ferritin) and HRQoL was reported independently of trial treatment group. P values were corrected for multiple comparisons where necessary by the Holm method. The effect of IV iron versus oral iron on time of cessation of breastfeeding was compared by estimation of hazard ratio (HR; 95% confidence intervals and P-values) by Cox proportional hazards regression adjusted for covariates selected for inclusion by backward stepwise regression (P for exclusion 0.22). The time

to cessation of breast-feeding was taken from the subject's baby growth booklet for all participants. Neonatal growth in the treatment groups was compared by multivariate third-order polynomial regression as an approximation to APEG growth assessment. All HRQoL statistical analyses were performed using Stata SE for Windows 11.1 (StataCorp, College Station, Tx USA).

RESULTS

Of the original 196 patients randomised to receive the trial medications (98 received IV plus oral iron; 98 received oral iron only), 183 patients completed the trial by the collection of blood for iron status estimation at the time of delivery. Data of HRQoL were collected from 126 of the 183 women who completed the original trial, representing 69% of the cohort who completed the trial, while 57 (31%) of the 183 patients had moved away, were uncontactable or did not respond to the researcher messages (see Figure 1 for description of patient flow). Basic demographic data of those patients included in the follow-up study showed that the median age was 29 years at enrolment (range, 21 to 43); and the median follow up was 32 months (range, 26 to 42) post-delivery. There were no significant differences in demographic or iron status measurements between any of the groups of women recruited to the trial. All pregnant women recruited in this study were Caucasians.

As reported in the original study (PMID: 20546462), at delivery the proportion of women with lower than normal ferritin levels was 53 of 67 (79%) for women with analysable iron status measurements who were treated with oral iron as compared to 3 of 66 (4.5%) for women who received IV iron (Fisher's exact $p<0.001$). The pre-treatment mean serum ferritin levels were low in both groups at 17 µg/L. However, the serum ferritin of those in the IV iron group increased markedly within four weeks of the IV therapy with 222 µg/L; 95% CI 194 to 249 µg/L ($p<0.001$). This substantial improvement was maintained after delivery with an increase of 108 µg/L; 95% CI 43 to 209 µg/L ($p<0.001$).[14] On the other hand the ferritin level did not show a significant increase in the oral iron group through

pregnancy and after delivery. Furthermore, the percentage of women at delivery with Hb level <116 g/L was 29% (25 of 85) in the oral iron group versus 16% (14 of 87) in the IV iron group (p=0.04) incidence rate ratio 0.55 (95% CI 0.31 to 0.98; p=0.043). After delivery, the mean Hb levels declined to 111.6 g/L (SD 14.2) in the oral iron versus 115.5 g/L (SD 10.8) in the IV iron group. This showed a continuing favourable effect of IV iron therapy of 5.8 g/L (95% CI 2.5 to 9.1; p=0.004) despite the blood loss of delivery.[14]

There were no significant differences in the birth weights of the babies in the two treatment groups with an average birth weight of 3.42 kg in both groups with a difference of 0.03 kg (p=0.77). There were also no differences in the gestational age at delivery in both treatment groups with mean of 39.1 weeks in the oral iron versus 38.9 weeks with only a slight difference of 0.2 weeks (p=0.74). There were no significant differences in placental cord Hb or ferritin levels in both treatment groups. The mean cord Hb was 165g/L (SD 9.6) in the oral iron group versus 157g/L (SD 14.1) in the IV iron group (difference -7; 95% CI -18 to 3; p=0.17). In the meantime the ferritin levels were 142 µg/L (SD 86) and 185 µg/L (SD 101) respectively (difference 43; 95% CI -59 to 145; p=0.41).

The HRQoL Physical Component Scale (difference 10.3; 95% CI 3.3 to 17.2; P=0.27; OR 2.39; 95% CI 1.32 to 4.32; P=0.004) and General Health (difference 15.1; 95% CI 6.0 to 24.2; P=0.31; OR 3.14; 95% CI 1.57 to 6.26; P=0.001) responses were improved in the IV compared to the oral iron group, but these differences became less apparent at subsequent assessment time points (Figure 2a and b).

Furthermore, there were strong associations between the level of iron status, independent of how that iron status was achieved, and a number of the HRQoL scales (Figure 2): notably improved General Health (slope {1SD log.-ferritin} 10.0; 7.2 to 12.7; P<0.001; OR 1.49; 95% CI 1.09 to 2.03; P=0.021), improved Vitality (slope {1SD log.-ferritin} 10.0; 7.3 to 12.8; P<0.001; OR 2.09; 95% CI 1.66 to 2.62; P<0.001), less Psychological Downheartedness ({1SD haemoglobin} OR 1.57; 95% CI 1.14 to

2.15; P=0.005), less Clinical Depression ({1SD log.-ferritin} OR 2.05; 95% CI 1.27 to 3.32; P=0.003), and overall improved Mental Component Scale (slope {1SD haemoglobin} 3.8; 2.5 to 5.0; P<0.001; OR 1.71; 95% CI 1.39 to 2.10; P<0.001)(Psychological Downheartedness and Clinical Depression analysis used raw scores rather than 100-point scales).

There was an increased duration of breastfeeding (HR for cessation was 0.70; 95% CI 0.50 to 0.99; p=0.046) in women in the IV iron group (Figure 3) where older women were more likely to breast feed longer (HR 0.76; 95% CI 1.00 to 1.52; P=0.006) (Table 3). Earlier cessation of breastfeeding was associated with downheartedness (HR 1.23; 95% CI 1.00 to 1.52; P=0.06). There was no difference between the oral iron or IV plus oral iron groups in the weight of the baby at birth (p=0.64), and no difference in the rate of weight gain (p=0.90).

The association between the physical symptom questions index from the clinical monitoring questionnaire and the Physical Component Scale of the HRQoL for the four time periods is shown in Table 4. There was significant association between the physical symptom questions index at 4 weeks after trial entry and each of the HRQoL recall time points, and that the association was strongest for the 4 weeks recall (OR 3.18; 2.14 to 4.74; P<0.001).

DISCUSSION

There are no data available studying the effects of both IV and oral iron on post-delivery psychological and physical welfare of the mother, the quality of the bonding to her baby and the rate of developmental progress of the baby. We are reporting on 126 patients in a follow up study of the effect of IV iron versus oral iron therapy on HRQoL during and after pregnancy. Our study demonstrates that there was an improvement in the self-assessed feeling of general health in both treatment groups from the pre-labour period to all subsequent periods. Although the improvement was significantly greater during pregnancy in the IV iron group 4 weeks after commencement of trial treatment (p=0.001), the difference persisted in the subsequent measurement periods at a lesser magnitude that did not achieve a statistical significance.

Regardless of treatment and regardless of which period was being considered, higher haemoglobin and higher ferritin levels were associated with better baby sleep quality, a longer period of breastfeeding and a higher benefit to the mother's general health.

The modified HRQoL questionnaire used in our study includes many useful and relevant aspects regarding general health, daily activities, levels of energy and depression. There was a substantial improvement of iron status in women who received IV iron compared to oral iron as demonstrated during the trial analysis (p<0.001). Limitations of our study include the modified questionnaire being in part a retrospective HRQoL evaluation which should ideally have been conducted within a shorter period of time. However, a correlation to a prospective evaluation of the studied subjects has been made in our study in order to overcome a possible recall bias. Therefore, the number of retrospective questions could be abbreviated, since the women were asked to recall their responses to each question at four different time points, so the full SF-36 was impractical and may have been judged to be an excessive burden on the women. Thus, we attempted to provide a retrospective form of validation by showing that the clinical HRQoL questions in the physical domain, recorded prospectively at week 4

after trial, were most strongly associated with the Physical Component Scales of the recall of modified SF-36 at week 4 compared to the other time points. This indicates that the retrospective methodology was able to provide an acceptable degree of accuracy in the differentiation of HRQoL levels at different time points despite the concerns that may have arisen with this issue. The assumption being made is that the way those patients judge their physical and mental condition will be relatively stable over time,[18] an assumption with which we agree may occur in patients with chronic diseases. However, this assumption may not hold for women during and after pregnancy. The expectations by the woman about how she should be feeling at the different stages of pregnancy, around the time of delivery, and when she is caring for one or more young infant or child may differ substantially at those different time points. At least in our analysis the judgment the woman is making about how to answer the questions is likely to be the same for each time point, since she had made that judgment at one point in time: the repeated measures analysis compares each woman with herself, thus substantially reducing the impact of variation between women in this judgment. Thus, for the purpose of generating a hypothesis concerning iron status and quality of life, we believe that our methodology has been adequate. Another limitation of our study was the relatively small number of women studied. However, it is worthwhile publishing our study due to lack of research that addresses HRQoL during and after pregnancy, particularly, in view of the emerging novel association between iron status and postnatal clinical depression as well as breastfeeding duration in our cohort of patients.

Regarding the incidental findings of the trend for unfavourable mental health component outcomes for women with male babies, there is only a single report in the literature addressing this issue with similar findings.[19] Perhaps this may be explained with the observation that male babies are usually more active and this may be associated with post natal depression.[19] However, due to lack of data, this issue should be addressed separately and studied thoroughly in future research.

Due to paucity of data regarding HRQoL during and after pregnancy, there are only very limited data available. Jansen *et al* studied the effect of delivery and postpartum changes on the HRQoL.[20] A cohort of 141 pregnant women were included in that study. HRQoL questionnaires were measuring the immediate effect of delivery on the quality of life. The HRQoL questionnaires were conducted less than 1 day after vaginal delivery and less than two days after delivery by caesarean section and compared to 3-6 weeks post delivery for both groups.[20] The study focused on patient's HRQoL recovery after both delivery interventions. In this study[20], the different time-points of conduction of the questionnaire may not necessarily reflect the HRQoL during pregnancy and subsequently after the postpartum period. Furthermore, the immediate questionnaire after delivery and 3-6 weeks time during the post-partum period may be at least, in theory, influenced by the event of delivery, in particular if complications occur, as well as the possible emotional and hormonal fluctuations during this period. It is worthwhile noting that the same study did not show association with Hb and QoL, however it did not investigate a possible effect of iron status on perceived HRQoL in conjunction with breastfeeding. This highlights our novel finding of the correlation between iron status and improved HRQoL during and after pregnancy.

In summary, there was a significant improvement in the general health of women who received IV iron ($p<0.001$), but this effect was found prominently 4 weeks after the IV iron treatment. The duration of breast-feeding was longer ($p=0.04$) in those women who had received IV iron. Women with better iron status were less downhearted ($p=0.005$) and less likely to develop postnatal clinical depression ($p=0.003$).

Our results would indicate that it is worthwhile considering Hb and iron status as a surrogate marker for assessment of women's wellbeing, not only during pregnancy, but also during the postnatal period.

Further studies are warranted to confirm and extend our findings, and to determine outcomes in different populations with IDA in order to improve the estimates of the magnitude of the benefits of intravenous iron for the management of iron deficiency anaemia.

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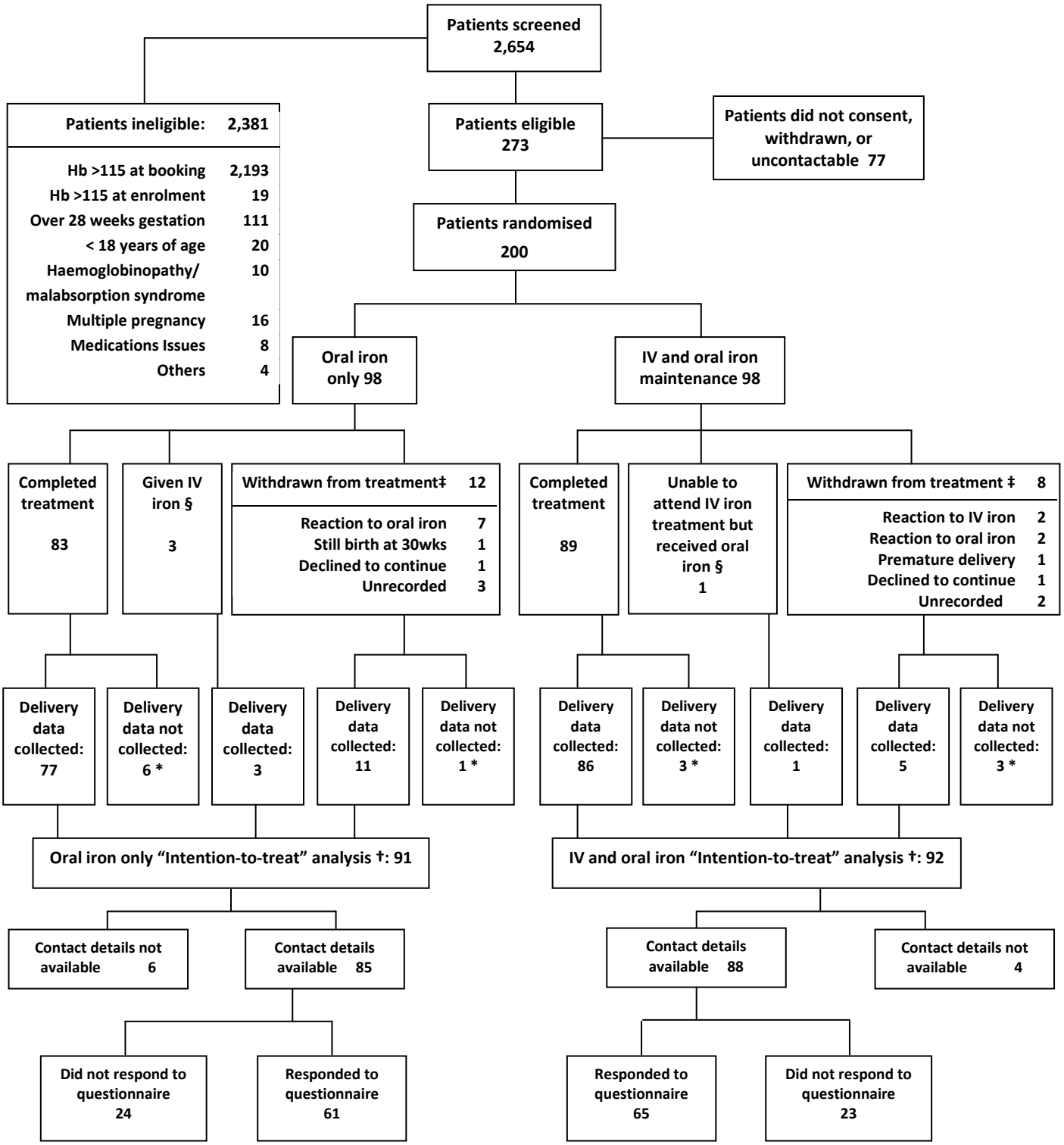
Figure 1. Trial flow diagram: disposition of study participants by treatment assignment.



Footnotes to Figure 1. Patients Flow Chart.

* Fourteen patients were admitted late in labour, and no blood samples were taken before delivery

† The primary hypothesis examined the change in haemoglobin levels between the time of booking and immediately prior to delivery; an "intention-to-treat" analysis was performed according to original randomization group on those patients who had blood samples taken before delivery, whether or not the treatment was completed as per protocol

‡ Twenty one patients withdrew from the trial treatments, and all but one of these patients agreed to continued collection of haematological and other trial data; eight patients gave no reason for withdrawal

§ Five patients did not complete the intended treatments, but did not themselves choose to withdraw; three patients in the oral iron group were treated with IV iron when their haemoglobin was judged not to have responded adequately to oral iron, whilst one patient was unable to attend for IV iron treatment

Table 1. Patients Characteristics

	IV iron group	**Oral iron group**
No of patients	64	62
Vaginal delivery	45	46
Caesarean section	19	16
Median age in years	28 years (range; 21-43)	28.5 years (Range; 22-42)
Mean age in years	27.5 years	28
Median time between trial intervention and delivery in months	2.7 months (range; 2.6-6)	2.8 months (range; 2.2-5.3)
Median time of follow-up in months	28 months	29 months
Baby birth weight in grams	Median 3523 g(range; 1315-4920)	Median 3480g (range; 1330-4928)
Median Initial Hb	105 g/L	108 g/L
Median Hb after intervention and prior to delivery	128 g/L	118 g/L
Median Hb post-delivery	118 g/L (range; 86-146)	112 g/L (range; 78-137)
Blood transfusion requirement	None	Two patients

Table 2. Comparison of the questions in the SF-36 and the abbreviated HRQoL questionnaire used in this study.

*Questionnaires	Original SF-36	Modified short-HRQoL
Time specified for subject response	Either in at the time of analysis or in past 4 weeks	Evaluated at four time periods: before treatment; after 4 weeks of treatment; after delivery; and during the past 4 weeks
Question: stem and detailed item	**Response and Question number:**	**Response and Question number:**
In general, would you say your health is:	Excellent; Very good; Good; Fair; Poor Q1	Same response Q1
The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	Yes, limited a lot Yes, limited a little No, not limited at all	Same response
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	Q3b	Q2a
Climbing several flights of stairs	Q3d	Q2b
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	Same response
Accomplished less than you would like	Q4b	Q3a
Were limited in the kind of work or other activities	Q4c	Q3b
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	Same response
Accomplished less than you would like	Q5b	Q6a
Did work or other activities less carefully than usual	Q5c	Q6b
Have you felt calm and peaceful?	Q9d	Q4a
Did you have a lot of energy?	Q9e	Q4b
Have you felt downhearted and depressed?	Q9f	Q4c
Have you been diagnosed with or treated for depression or postnatal depression since the birth of your baby?	Not included	Diagnosed: Yes/No Treated: Yes/No Q4d
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	All of the time; Most of the time; Some of the time; A little of the time; None of the time Q10	Same response Q5
During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all; A little bit; Moderately; Quite a bit; Extremely Q8	Not included

*** Not all of the original SF-36 questions are included in this list. All the questions shown in this list, except for the last original SF-36 question about pain, were included in the questionnaire administered in this study. Where the questionnaire response was the same this is indicated, and where the response differed from the original SF-36 wording the new responses were shown. The order in which the questions (e.g. Q1 as first question, or Q5b as question subset 5 second question) were administered in the original and modified questionnaires is shown.**

Figure 2a and 2b. Comparison of physical component scale of HRQoL scores in the IV plus oral iron versus the oral iron group, and separate association with iron status

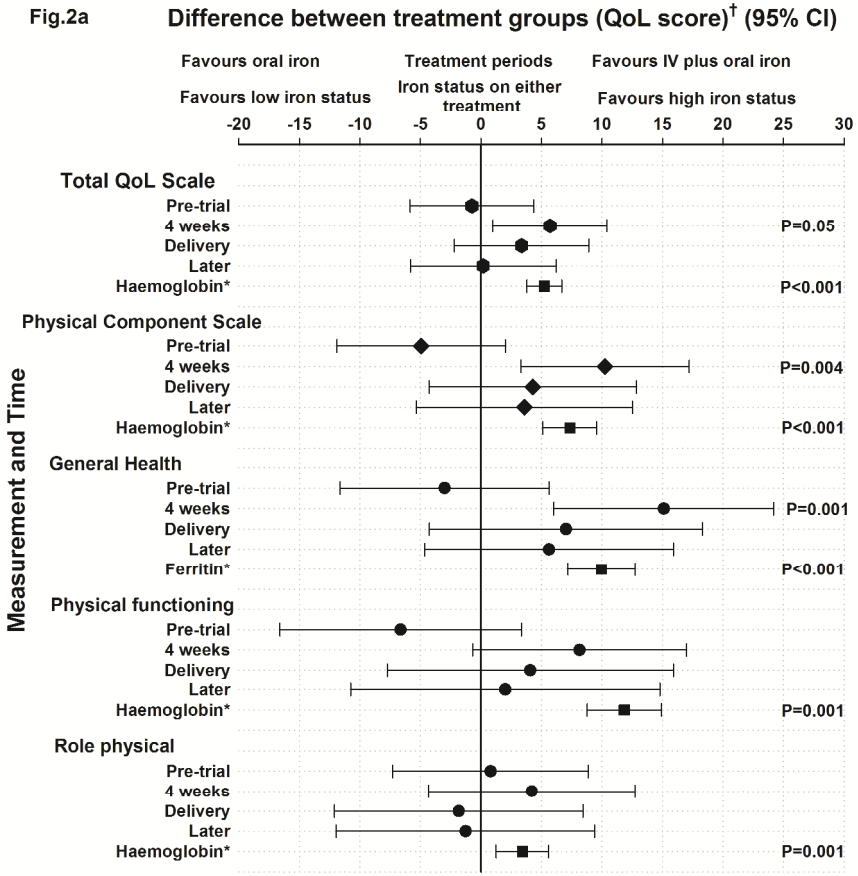
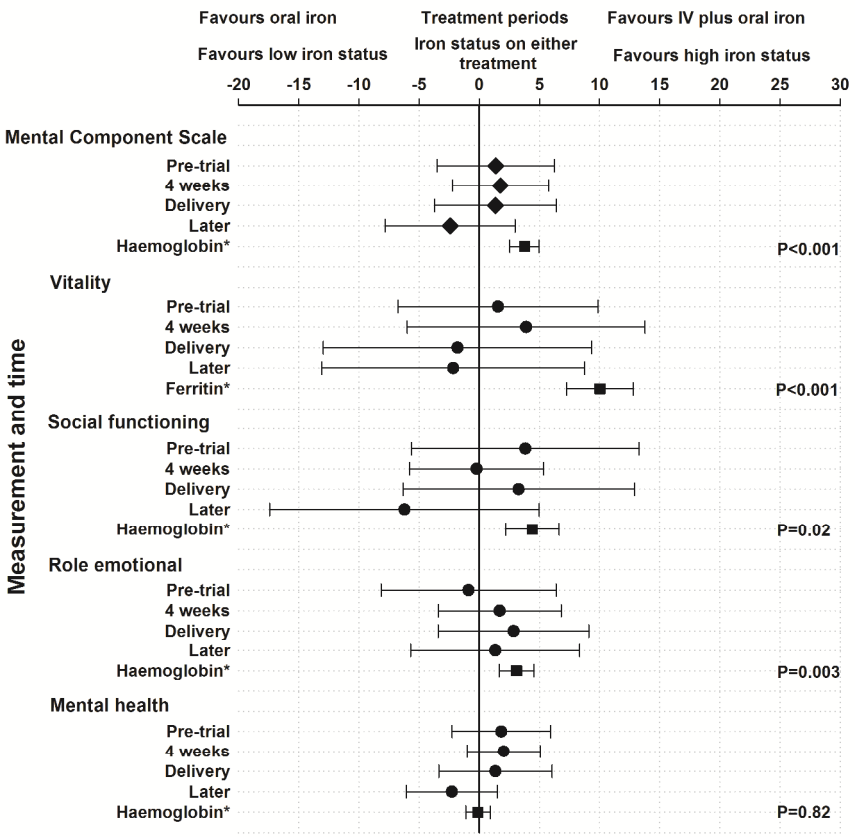


Fig.2b Difference between treatment groups (QoL score)† (95% CI)



† Comparison of the effect of IV plus oral iron versus oral iron on physical **(Figure 2a)** and mental **(Figure 2b)** components of the HRQoL scores at different time periods (before starting iron, 4 weeks after starting iron, at delivery and when the mother responded to questionnaire), estimated using ordinal logistic regression adjusted for significant demographic confounders but not including iron status, corrected for repeated measures and multiple comparisons (Holm method).

* The effect of iron status on PCS and MCS scores was estimated separately without including treatment group in the analysis.

Table 3. Effect of IV iron versus oral iron on rate of cessation of breast feeding

	HR[1]	95% CI	P-value
IV plus oral	0.70	(0.50 to 0.99)	0.046
Maternal age	0.76	(0.63 to 0.92)	0.006
Downheartedness	1.23	(1.00 to 1.52)	0.055
Current alcohol intake	1.34	(0.88 to 2.03)	0.18
Mode of delivery:			
NVD	1.00		
LSCS	1.24	(0.84 to 1.82)	0.29
Forceps	1.39	(0.85 to 2.27)	0.19

[1] **The likelihood of cessation of breast feeding in the IV plus oral iron group was compared with that of the oral iron only group: estimated using Cox proportional hazards regression corrected for repeated-measures and adjusted for the covariates shown, expressed as hazards ratios (95% confidence intervals; P-values). Covariates included in the final multivariate model were selected by stepwise regression. The standardized normal transformation of maternal age was used ({mother's age – group mean age}/ group standard deviation of age): mean age 28.1 ± 5.6 years.** Hazards ratio (HR) less than 1.00 indicates a slower rate of cessation of breast-feeding, whilst an HR greater than 1.00 indicates a faster rate of ceasing breast-feeding.

[2] Abbreviations: NVD – normal vaginal delivery; LSCS – lower segment caesarean section

Table 4. Association between the physical symptom questions[3] in from the prospective clinical monitoring questionnaire and the Physical Component Scale of the retrospective HRQoL for the four time periods.

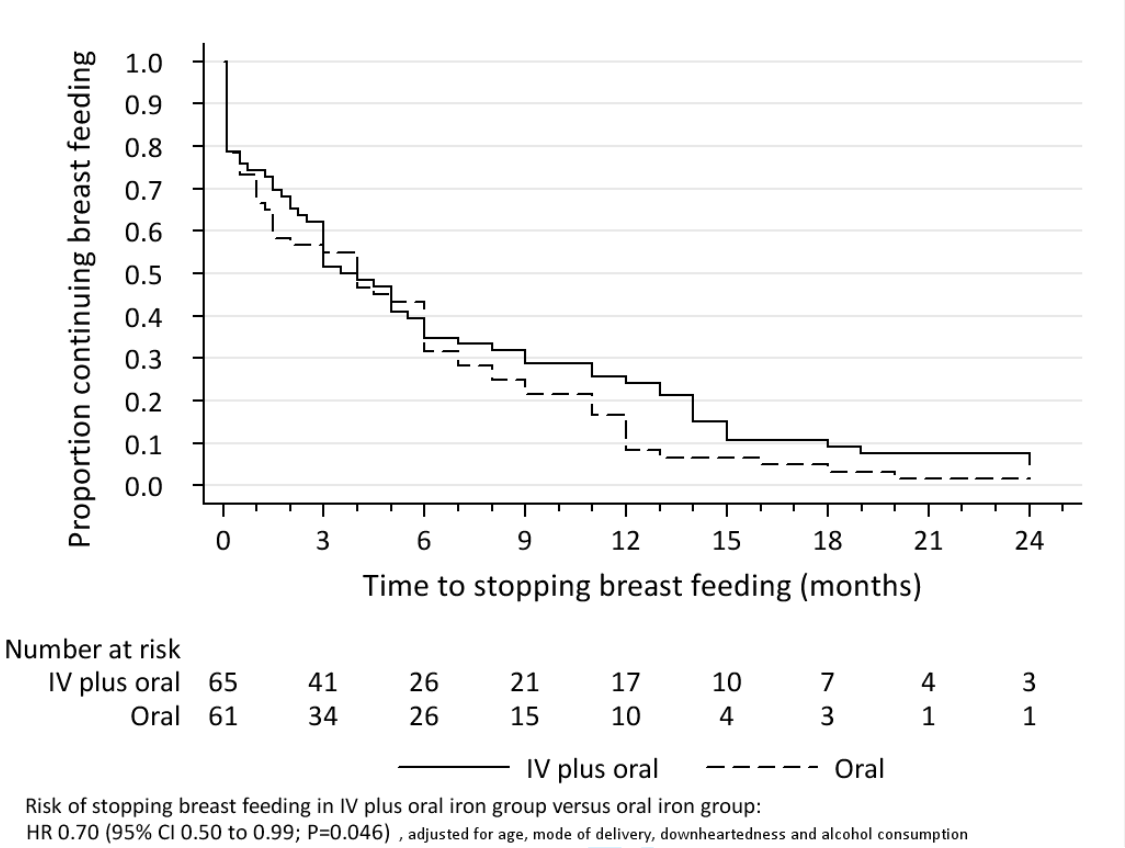
Time	Slope (SD)[1]	OR[2a]	95%CI	P-value	OR[2b]	95%CI	P-value
Pre-trial	2.67 (13.0) [1]	1.46	(1.01 to 2.11)	0.043	1.00		
4 weeks	8.07 (18.6)	3.18	(2.11 to 4.80)	<0.001	2.18	(1.44 to 3.28)	<0.001
Delivery	4.91 (12.2)	2.14	(1.37 to 3.35)	<0.001	1.46	(0.94 to 2.29)	0.10
Post-delivery	4.31 (14.1)	1.98	(1.28 to 3.08)	<0.001	1.36	(0.88 to 2.10)	0.17

1 The slope (standard deviation) of the association between the physical symptom questions in from the clinical monitoring questionnaire and the Physical Component Scale of the HRQoL for the four time periods was estimated by repeated measures general linear modeling for illustrative purposes only (mean index score at pre-trial was 74.3 of 100).

2 The strength of that [a)] absolute association at each time point, and [b)] the relative association at the other time points was compared to the pre-trial time point and was estimated using repeated measures ordered logistic regression, expressed as odds ratios (OR; 95% confidence intervals; P-values).

3 The scores for four questions were combined as a single index: Do you have energy? Do you feel fatigued or sleepy? Do you feel light-headed (dizzy)? Do you feel short of breath? Responses: Not at all; A little of the time; Sometimes; Most of the time; Always.

Figure 3. Effect of IV plus oral iron versus oral iron on rate of cessation of breast-feeding



Risk of stopping breast feeding in IV plus oral iron group versus oral iron group:
HR 0.70 (95% CI 0.50 to 0.99; P=0.046) , adjusted for age, mode of delivery, downheartedness and alcohol consumption

The difference arises in those women whose breast feeding duration is in the top 30% (70-80th centiles who breast-feed for at least 12 months, about 2 months longer {75th centile difference 2.25 months; 95% CI -2.79 to 7.30; P=0.38}), and particularly in the top 10% (who breast-feed for at least 15 months, about 6 months longer {90th percentile difference 6.22 months; 95% CI 0.36 to 12.1; P=0.038}).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page
Title and abstract	1	(*a*) The title is informative regarding the study design	1
		(*b*) Abstract was formulated as background and aims of the study, Patients and methods, results and conclusion.	3
Introduction			
Background/rationale	2	Scientific background and the rationale for the study were stated	5,6
Objectives	3	Aims and objective were mentioned	6
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	The setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	The outcomes, exposures, predictors, potential confounders, and effect modifiers are clearly mentioned.	8
Data sources/ measurement	8*	Each variable of interest data and details of methods of measurement was given. Comparability of assessment methods were explained	7,8
Bias	9	The authors declare no conflict of interest in relation with this study	1
Study size	10	The study size was explained	9
Quantitative variables	11	Variables were explained in the analyses	8,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Numbers of individuals at each stage of study were mentioned	9,10

		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10,11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-11
Discussion			
Key results	18	Key results with reference to study objectives were summarised	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**:1453-7

Three-year Follow-up of a Randomized Clinical Trial of Intravenous versus Oral Iron for Anaemia in Pregnancy

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Three-year Follow-up of a Randomized Clinical Trial of Intravenous versus Oral Iron for Anaemia in Pregnancy

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ARTICLE SUMMARY

Article focus

- Health-related quality of life (HRQoL) assessment during and after pregnancy in 126 women with iron deficiency who received either a single infusion of intravenous iron polymaltose followed by oral iron maintenance or oral iron only.
- Study of postnatal depression and its association with treatment arms and iron status.
- Assessment of breastfeeding duration and correlation to mothers' iron status.

Key-Messages

- HRQoL during and after pregnancy is improved significantly in anaemic pregnant women by repletion of their iron stores during pregnancy.
- About 80% of the intravenous iron group showed a maintained normal ferritin until delivery with long-term benefits such as prolongation of the breastfeeding period and less postnatal clinical depression.
- There were strong associations between iron status and a number of the HRQoL scales with improved general health (P=0.021), improved physical energy (P=0.016), less psychological downheartedness (P=0.005), less clinical depression (P=0.003), and an overall improved mental component scale (P<0.001). The duration of breastfeeding was longer (P=0.046) in women who had received intravenous iron.

Strengths and limitations

- This study reports a novel finding in terms of a correlation between both postnatal depression and the breastfeeding period with iron status.
- There are limited data available concerning the quality of life during and after pregnancy, which makes the scientific input of the current study important.
- Limitations of our study include that the modified questionnaire was in part a retrospective HRQoL evaluation, and this should ideally have been prospectively conducted.
- Another limitation is the relatively small number of women studied.

ABSTRACT

Background: To date, there are no data available concerning the impact of iron therapy on the long-term wellbeing and health-related quality of life (HRQoL) in pregnancy.

Objective: To assess the long-term effect of iron therapy on HRQoL in pregnancy.

Design: This is a follow-up study conducted between January 2010 and January 2011 of an earlier randomised open-label clinical trial of intravenous and oral iron versus oral iron for pregnancy-related iron deficiency anaemia. We used a modified version of the SF-36 questionnaire together with the original prospective HRQoL data collected during and after pregnancy.

Participants and Interventions: Of the original evaluable 183 pregnant Caucasian women randomised to receive oral iron or a single intravenous iron polymaltose infusion followed by oral iron maintenance, 126 women completed the follow up HRQoL study.

Methods: The participants were followed-up 4 weeks after treatment, pre-delivery, and post-delivery for a median period of 32 months (range, 26-42) with a wellbeing and HRQoL questionnaire using a modified SF-36 QoL-survey and child growth charts as set by the Australasian Paediatric Endocrine Group (APEG).

Results: Patients who received intravenous iron demonstrated significantly higher haemoglobin and serum ferritin levels ($p<0.001$). There were strong associations between iron status and a number of the HRQoL parameters, with improved general health ($P<0.001$), improved vitality (physical energy) ($P<0.001$), less psychological downheartedness ($P=0.005$), less clinical depression ($P=0.003$), and overall improved mental health ($P<0.001$). The duration of breastfeeding was longer ($P=0.046$) in the intravenous iron group. The babies born in both groups recorded similarly on APEG growth chart assessments.

Conclusion: Our data suggest that HRQoL is improved until after pregnancy in anaemic pregnant women by repletion of their iron stores during pregnancy. About 80% of the intravenous iron group showed a maintained normal ferritin until delivery with long-term benefits. Further studies to confirm these findings are warranted.

Trial registration: Australian New Zealand Clinical Trial Registry (http://www.ANZCTR.org.au) under ACTRN 12609000177257 and in the World Health Organization Clinical Trials Registry (http://www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202).

Funding: This research received a grant from the Clifford Craig Medical Research Trust, Launceston, Tasmania, Australia.

Key words: Quality of life assessment, iron deficiency anaemia, oral iron, intravenous iron, pregnancy, long-term effect.

Short title: Quality of life in pregnancy

INTRODUCTION

Currently, there are no data available concerning quality of life outcomes and other long-term effects of intravenous versus oral iron therapy of anaemia during pregnancy. In addition to the physical impact of iron deficiency anaemia (IDA) on pregnant women,[1-3] IDA is a potential risk factor for preterm delivery and subsequent low birth weight, and may be associated with inferior neonatal health.[3-4] Infants born to women with IDA are more likely to become anaemic themselves, which in turn is known to have a potential effect on an infant's mental and motor development.[5-9] Although iron supplementation during pregnancy is a widely practised public health measure, there are some concerns regarding iron replacement therapy and its long-term effect, especially the intravenous form.[10,11] Therapeutic response to oral iron therapy is not always adequate in pregnant women, due to difficulties associated with oral intake of the tablets and their side effects, which impacts negatively on compliance.[3,10,11]

In the past, intravenous iron was associated with undesirable and sometimes serious side effects that limited its use.[12] Recently, new type II iron complexes have been developed with the potential to reverse iron deficiency with less side effects than their predecessors.[12-14] Despite increasing evidence for the safety of the newer preparations in both pregnant and general populations, intravenous iron continues to be underutilised.[15]

Earlier, we reported on a randomised controlled trial (PMID: 20546462) of intravenous (IV) followed by oral iron therapy versus oral iron therapy only for moderate iron deficiency anaemia in pregnancy.[14] The results of the earlier analysis showed that intravenous iron polymaltose was associated with greater improvements in haemoglobin levels and iron stores compared to oral iron alone in pregnancy-related IDA.[14] Here, we report the results of a follow-up assessment of the same cohort of patients. We studied the effects of both treatment types on the perceived health-related quality of life (HRQoL) as measured by a modified SF-36 questionnaire. The effect of iron therapy on

breastfeeding rates and on the general wellbeing of the babies born to these women was measured by child growth charts set by the Australasian Paediatric Endocrine Group (APEG).

PATIENTS AND METHODS

Rationale and objectives

An initial prospective randomised controlled trial was conducted between March 2007 and January 2009 at the Launceston General Hospital (LGH), a tertiary referral centre for Northern Tasmania, Australia. The initial study assessed haemoglobin and serum ferritin levels after IV followed by oral iron therapy versus oral iron therapy only. The current study constitutes a follow-up on the earlier one and took place between January 2010 and January 2011 and focussed on HRQoL, breastfeeding duration and child health. Informed consent was obtained from all participants in accordance with the Declaration of Helsinki. The original and the follow-up studies were approved by the Tasmanian Human Research Ethics Committee and registered in the Australian New Zealand Clinical Trials Registry (http://www.ANZCTR.org.au/ACTRN12609000177257.aspx) and the World Health Organization Clinical Trials Registry (http://www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202).

In the original study, we prospectively assessed HRQoL at baseline prior to treatment in the second trimester, 4 weeks after initiation of treatment, in the third trimester before delivery, and at 6-8 weeks post delivery. In the follow-up study, a HRQoL questionnaire was completed that incorporated the original questionnaire plus additional parameters such as the length of the breastfeeding period and occurrence of postnatal depression as well as child growth data. This was performed at a median of 32 months post intervention in order to assess the long-term effects of both treatment types on mothers' HRQoL in relation to data from the earlier study. This questionnaire, although completed

prospectively, had a retrospective component that asked the participating mothers the same questions again that they had previously answered prospectively. These data were compared with the mothers' original prospective QoL data for validation purposes.

Participants

Pregnant women aged 18 years or above who presented to the LGH with IDA between 2007 and 2009 were invited to participate. In the original study (Figure 1), 196 Caucasian pregnant women aged 18 years or above were identified who had moderate IDA, defined as haemoglobin (Hb) ≤115 g/L (reference range (RR) 120-160 g/L), and low iron stores, based on serum ferritin levels <30 µg/L (RR 30-440 µg/L).

Of the original evaluable 183 pregnant Caucasian women randomised to receive oral iron or a single intravenous iron polymaltose infusion, 126 women completed the QoL follow-up study (Table 1). The median age was 29 years at enrolment (range, 21 to 43); and the median follow-up period was 32 months (range, 26 to 42) with an average follow-up period of 36 months post delivery.

Randomisation and interventions

Informed consent was obtained from all patients. Treatment arms were allocated in blocks of 10 by computer-generated random assignment, and allocation was done by concealed envelopes. This was done by the LGH Pharmacy Department in order to avoid possible bias. The oral-only treatment arm comprised iron sulphate 250 mg tablets once daily, (elemental iron 80 mg, Abbott, Australasia Pty Ltd) to be taken daily within two days after booking until delivery. The IV arm required a single intravenous infusion of iron polymaltose (Ferrosig, Sigma Pharmaceuticals, Australia) within 1 week after first antenatal visit followed by oral iron identical to the other arm. Pre-enrolment, there were no significant differences in the dietary iron intake or supplement intake between the two groups based

on a specially-designed questionnaire addressing these issues.[14] Patients assigned to IV iron polymaltose received a 100 mg test dose dissolved in 50-100 mL normal saline infused over 30 minutes. Clinical observation and vital signs were assessed initially and every 15 min from the start of the infusion. After the test-dose was tolerated, the remainder of the iron polymaltose dose was infused. The total dose of IV iron polymaltose was calculated according to the patients' body weight at their first antenatal visit and entry Hb level according to the product guidelines; iron dose in mg (50 mg per 1 mL) = body weight (maximum 90) in kg x target Hb (120 g/L) - actual Hb (in g/L) x constant factor (0.24) + iron depot (500).[14]

Outcome measurement

Two Health-Related Quality of Life (HRQoL) questionnaires were administered during the initial and follow-up studies. First, a clinical questionnaire was completed prospectively by trained midwives at 4 weeks after initiation of treatment, at 28 and 34 weeks gestation, and then 6-8 weeks post delivery. This questionnaire assessed four aspects: energy levels, activity, tolerance and side effects of the treatment. This was used to guide individual patient clinical decision-making as well as to provide a safety audit of the trial treatments.[14] Second, a prospective/retrospective survey was conducted between June and October 2010 by trained research personnel via phone interview using a modified version of the SF-36 HRQoL questionnaire, similar to a version published previously.[16,17] Additional modifications for this study included: (1) use of eleven of the 36 questions (Table 2), and (2) the women were asked to recall their response to each of the questions at four timepoints, pre-trial prior to commencement of iron therapy during the pregnancy, four weeks after the start of iron therapy, one week after delivery, and the last four weeks prior to the telephone questionnaire contact (Table 2). This was compared in a retrospective fashion to the same questions answered earlier prospectively by the participants at these different timepoints. In order to validate the retrospective use of the modified

SF-36 questionnaire to assess the women's HRQoL during and after pregnancy, we estimated the associations of the physical activity component of the prospective monitoring questionnaire following entry into the trial with the Physical Component Scale values of the modified SF-36 at each of the timepoints. We hypothesized that the association would be greatest at 4 weeks after enrolment compared to trial entry, time of delivery or at the time of questionnaire completion. In addition, data concerning breastfeeding and the health of the child were collected from the baby's growth booklet. This included breastfeeding duration, baby gender, age, weight and previous hospitalisation, if any, in addition to the baby's sleep quality since birth and specific growth data for the children as set by the Australasian Paediatric Endocrine Group (APEG). Haemoglobin and ferritin levels for participants at delivery were available for all participants; however no further testing was performed during the follow up. The principal investigators, including the statistician, evaluated the questionnaire results data.

Statistical methods

The HRQoL scores that form the raw data for this analysis are rank-order in nature. Means and standard deviations of the scores were estimated using generalised estimating equations for illustrative purposes only. Physical and mental composite scores were calculated in the modified SF-36 according to the SF-12 scoring guidelines.[16,17] Group comparison and covariate effect size calculation, odds ratios (OR with 95% confidence intervals and P values) were estimated using repeated measures of ordinal logistic regression, with covariates selected for inclusion by backward stepwise regression (P for exclusion 0.22) from maternal age, haemoglobin, ferritin, Socio-Economic Indexes for Areas (SEIFA; based on the Collector District of residence of mothers), quality of sleep, use and duration of breastfeeding, hospitalization of the baby, baby gender and mode of delivery. This included randomisation group covariate interactions in the starting model with exclusion of those interactions using the above criteria. When iron status was selected for inclusion in the model, the association

between iron status (ferritin) and HRQoL was reported independently of trial treatment group. P values were corrected for multiple comparisons where necessary by the Holm method. The effect of IV iron versus oral iron on time of cessation of breastfeeding was compared by estimation of hazard ratio (HR) with 95% confidence intervals and P-values by Cox proportional hazards regression adjusted for covariates selected for inclusion by backward stepwise regression (P for exclusion 0.22). The time to cessation of breast-feeding was taken from the subject's baby growth booklet for all participants. Neonatal growth in the treatment groups was compared by multivariate third-order polynomial regression as an approximation to APEG growth assessment. The iron status variables used in the multivariate regression models were selected by stepwise regression. All HRQoL statistical analyses were performed using Stata SE for Windows 11.1 (StataCorp, College Station, Tx USA).

RESULTS

Of the original 196 patients randomised to receive the trial medications (98 IV plus oral iron; 98 oral iron only), 183 patients completed the trial by collection of blood for iron status at the time of delivery. Data of HRQoL were collected from 126 of the 183 women who completed the original trial, representing 69% of the original cohort, while 57 (31%) of the 183 patients had moved away, were uncontactable or did not respond to follow-up requests (see Figure 1 for description of patient flow). The median age of the patients included in the follow-up study was 29 years at enrolment (range, 21 to 43) and the median follow up was 32 months (range, 26 to 42) post delivery. There were no significant differences in demographic or iron status measurements between any of the groups of women recruited to the trial. All participants were Caucasians.

As reported in the original study,[14] at delivery the proportion of women with lower than normal ferritin levels was 53 of 67 (79%) for women with analysable iron status measurements who were treated with oral iron as compared to 3 of 66 (4.5%) for women who received IV iron (Fisher's exact p<0.001). The pretreatment mean serum ferritin levels were low in both groups at 17 µg/L. However, the serum ferritin of those in the IV iron group increased markedly within four weeks of the IV therapy with a mean level of 222 µg/L; 95% CI 194 to 249 µg/L (p<0.001). This substantial improvement was maintained after delivery with a mean level of 108 µg/L; 95% CI 43 to 209 µg/L (p<0.001).[14] On the other hand, ferritin levels did not show a significant increase in the oral iron group through pregnancy and after delivery. Furthermore, the percentage of women at delivery with Hb levels <116 g/L was 29% (25 of 85) in the oral iron group versus 16% (14 of 87) in the IV iron group (p=0.04) incidence rate ratio 0.55 (95% CI 0.31 to 0.98; p=0.043). After delivery, the mean Hb levels declined to 111.6 g/L (SD 14.2) in the oral iron versus 115.5 g/L (SD 10.8) in the IV iron group. This showed a continuing favourable effect of IV iron therapy (95% CI 2.5 to 9.1; p=0.004) despite the loss of blood at delivery.[14]

There were no significant differences in the birth weights of the babies in the two treatment groups, with an average birth weight of 3.42 kg in both groups with a difference of 0.03 kg (p=0.77). There were also no differences in the gestational age at delivery in both treatment groups with mean of 39.1 weeks in the oral iron versus 38.9 weeks in the IV iron group, with only a slight difference of 0.2 weeks (p=0.74). There were no significant differences in placental cord Hb or ferritin levels in both treatment groups. The mean cord Hb was 165g/L (SD 9.6) in the oral iron group versus 157g/L (SD 14.1) in the IV iron group (difference -7; 95% CI -18 to 3; p=0.17). The ferritin levels were 142 µg/L (SD 86) and 185 µg/L (SD 101) respectively (difference 43; 95% CI -59 to 145; p=0.41).

The HRQoL Physical Component Scale (difference 10.3; 95% CI 3.3 to 17.2; P=0.27; OR 2.39; 95% CI 1.32 to 4.32; P=0.004) and General Health (difference 15.1; 95% CI 6.0 to 24.2; P=0.31; OR 3.14; 95% CI 1.57 to 6.26; P=0.001) responses were improved in the IV compared to the oral iron group, but these differences became less apparent at subsequent assessment timepoints (Figure 2a and b). Furthermore, there were strong associations between the level of iron status, independent of how that iron status was achieved, and a number of the HRQoL scales (Figure 2): notably improved general health (slope {1SD log.-ferritin} 10.0; 7.2 to 12.7; P<0.001; OR 1.49; 95% CI 1.09 to 2.03; P=0.021), improved vitality (slope {1SD log.-ferritin} 10.0; 7.3 to 12.8; P<0.001; OR 2.09; 95% CI 1.66 to 2.62; P<0.001), less psychological downheartedness ({1SD haemoglobin} OR 1.57; 95% CI 1.14 to 2.15; P=0.005), less clinical depression ({1SD log.-ferritin} OR 2.05; 95% CI 1.27 to 3.32; P=0.003), and overall improved mental component scale (slope {1SD haemoglobin} 3.8; 2.5 to 5.0; P<0.001; OR 1.71; 95% CI 1.39 to 2.10; P<0.001) (Psychological Downheartedness and Clinical Depression analysis used raw scores rather than 100-point scales).

There was an increased duration of breastfeeding (HR for cessation was 0.70; 95% CI 0.50 to 0.99; p=0.046) in women in the IV iron group (Figure 3), where higher maternal age was associated with longer breastfeeding (HR 0.76; 95% CI 1.00 to 1.52; P=0.006) (Table 3). Earlier cessation of breastfeeding was associated with downheartedness (HR 1.23; 95% CI 1.00 to 1.52; P=0.06). There was no difference between the oral iron or IV plus oral iron groups in the weight of the baby at birth (p=0.64), and no difference in the rate of weight gain (p=0.90).

The correlation between the prospective physical symptom questions index from the clinical monitoring questionnaire and the Physical Component Scale of the retrospective HRQoL for the four time periods is shown in Table 4. There was a significant association between the physical symptom

questions index at 4 weeks after trial entry and each of the HRQoL recall timepoints, and the correlation was strongest for the 4 weeks recall (OR 3.18; 2.14 to 4.74; P<0.001).

Another finding of our study was an association between male gender babies and an unfavourable mental health component outcome for participant women across the two groups. Of the seven component questions, two showed a significant association, with women who had male babies less likely to be calm and peaceful (OR=0.55, 0.32-0.97, p=0.039). There were no statistical differences in terms of HRQoL assessment regarding the method of delivery between women who delivered normally and those who had caesarean section.

DISCUSSION

Prior to our study, there were no data available concerning the effects of either IV or oral iron supplementation for anaemia on post-delivery psychological and physical welfare of mothers, the quality of the bonding to the baby and the rate of developmental progress of the baby. We are reporting on 126 patients in a follow up study of the effect of IV iron versus oral iron therapy on HRQoL during and after pregnancy. Our study demonstrates that there was an improvement in the self-assessed feeling of general health in both treatment groups from the pre-labour period to all subsequent periods. Although the improvement was significantly greater during pregnancy in the IV iron group 4 weeks after commencement of trial treatment (p=0.001), the difference persisted in the subsequent measurement periods at a lesser magnitude that did not achieve statistical significance.

Regardless of treatment and regardless of which period was being considered, higher haemoglobin and higher ferritin levels were associated with better baby sleep quality, a longer period of breastfeeding and a higher level of mothers' general health.

The modified HRQoL questionnaire used in our study includes many useful and relevant aspects regarding general health, daily activities, levels of energy and depression. There was a substantial improvement of iron status in women who received IV iron compared to oral iron as demonstrated during the trial analysis ($p<0.001$). Limitations of our study include the modified questionnaire being in part a retrospective HRQoL evaluation which should ideally have been conducted within a shorter period of time. However, a correlation to a prospective evaluation of the studied subjects has been made in our study in order to overcome a possible recall bias. Therefore, we were able to minimise the number of retrospective questions, since the women were asked to recall their responses to each question at four different timepoints. The full SF-36 was impractical and may have been judged to be an excessive burden on the women. Thus, we attempted to provide a retrospective form of validation by showing that the clinical HRQoL questions in the physical domain, recorded prospectively at week 4 after trial, were most strongly associated with the Physical Component Scales of the recall of modified SF-36 at week 4 compared to the other timepoints. This indicates that the retrospective methodology was able to provide an acceptable degree of accuracy in the differentiation of HRQoL levels at different timepoints despite the concerns that may have arisen with this issue. The assumption being made is that the way those patients judge their physical and mental condition will be relatively stable over time,[18] an assumption with which we agree may occur in patients with chronic diseases. However, this assumption may not hold for women during and after pregnancy. The expectations by the woman about how she should be feeling at the different stages of pregnancy, around the time of delivery, and when she is caring for one or more young infant or child may differ substantially at those different timepoints. At least in our analysis, the judgment the woman is making about how to answer the questions is likely to be the same for each timepoint, since she had made that judgment at one point in time: the repeated measures analysis compares each woman with herself, thus substantially reducing the impact of variation between women in this judgment. Thus, for the

purpose of generating a hypothesis concerning iron status and quality of life, we believe that our methodology has been adequate. Another limitation of our study is the relatively small number of women studied. Nevertheless, prior to our study there was a lack of research that addressed HRQoL during and after pregnancy, and particularly the association between iron status and postnatal clinical depression as well as breastfeeding duration in our cohort of patients provides a novel finding and a basis for further research.

An incidental finding of our study was a trend for unfavourable mental health component outcomes for women with male babies there is only a single report in the literature that addressed this issue and reported similar findings.[19] Perhaps this may be explained with the observation that male babies are usually more active, and this may be associated with post natal depression.[19] However, due to lack of more detailed data, this issue should be addressed separately and studied in future research.

Due to paucity of data regarding HRQoL during and after pregnancy, there are only limited data available from other studies. Jansen *et al* studied the effect of delivery and postpartum changes on the HRQoL.[20] A cohort of 141 pregnant women were included in that study. HRQoL questionnaires were measuring the immediate effect of delivery on the quality of life. The HRQoL questionnaires were conducted less than 1 day after vaginal delivery and less than two days after delivery by caesarean section and compared to 3-6 weeks post delivery for both groups.[20] The study focused on patients' HRQoL recovery after both delivery interventions. In that study,[20] the different timepoints of completion of the questionnaire (immediately post-delivery and 3-6 weeks thereafter) may not necessarily reflect the HRQoL during pregnancy and subsequently after the postpartum period. Furthermore, the immediate questionnaire after delivery and at 3-6 weeks time in the postpartum period may have been influenced, at least in theory, by the event of delivery, in particular when complications occurred, as well as by the possible emotional and hormonal fluctuations during this period. It is worthwhile to note that the same study did not show any association between Hb and

QoL; however it did not investigate a possible effect of iron status on perceived HRQoL in conjunction with breastfeeding. This highlights our novel finding of the correlation between iron status and improved HRQoL during and after pregnancy.

In summary, we found a significant improvement in the general health of women who received IV iron ($p<0.001$), but this effect was found prominently 4 weeks after the IV iron treatment. The duration of breast-feeding was longer ($p=0.04$) in those women who had received IV iron. Women with better iron status were less downhearted ($p=0.005$) and less likely to develop postnatal clinical depression ($p=0.003$).

Our results indicate that it is worthwhile considering Hb and iron status as a surrogate marker for assessment of women's wellbeing, not only during pregnancy, but also during the postnatal period.

Further studies are warranted to confirm and extend our findings, and to determine outcomes in different populations with IDA in order to improve the estimates of the magnitude of the benefits of intravenous iron for the management of iron deficiency anaemia.

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CONTRIBUTORSHIP STATEMENT

Authors' contributions statement:

Alhossain A. Khalafallah is the principal investigator of the study who organised and coordinated all aspects of the research including all steps of the manuscript preparation. He is responsible for the study concept, design, recruitment of patients, writing, reviewing, editing and approving the manuscript in its final form as well as all aspects of the research.

Amanda Dennis, Kath Ogden, Iain Robertson and Madeline Ball contributed to study design, analysis and interpretation of data, and revised the manuscript.

Ruth Charlton, Jackie Bellette, Jessica Shady and Nep Blesingk conducted the interviews with patients, collected the data, drafted the article and finally approved the manuscript.

COMPETING INTERSTS STATEMENT

There are no competing interests.

DATA SHARING STATEMENT

There is no additional data available.

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Footnotes to Figure 1. Patients Flow Chart.

* Fourteen patients were admitted late in labour, and no blood samples were taken before delivery.

† The primary hypothesis examined the change in haemoglobin levels between the time of booking and immediately prior to delivery; an "intention-to-treat" analysis was performed according to original randomisation group on those patients who had blood samples taken before delivery, whether or not the treatment was completed as per protocol.

‡ Twenty-one patients withdrew from the trial treatments, and all but one of these patients agreed to continued collection of haematological and other trial data; eight patients gave no reason for withdrawal.

§ Five patients did not complete the intended treatments, but did not choose to withdraw themselves; three patients in the oral iron group were treated with IV iron when their haemoglobin was judged not to have responded adequately to oral iron, while one patient was unable to attend for IV iron treatment.

Table 1. Patient characteristics

	IV iron group	**Oral iron group**
No of patients	64	62
Vaginal delivery	45	46
Caesarean section	19	16
Median age in years	28 years (range; 21-43)	28.5 years (Range; 22-42)
Mean age in years	27.5 years	28
Median time between trial intervention and delivery in months	2.7 months (range; 2.6-6)	2.8 months (range; 2.2-5.3)
Median time of follow-up in months	28 months	29 months
Baby birth weight in grams	Median 3523 g (range; 1315-4920)	Median 3480 g (range; 1330-4928)
Median Initial Hb	105 g/L	108 g/L
Median Hb after intervention and prior to delivery	128 g/L	118 g/L
Median Hb post-delivery	118 g/L (range; 86-146)	112 g/L (range; 78-137)
Blood transfusion requirement	None	Two patients

Table 2. Comparison of the questions in the SF-36 and the abbreviated HRQoL questionnaire used in this study.

*Questionnaires	Original SF-36	Modified short-HRQoL
Time specified for subject response	Either in at the time of analysis or in past 4 weeks	Evaluated at four time periods: before treatment; after 4 weeks of treatment; after delivery; and during the past 4 weeks before interview
Question: stem and detailed item†	**Question number and response options**	**Question number and response options**
In general, would you say your health is:	Q1: Excellent; Very good; Good; Fair; Poor	Q1: Excellent; Very good; Good; Fair; Poor
The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	Yes, limited a lot; Yes, limited a little; No, not limited at all	Yes, limited a lot; Yes, limited a little; No, not limited at all
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	Q3b	Q2a
Climbing several flights of stairs	Q3d	Q2b
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	All of the time; Most of the time; Some of the time; A little of the time; None of the time
Accomplished less than you would like	Q4b	Q3a
Were limited in the kind of work or other activities	Q4c	Q3b
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	All of the time; Most of the time; Some of the time; A little of the time; None of the time
Accomplished less than you would like	Q5b	Q6a
Did work or other activities less carefully than usual	Q5c	Q6b
Have you felt calm and peaceful?	Q9d	Q4a
Did you have a lot of energy?	Q9e	Q4b
Have you felt downhearted and depressed?	Q9f	Q4c
Have you been diagnosed with or treated for depression or postnatal depression since the birth of your baby?	Not included	Q4d: Diagnosed: Yes/No; Treated: Yes/No
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	Q10: All of the time; Most of the time; Some of the time; A little of the time; None of the time	Q5: All of the time; Most of the time; Some of the time; A little of the time; None of the time
During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Q8: Not at all; A little bit; Moderately; Quite a bit; Extremely	Not included

*** Not all of the original SF-36 questions are included in this list. All the questions shown in this list, except for the last original SF-36 question about pain, were included in the questionnaire administered in this study. Where the questionnaire response was the same this is indicated, and where the response differed from the original SF-36 wording the new responses were shown. The order in which the questions (e.g. Q1 as first question, or Q5b as question subset 5 second question) were administered in the original and modified questionnaires is shown.**

† Questions: Q1, Q2, etc. denotes question numbers.

Figure 2a and 2b. Comparison of physical component scale of HRQoL scores in the IV plus oral iron versus the oral iron group, and separate association with iron status

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† Comparison of the effect of IV plus oral iron versus oral iron on physical **(Figure 2a)** and mental **(Figure 2b)** components of the HRQoL scores at different time periods (before starting iron, 4 weeks after starting iron, at delivery and when the mother responded to questionnaire), estimated using ordinal logistic regression adjusted for significant demographic confounders but not including iron status, corrected for repeated measures and multiple comparisons (Holm method).

* The effect of iron status on physical component and mental component scores was estimated separately without including treatment group in the analysis. The timepoint "Later" is referring to the post delivery follow-up assessment.

Table 3. Effect of IV iron versus oral iron on rate of cessation of breast feeding.

	HR[1]	95% CI	P-value
IV plus oral	0.70	(0.50 to 0.99)	0.046
Maternal age	0.76	(0.63 to 0.92)	0.006
Downheartedness	1.23	(1.00 to 1.52)	0.055
Current alcohol intake	1.34	(0.88 to 2.03)	0.18
Mode of delivery:			
NVD	1.00		
LSCS	1.24	(0.84 to 1.82)	0.29
Forceps	1.39	(0.85 to 2.27)	0.19

[1] **The likelihood of cessation of breast feeding in the IV plus oral iron group was compared with that of the oral iron only group: estimated using Cox proportional hazards regression corrected for repeated-measures and adjusted for the covariates shown, expressed as hazards ratios (95% confidence intervals; P-values). Covariates included in the final multivariate model were selected by stepwise regression. The standardized normal transformation of maternal age was used ({mother's age – group mean age}/ group standard deviation of age): mean age 28.1 ± 5.6 years.** Hazard ratio (HR) less than 1.00 indicates a slower rate of cessation of breast-feeding, whilst an HR greater than 1.00 indicates a faster rate of ceasing breast-feeding.

[2] Abbreviations: NVD – normal vaginal delivery; LSCS – lower segment caesarean section

Table 4. Correlation between the physical symptom questions[3] from the prospective clinical monitoring questionnaire and the Physical Component Scale of the retrospective HRQoL for the four time periods.

Time	Slope (SD)[1]	OR[2a]	95%CI	P-value	OR[2b]	95%CI	P-value
Pre-trial	2.67 (13.0) [1]	1.46	(1.01 to 2.11)	0.043	1.00		
4 weeks	8.07 (18.6)	3.18	(2.11 to 4.80)	<0.001	2.18	(1.44 to 3.28)	<0.001
Delivery	4.91 (12.2)	2.14	(1.37 to 3.35)	<0.001	1.46	(0.94 to 2.29)	0.10
Post-delivery	4.31 (14.1)	1.98	(1.28 to 3.08)	<0.001	1.36	(0.88 to 2.10)	0.17

1 The slope (standard deviation) of the association between the physical symptom questions from the clinical monitoring questionnaire and the Physical Component Scale of the HRQoL for the four time periods was estimated by repeated measures general linear modeling for illustrative purposes only (mean index score at pre-trial was 74.3 of 100).

2 The strength of the [a)] absolute association at each timepoint, and [b)] the relative association at the other timepoints was compared to the pre-trial timepoint and was estimated using repeated measures ordered logistic regression and expressed as odds ratios (OR; 95% confidence intervals; P-values).

3 The scores for four questions were combined as a single index: Do you have energy? Do you feel fatigued or sleepy? Do you feel light-headed (dizzy)? Do you feel short of breath? Responses: Not at all; A little of the time; Sometimes; Most of the time; Always.

Three-year Follow-up of a Randomized Clinical Trial of Intravenous versus Oral Iron for Anaemia in Pregnancy demonstrates that Intravenous Iron Therapy is Associated with Improved Maternal Quality of Life, Less Postnatal Depression and Longer Breastfeeding

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ARTICLE SUMMARY

Article focus

- Health-related quality of life (HRQoL) assessment during and after pregnancy in 126 women with iron deficiency who received either a single infusion of intravenous iron polymaltose followed by oral iron maintenance or oral iron only.
- Study of postnatal depression and its association with treatment arms and iron status.
- Assessment of breastfeeding duration and correlation to mothers' iron status.

Key-Messages

- HRQoL **during and after pregnancy** is improved significantly in anaemic pregnant women by repletion of their iron stores during pregnancy.
- About 80% of the intravenous iron group showed a maintained normal ferritin until delivery with long-term benefits such as prolongation of the breastfeeding period and less postnatal clinical depression.
- There were strong associations between iron status and a number of the HRQoL scales with improved general health (P=0.021), improved physical energy (P=0.016), less psychological downheartedness (P=0.005), less clinical depression (P=0.003), and an overall improved mental component scale (P<0.001). The duration of breastfeeding was longer (P=0.046) in women who had received intravenous iron.

Strengths and limitations

- This study reports a novel finding in terms of a correlation between both postnatal depression and the breastfeeding period with iron status.
- There are limited data available concerning the quality of life during and after pregnancy, which makes the scientific input of the current study important. ~~albeit the relatively small number of pregnant women studied.~~
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- Limitations of our study include that the modified questionnaire was in part a retrospective HRQoL evaluation, and this should ideally have been prospectively conducted.
- Another limitation is the relatively small number of women studied.

ABSTRACT

Background: To date, there are no data available concerning the impact of iron therapy on the long-term wellbeing and health-related quality of life (HRQoL) in pregnancy. ~~of the mothers in particular with regards to postnatal depression and the duration of breast-feeding.~~

Objective: To assess the long-term effect of iron therapy on HRQoL in pregnancy.

Design: **This is a follow-up study conducted between January 2010 and January 2011 of an earlier randomised open-label clinical trial of intravenous and oral iron versus oral iron for pregnancy-related iron deficiency anaemia.** We used a modified version of the SF-36 questionnaire together with the original prospective HRQoL data collected **during and after pregnancy**.

Participants and Interventions: Of the original evaluable 183 pregnant Caucasian women randomised to receive oral iron or a single intravenous iron polymaltose infusion followed by oral iron maintenance, 126 women completed the follow up HRQoL study.

Methods: The participants were followed-up 4 weeks after treatment, pre-delivery, and post-delivery for a median period of 32 months (range, 26-42) with a wellbeing and HRQoL questionnaire using a modified SF-36 QoL-survey and child growth charts as set by the Australasian Paediatric Endocrine Group (APEG).

Results: Patients who received intravenous iron demonstrated significantly higher haemoglobin and serum ferritin levels ($p<0.001$). There were strong associations between iron status and a number of the HRQoL parameters, with improved general health ($P<0.001$), improved vitality (physical energy) ($P<0.001$), less psychological downheartedness ($P=0.005$), less clinical depression ($P=0.003$), and overall improved mental health ($P<0.001$). The duration of breastfeeding was longer ($P=0.046$) in the intravenous iron group. The babies born in both groups recorded similarly on APEG growth chart assessments.

Conclusion: Our data suggest that HRQoL is improved **until after pregnancy** in anaemic pregnant women by repletion of their iron stores **during pregnancy**. About 80% of the intravenous iron group showed a maintained normal ferritin until delivery with long-term benefits. Further studies to confirm these findings are warranted.

Trial registration: Australian New Zealand Clinical Trial Registry (http://www.ANZCTR.org.au) under ACTRN 12609000177257 and in the World Health Organization Clinical Trials Registry (http://www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202).

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Key words: Quality of life assessment, iron deficiency anaemia, oral iron, intravenous iron, pregnancy, long-term effect.

Short title: Quality of life in pregnancy

INTRODUCTION

Currently, there are no data available concerning quality of life outcomes and other long-term effects of intravenous versus oral iron therapy of anaemia during pregnancy. In addition to the physical impact of iron deficiency anaemia (IDA) on pregnant women,[1-3] IDA is a potential risk factor for preterm delivery and subsequent low birth weight, and may be associated with inferior neonatal health.[3-4] Infants born to women with IDA are more likely to become anaemic themselves, which in turn is known to have a potential effect on an infant's mental and motor development.[5-9] Although iron supplementation during pregnancy is a widely practised public health measure, there are some concerns regarding iron replacement therapy and its long-term effect, especially the intravenous form.[10,11] Therapeutic response to oral iron therapy is not always adequate in pregnant women, due to difficulties associated with oral intake of the tablets and their side effects, which impacts negatively on compliance.[3,10,11]

In the past, intravenous iron was associated with undesirable and sometimes serious side effects that limited its use.[12] Recently, new type II iron complexes have been developed with the potential to reverse iron deficiency with less side effects than their predecessors.[12-14] Despite increasing evidence for the safety of the newer preparations in both pregnant and general populations, intravenous iron continues to be underutilised.[15]

Earlier, we reported on a randomised controlled trial (PMID: 20546462) of intravenous (IV) followed by oral iron therapy versus oral iron therapy only for moderate iron deficiency anaemia in pregnancy.[14] **The results of the earlier analysis** showed that intravenous iron polymaltose was associated with greater improvements in haemoglobin levels and iron stores compared to oral iron alone in pregnancy-related IDA.[14] **Here, we report the results of a follow-up assessment of the same cohort of patients.** We studied the effects of both treatment types on the perceived health-related quality of life (HRQoL) as measured by a modified SF-36 questionnaire. The effect of iron

therapy on breastfeeding rates and on the general wellbeing of the babies born to these women was measured by child growth charts set by the Australasian Paediatric Endocrine Group (APEG).

PATIENTS AND METHODS

Rationale and objectives

An initial prospective randomised controlled trial was conducted between March 2007 and January 2009 at the Launceston General Hospital (LGH), a tertiary referral centre for Northern Tasmania, Australia. The initial study assessed haemoglobin and serum ferritin levels after IV followed by oral iron therapy versus oral iron therapy only. **The current study constitutes a follow-up on the earlier one and took place between January 2010 and January 2011 and focussed on HRQoL, breastfeeding duration and child health.** Informed consent was obtained from all participants in accordance with the Declaration of Helsinki. The original and the follow-up studies were approved by the Tasmanian Human Research Ethics Committee and registered in the Australian New Zealand Clinical Trials Registry (http://www.ANZCTR.org.au/ACTRN12609000177257.aspx) and the World Health Organization Clinical Trials Registry (http://www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202).

In the original study, we prospectively assessed HRQoL at baseline prior to treatment in the second trimester, 4 weeks after initiation of treatment, in the third trimester before delivery, and at 6-8 weeks post delivery. In the follow-up study, a HRQoL questionnaire was completed that incorporated the original questionnaire plus additional parameters such as the length of the breastfeeding period and occurrence of postnatal depression as well as child growth data. This was performed at a median of 32 months post intervention in order to assess the long-term effects of both treatment types on mothers' HRQoL in relation to data from the earlier study. This questionnaire, although completed

prospectively, had a retrospective component that asked the participating mothers the same questions again that they had previously answered prospectively. These data were compared with the mothers' original prospective QoL data for validation purposes.

Participants

Pregnant women aged 18 years or above who presented to the LGH with IDA between 2007 and 2009 were invited to participate. In the original study (Figure 1), 196 Caucasian pregnant women aged 18 years or above were identified who had moderate IDA, defined as haemoglobin (Hb) ≤115 g/L (reference range (RR) 120-160 g/L), and low iron stores, based on serum ferritin levels <30 µg/L (RR 30-440 µg/L).

Of the original evaluable 183 pregnant Caucasian women randomised to receive oral iron or a single intravenous iron polymaltose infusion, 126 women completed the QoL follow-up study (Table 1). The median age was 29 years at enrolment (range, 21 to 43); and the median follow-up period was 32 months (range, 26 to 42) with an average follow-up period of 36 months post delivery.

Randomisation and interventions

Informed consent was obtained from all patients. Treatment arms were allocated in blocks of 10 by computer-generated random assignment, and allocation was done by concealed envelopes. This was done by the LGH Pharmacy Department in order to avoid possible bias. The oral-only treatment arm comprised iron sulphate 250 mg tablets once daily, (elemental iron 80 mg, Abbott, Australasia Pty Ltd) to be taken daily within two days after booking until delivery. The IV arm required a single intravenous infusion of iron polymaltose (Ferrosig, Sigma Pharmaceuticals, Australia) within 1 week after first antenatal visit followed by oral iron identical to the other arm. Pre-enrolment, there were no significant differences in the dietary iron intake or supplement intake between the two groups based

on a specially-designed questionnaire addressing these issues.[14] Patients assigned to IV iron polymaltose received a 100 mg test dose dissolved in 50-100 mL normal saline infused over 30 minutes. Clinical observation and vital signs were assessed initially and every 15 min from the start of the infusion. After the test-dose was tolerated, the remainder of the iron polymaltose dose was infused. The total dose of IV iron polymaltose was calculated according to the patients' body weight at their first antenatal visit and entry Hb level according to the product guidelines; iron dose in mg (50 mg per 1 mL) = body weight (maximum 90) in kg x target Hb (120 g/L) - actual Hb (in g/L) x constant factor (0.24) + iron depot (500).[14]

Outcome measurement

Two Health-Related Quality of Life (HRQoL) questionnaires were administered during the initial and follow-up studies. First, a clinical questionnaire was completed prospectively by trained midwives at 4 weeks after initiation of treatment, at 28 and 34 weeks gestation, and then 6-8 weeks post delivery. This questionnaire assessed four aspects: energy levels, activity, tolerance and side effects of the treatment. This was used to guide individual patient clinical decision-making as well as to provide a safety audit of the trial treatments.[14] Second, a prospective/retrospective survey was conducted between June and October 2010 by trained research personnel via phone interview using a modified version of the SF-36 HRQoL questionnaire, similar to a version published previously.[16,17] Additional modifications for this study included: (1) use of eleven of the 36 questions (Table 2), and (2) the women were asked to recall their response to each of the questions at four time points, pre-trial prior to commencement of iron therapy during the pregnancy, four weeks after the start of iron therapy, one week after delivery, and the last four weeks prior to the telephone questionnaire contact (Table 2). This was compared in a retrospective fashion to the same questions answered earlier prospectively by the participants at these different timepoints. In order to validate the retrospective use of the modified

SF-36 questionnaire to assess the women's HRQoL during and after pregnancy, **we estimated** the associations of the physical activity component of the prospective monitoring questionnaire following entry into the trial with the Physical Component Scale values of the modified SF-36 at each of the timepoints. We hypothesized that the association would be greatest at 4 weeks after enrolment compared to trial entry, time of delivery or at the time of questionnaire completion. In addition, data concerning breastfeeding and the health of the child were collected from the baby's growth booklet. This included breastfeeding duration, baby gender, age, weight and previous hospitalisation, if any, in addition to the baby's sleep quality since birth and specific growth data for the children as set by the Australasian Paediatric Endocrine Group (APEG). Haemoglobin and ferritin levels for participants at delivery were available for all participants; however no further testing was performed during the follow up. The principal investigators, including the statistician, evaluated the questionnaire results data.

Statistical methods

The HRQoL scores that form the raw data for this analysis are rank-order in nature. Means and standard deviations of the scores were estimated using generalised estimating equations for illustrative purposes only. Physical and mental composite scores were calculated in the modified SF-36 according to the SF-12 scoring guidelines.[16,17] Group comparison and covariate effect size calculation, odds ratios (OR with 95% confidence intervals and P values) were estimated using repeated measures of ordinal logistic regression, with covariates selected for inclusion by backward stepwise regression (P for exclusion 0.22) from maternal age, haemoglobin, ferritin, Socio-Economic Indexes for Areas (SEIFA; based on the Collector District of residence of mothers), quality of sleep, use and duration of breastfeeding, hospitalization of the baby, baby gender and mode of delivery. This included randomisation group covariate interactions in the starting model with exclusion of those interactions using the above criteria. When iron status was selected for inclusion in the model, the association

between iron status (ferritin) and HRQoL was reported independently of trial treatment group. P values were corrected for multiple comparisons where necessary by the Holm method. The effect of IV iron versus oral iron on time of cessation of breastfeeding was compared by estimation of hazard ratio (HR) with 95% confidence intervals and P-values by Cox proportional hazards regression adjusted for covariates selected for inclusion by backward stepwise regression (P for exclusion 0.22). The time to cessation of breast-feeding was taken from the subject's baby growth booklet for all participants. Neonatal growth in the treatment groups was compared by multivariate third-order polynomial regression as an approximation to APEG growth assessment. The iron status variables used in the multivariate regression models were selected by stepwise regression. All HRQoL statistical analyses were performed using Stata SE for Windows 11.1 (StataCorp, College Station, Tx USA).

RESULTS

Of the original 196 patients randomised to receive the trial medications (98 IV plus oral iron; 98 oral iron only), 183 patients completed the trial by collection of blood for iron status at the time of delivery. Data of HRQoL were collected from 126 of the 183 women who completed the original trial, representing 69% of the original cohort, while 57 (31%) of the 183 patients had moved away, were uncontactable or did not respond to follow-up requests (see Figure 1 for description of patient flow). The median age of the patients included in the follow-up study was 29 years at enrolment (range, 21 to 43) and the median follow up was 32 months (range, 26 to 42) post delivery. There were no significant differences in demographic or iron status measurements between any of the groups of women recruited to the trial. All participants were Caucasians.

As reported in the original study,[14] at delivery the proportion of women with lower than normal ferritin levels was 53 of 67 (79%) for women with analysable iron status measurements who were treated with oral iron as compared to 3 of 66 (4.5%) for women who received IV iron (Fisher's exact p<0.001). The pretreatment mean serum ferritin levels were low in both groups at 17 µg/L. However, the serum ferritin of those in the IV iron group increased markedly within four weeks of the IV therapy with a mean level of 222 µg/L; 95% CI 194 to 249 µg/L (p<0.001). This substantial improvement was maintained after delivery with a mean level of 108 µg/L; 95% CI 43 to 209 µg/L (p<0.001).[14] On the other hand, ferritin levels did not show a significant increase in the oral iron group through pregnancy and after delivery. Furthermore, the percentage of women at delivery with Hb levels <116 g/L was 29% (25 of 85) in the oral iron group versus 16% (14 of 87) in the IV iron group (p=0.04) incidence rate ratio 0.55 (95% CI 0.31 to 0.98; p=0.043). After delivery, the mean Hb levels declined to 111.6 g/L (SD 14.2) in the oral iron versus 115.5 g/L (SD 10.8) in the IV iron group. This showed a continuing favourable effect of IV iron therapy (95% CI 2.5 to 9.1; p=0.004) despite the loss of blood at delivery.[14]

There were no significant differences in the birth weights of the babies in the two treatment groups, with an average birth weight of 3.42 kg in both groups with a difference of 0.03 kg (p=0.77). There were also no differences in the gestational age at delivery in both treatment groups with mean of 39.1 weeks in the oral iron versus 38.9 weeks in the IV iron group, with only a slight difference of 0.2 weeks (p=0.74). There were no significant differences in placental cord Hb or ferritin levels in both treatment groups. The mean cord Hb was 165g/L (SD 9.6) in the oral iron group versus 157g/L (SD 14.1) in the IV iron group (difference -7; 95% CI -18 to 3; p=0.17). The ferritin levels were 142 µg/L (SD 86) and 185 µg/L (SD 101) respectively (difference 43; 95% CI -59 to 145; p=0.41).

The HRQoL Physical Component Scale (difference 10.3; 95% CI 3.3 to 17.2; P=0.27; OR 2.39; 95% CI 1.32 to 4.32; P=0.004) and General Health (difference 15.1; 95% CI 6.0 to 24.2; P=0.31; OR 3.14; 95% CI 1.57 to 6.26; P=0.001) responses were improved in the IV compared to the oral iron group, but these differences became less apparent at subsequent assessment timepoints (Figure 2a and b). Furthermore, there were strong associations between the level of iron status, independent of how that iron status was achieved, and a number of the HRQoL scales (Figure 2): notably improved general health (slope {1SD log.-ferritin} 10.0; 7.2 to 12.7; P<0.001; OR 1.49; 95% CI 1.09 to 2.03; P=0.021), improved vitality (slope {1SD log.-ferritin} 10.0; 7.3 to 12.8; P<0.001; OR 2.09; 95% CI 1.66 to 2.62; P<0.001), less psychological downheartedness ({1SD haemoglobin} OR 1.57; 95% CI 1.14 to 2.15; P=0.005), less clinical depression ({1SD log.-ferritin} OR 2.05; 95% CI 1.27 to 3.32; P=0.003), and overall improved mental component scale (slope {1SD haemoglobin} 3.8; 2.5 to 5.0; P<0.001; OR 1.71; 95% CI 1.39 to 2.10; P<0.001) (Psychological Downheartedness and Clinical Depression analysis used raw scores rather than 100-point scales).

There was an increased duration of breastfeeding (HR for cessation was 0.70; 95% CI 0.50 to 0.99; p=0.046) in women in the IV iron group (Figure 3), where higher maternal age was associated with longer breastfeeding (HR 0.76; 95% CI 1.00 to 1.52; P=0.006) (Table 3). Earlier cessation of breastfeeding was associated with downheartedness (HR 1.23; 95% CI 1.00 to 1.52; P=0.06). There was no difference between the oral iron or IV plus oral iron groups in the weight of the baby at birth (p=0.64), and no difference in the rate of weight gain (p=0.90).

The correlation between the prospective physical symptom questions index from the clinical monitoring questionnaire and the Physical Component Scale of the retrospective HRQoL for the four time periods is shown in Table 4. There was a significant association between the physical symptom

questions index at 4 weeks after trial entry and each of the HRQoL recall time points, and the correlation was strongest for the 4 weeks recall (OR 3.18; 2.14 to 4.74; P<0.001).

Another finding of our study was an association between male gender babies and an unfavourable mental health component outcome for participant women across the two groups. Of the seven component questions, two showed a significant association, with women who had male babies less likely to be calm and peaceful (OR=0.55, 0.32-0.97, p=0.039). There were no statistical differences in terms of HRQoL assessment regarding the method of delivery between women who delivered normally and those who had caesarean section.

DISCUSSION

Prior to our study, there were no data available concerning the effects of either IV or oral iron supplementation for anaemia on post-delivery psychological and physical welfare of mothers, the quality of the bonding to the baby and the rate of developmental progress of the baby. We are reporting on 126 patients in a follow up study of the effect of IV iron versus oral iron therapy on HRQoL during and after pregnancy. Our study demonstrates that there was an improvement in the self-assessed feeling of general health in both treatment groups from the pre-labour period to all subsequent periods. Although the improvement was significantly greater during pregnancy in the IV iron group 4 weeks after commencement of trial treatment (p=0.001), the difference persisted in the subsequent measurement periods at a lesser magnitude that did not achieve statistical significance.

Regardless of treatment and regardless of which period was being considered, higher haemoglobin and higher ferritin levels were associated with better baby sleep quality, a longer period of breastfeeding and a higher level of mothers' general health.

The modified HRQoL questionnaire used in our study includes many useful and relevant aspects regarding general health, daily activities, levels of energy and depression. There was a substantial improvement of iron status in women who received IV iron compared to oral iron as demonstrated during the trial analysis ($p<0.001$). Limitations of our study include the modified questionnaire being in part a retrospective HRQoL evaluation which should ideally have been conducted within a shorter period of time. However, a correlation to a prospective evaluation of the studied subjects has been made in our study in order to overcome a possible recall bias. Therefore, we were able to minimise the number of retrospective questions, since the women were asked to recall their responses to each question at four different time points. The full SF-36 was impractical and may have been judged to be an excessive burden on the women. Thus, we attempted to provide a retrospective form of validation by showing that the clinical HRQoL questions in the physical domain, recorded prospectively at week 4 after trial, were most strongly associated with the Physical Component Scales of the recall of modified SF-36 at week 4 compared to the other time points. This indicates that the retrospective methodology was able to provide an acceptable degree of accuracy in the differentiation of HRQoL levels at different timepoints despite the concerns that may have arisen with this issue. The assumption being made is that the way those patients judge their physical and mental condition will be relatively stable over time,[18] an assumption with which we agree may occur in patients with chronic diseases. However, this assumption may not hold for women during and after pregnancy. The expectations by the woman about how she should be feeling at the different stages of pregnancy, around the time of delivery, and when she is caring for one or more young infant or child may differ substantially at those different time points. At least in our analysis, the judgment the woman is making about how to answer the questions is likely to be the same for each time point, since she had made that judgment at one point in time: the repeated measures analysis compares each woman with herself, thus substantially reducing the impact of variation between women in this judgment. Thus, for the

purpose of generating a hypothesis concerning iron status and quality of life, we believe that our methodology has been adequate. Another limitation of our study is the relatively small number of women studied. Nevertheless, prior to our study there was a lack of research that addressed HRQoL during and after pregnancy, and particularly the association between iron status and postnatal clinical depression as well as breastfeeding duration in our cohort of patients provides a novel finding and a basis for further research.

An incidental finding of our study was a trend for unfavourable mental health component outcomes for women with male babies there is only a single report in the literature that addressed this issue and reported similar findings.[19] Perhaps this may be explained with the observation that male babies are usually more active, and this may be associated with post natal depression.[19] However, due to lack of more detailed data, this issue should be addressed separately and studied in future research.

Due to paucity of data regarding HRQoL during and after pregnancy, there are only limited data available from other studies. Jansen *et al* studied the effect of delivery and postpartum changes on the HRQoL.[20] A cohort of 141 pregnant women were included in that study. HRQoL questionnaires were measuring the immediate effect of delivery on the quality of life. The HRQoL questionnaires were conducted less than 1 day after vaginal delivery and less than two days after delivery by caesarean section and compared to 3-6 weeks post delivery for both groups.[20] The study focused on patients' HRQoL recovery after both delivery interventions. In that study,[20] the different time points of completion of the questionnaire (immediately post-delivery and 3-6 weeks thereafter) may not necessarily reflect the HRQoL during pregnancy and subsequently after the postpartum period. Furthermore, the immediate questionnaire after delivery and at 3-6 weeks time in the postpartum period may have been influenced, at least in theory, by the event of delivery, in particular when complications occurred, as well as by the possible emotional and hormonal fluctuations during this period. It is worthwhile to note that the same study did not show any association between Hb and

QoL; however it did not investigate a possible effect of iron status on perceived HRQoL in conjunction with breastfeeding. This highlights our novel finding of the correlation between iron status and improved HRQoL during and after pregnancy.

In summary, we found a significant improvement in the general health of women who received IV iron ($p<0.001$), but this effect was found prominently 4 weeks after the IV iron treatment. The duration of breast-feeding was longer ($p=0.04$) in those women who had received IV iron. Women with better iron status were less downhearted ($p=0.005$) and less likely to develop postnatal clinical depression ($p=0.003$).

Our results indicate that it is worthwhile considering Hb and iron status as a surrogate marker for assessment of women's wellbeing, not only during pregnancy, but also during the postnatal period.

Further studies are warranted to confirm and extend our findings, and to determine outcomes in different populations with IDA in order to improve the estimates of the magnitude of the benefits of intravenous iron for the management of iron deficiency anaemia.

Acknowledgements:

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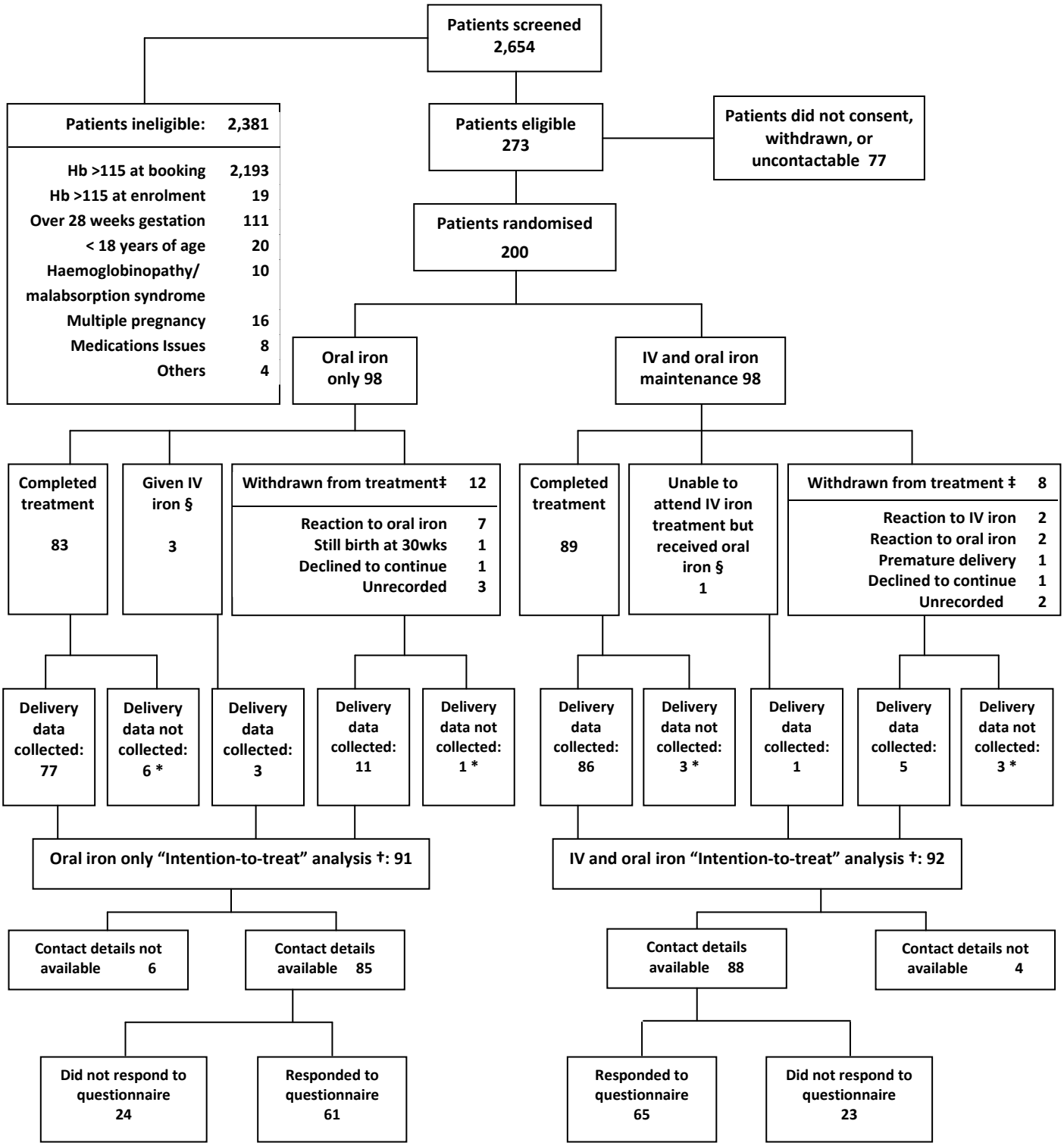
Figure 1. Trial flow diagram: disposition of study participants by treatment assignment.



Footnotes to Figure 1. Patients Flow Chart.

* Fourteen patients were admitted late in labour, and no blood samples were taken before delivery.

† The primary hypothesis examined the change in haemoglobin levels between the time of booking and immediately prior to delivery; an "intention-to-treat" analysis was performed according to original randomisation group on those patients who had blood samples taken before delivery, whether or not the treatment was completed as per protocol.

‡ Twenty-one patients withdrew from the trial treatments, and all but one of these patients agreed to continued collection of haematological and other trial data; eight patients gave no reason for withdrawal.

§ Five patients did not complete the intended treatments, but did not choose to withdraw themselves; three patients in the oral iron group were treated with IV iron when their haemoglobin was judged not to have responded adequately to oral iron, while one patient was unable to attend for IV iron treatment.

Table 1. Patient characteristics

	IV iron group	**Oral iron group**
No of patients	64	62
Vaginal delivery	45	46
Caesarean section	19	16
Median age in years	28 years (range; 21-43)	28.5 years (Range; 22-42)
Mean age in years	27.5 years	28
Median time between trial intervention and delivery in months	2.7 months (range; 2.6-6)	2.8 months (range; 2.2-5.3)
Median time of follow-up in months	28 months	29 months
Baby birth weight in grams	Median 3523 g (range; 1315-4920)	Median 3480 g (range; 1330-4928)
Median Initial Hb	105 g/L	108 g/L
Median Hb after intervention and prior to delivery	128 g/L	118 g/L
Median Hb post-delivery	118 g/L (range; 86-146)	112 g/L (range; 78-137)
Blood transfusion requirement	None	Two patients

Table 2. Comparison of the questions in the SF-36 and the abbreviated HRQoL questionnaire used in this study.

*Questionnaires	Original SF-36	Modified short-HRQoL
Time specified for subject response	Either in at the time of analysis or in past 4 weeks	Evaluated at four time periods: before treatment; after 4 weeks of treatment; after delivery; and during the past 4 weeks before interview
Question: stem and detailed item†	**Question number and response options**	**Question number and response options**
In general, would you say your health is:	Q1: Excellent; Very good; Good; Fair; Poor	Q1: Excellent; Very good; Good; Fair; Poor
The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	Yes, limited a lot; Yes, limited a little; No, not limited at all	Yes, limited a lot; Yes, limited a little; No, not limited at all
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	Q3b	Q2a
Climbing several flights of stairs	Q3d	Q2b
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	All of the time; Most of the time; Some of the time; A little of the time; None of the time
Accomplished less than you would like	Q4b	Q3a
Were limited in the kind of work or other activities	Q4c	Q3b
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	All of the time; Most of the time; Some of the time; A little of the time; None of the time
Accomplished less than you would like	Q5b	Q6a
Did work or other activities less carefully than usual	Q5c	Q6b
Have you felt calm and peaceful?	Q9d	Q4a
Did you have a lot of energy?	Q9e	Q4b
Have you felt downhearted and depressed?	Q9f	Q4c
Have you been diagnosed with or treated for depression or postnatal depression since the birth of your baby?	Not included	Q4d: Diagnosed: Yes/No; Treated: Yes/No
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	Q10: All of the time; Most of the time; Some of the time; A little of the time; None of the time	Q5: All of the time; Most of the time; Some of the time; A little of the time; None of the time
During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Q8: Not at all; A little bit; Moderately; Quite a bit; Extremely	Not included

*** Not all of the original SF-36 questions are included in this list. All the questions shown in this list, except for the last original SF-36 question about pain, were included in the questionnaire administered in this study. Where the questionnaire response was the same this is indicated, and where the response differed from the original SF-36 wording the new responses were shown. The order in which the questions (e.g. Q1 as first question, or Q5b as question subset 5 second question) were administered in the original and modified questionnaires is shown.**

† Questions: Q1, Q2, etc. denotes question numbers.

Figure 2a and 2b. Comparison of physical component scale of HRQoL scores in the IV plus oral iron versus the oral iron group, and separate association with iron status

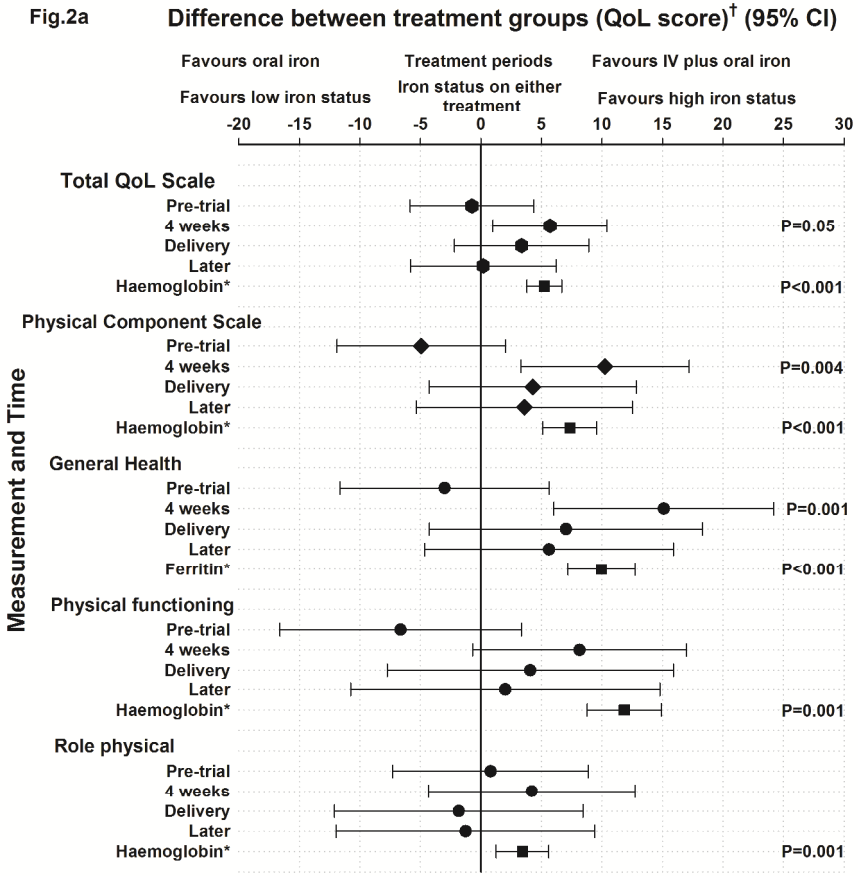
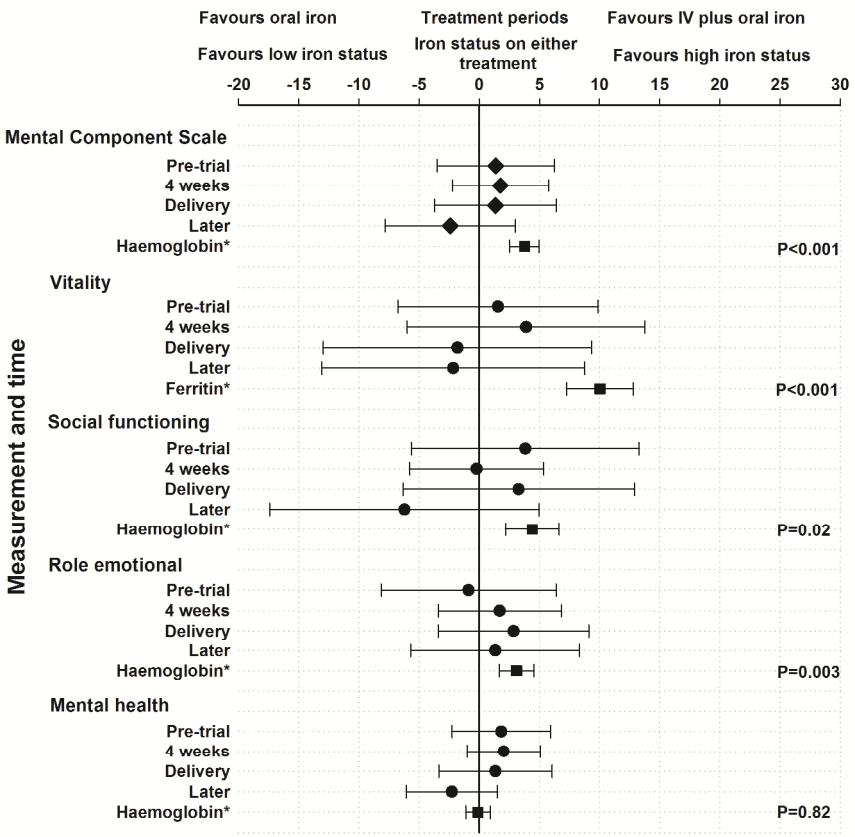


Fig.2b Difference between treatment groups (QoL score)† (95% CI)



† Comparison of the effect of IV plus oral iron versus oral iron on physical **(Figure 2a)** and mental **(Figure 2b)** components of the HRQoL scores at different time periods (before starting iron, 4 weeks after starting iron, at delivery and when the mother responded to questionnaire), estimated using ordinal logistic regression adjusted for significant demographic confounders but not including iron status, corrected for repeated measures and multiple comparisons (Holm method).

* The effect of iron status on physical component and mental component scores was estimated separately without including treatment group in the analysis. The time point "Later" is referring to the post delivery follow-up assessment.

Table 3. Effect of IV iron versus oral iron on rate of cessation of breast feeding.

	HR[1]	95% CI	P-value
IV plus oral	0.70	(0.50 to 0.99)	0.046
Maternal age	0.76	(0.63 to 0.92)	0.006
Downheartedness	1.23	(1.00 to 1.52)	0.055
Current alcohol intake	1.34	(0.88 to 2.03)	0.18
Mode of delivery:			
NVD	1.00		
LSCS	1.24	(0.84 to 1.82)	0.29
Forceps	1.39	(0.85 to 2.27)	0.19

[1] **The likelihood of cessation of breast feeding in the IV plus oral iron group was compared with that of the oral iron only group: estimated using Cox proportional hazards regression corrected for repeated-measures and adjusted for the covariates shown, expressed as hazards ratios (95% confidence intervals; P-values). Covariates included in the final multivariate model were selected by stepwise regression. The standardized normal transformation of maternal age was used ({mother's age – group mean age}/ group standard deviation of age): mean age 28.1 ± 5.6 years.** Hazard ratio (HR) less than 1.00 indicates a slower rate of cessation of breast-feeding, whilst an HR greater than 1.00 indicates a faster rate of ceasing breast-feeding.

[2] Abbreviations: NVD – normal vaginal delivery; LSCS – lower segment caesarean section

Table 4. Correlation between the physical symptom questions[3] from the prospective clinical monitoring questionnaire and the Physical Component Scale of the retrospective HRQoL for the four time periods.

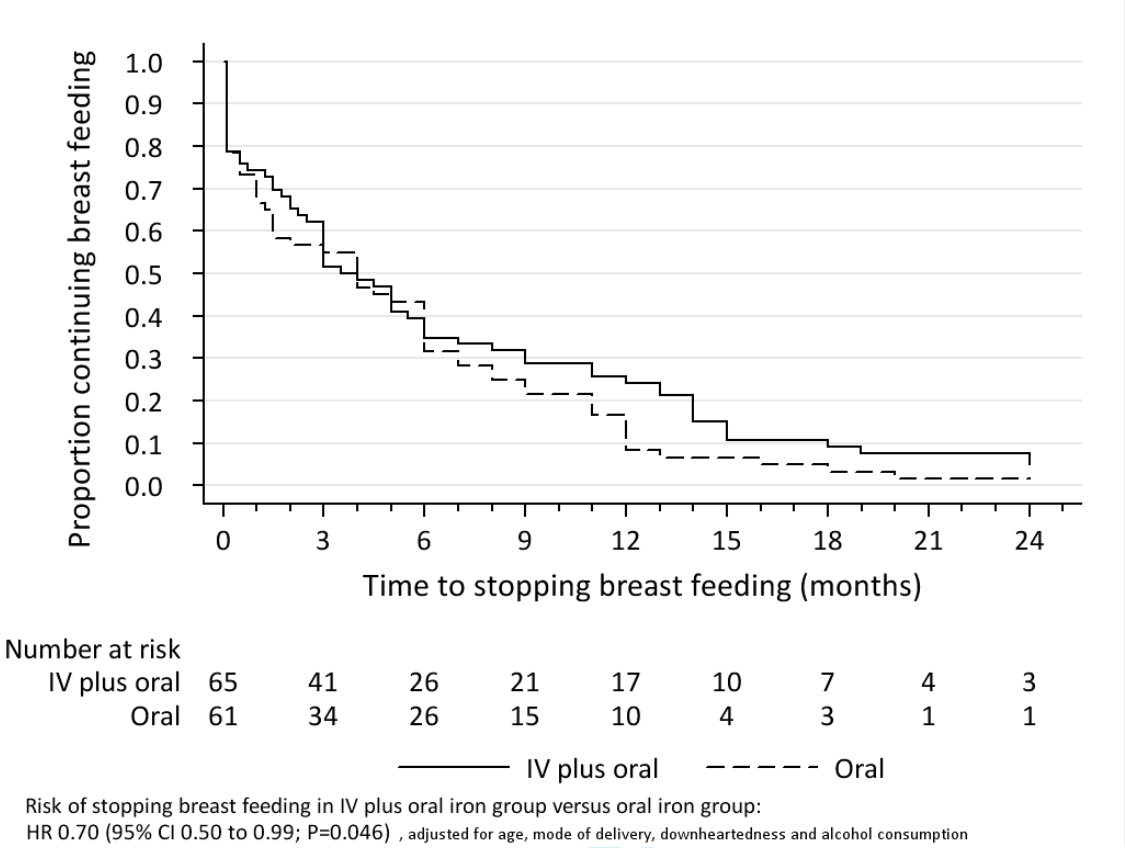
Time	Slope (SD)[1]	OR[2a]	95%CI	P-value	OR[2b]	95%CI	P-value
Pre-trial	2.67 (13.0) [1]	1.46	(1.01 to 2.11)	0.043	1.00		
4 weeks	8.07 (18.6)	3.18	(2.11 to 4.80)	<0.001	2.18	(1.44 to 3.28)	<0.001
Delivery	4.91 (12.2)	2.14	(1.37 to 3.35)	<0.001	1.46	(0.94 to 2.29)	0.10
Post-delivery	4.31 (14.1)	1.98	(1.28 to 3.08)	<0.001	1.36	(0.88 to 2.10)	0.17

1 The slope (standard deviation) of the association between the physical symptom questions from the clinical monitoring questionnaire and the Physical Component Scale of the HRQoL for the four time periods was estimated by repeated measures general linear modeling for illustrative purposes only (mean index score at pre-trial was 74.3 of 100).

2 The strength of the [a)] absolute association at each time point, and [b)] the relative association at the other time points was compared to the pre-trial time point and was estimated using repeated measures ordered logistic regression and expressed as odds ratios (OR; 95% confidence intervals; P-values).

3 The scores for four questions were combined as a single index: Do you have energy? Do you feel fatigued or sleepy? Do you feel light-headed (dizzy)? Do you feel short of breath? Responses: Not at all; A little of the time; Sometimes; Most of the time; Always.

Figure 3. Effect of IV plus oral iron versus oral iron on rate of cessation of breastfeeding.



Risk of stopping breast feeding in IV plus oral iron group versus oral iron group:
HR 0.70 (95% CI 0.50 to 0.99; P=0.046) , adjusted for age, mode of delivery, downheartedness and alcohol consumption

The difference arises in those women whose breastfeeding duration is in the top 30% (70-80th centiles who breastfeed for at least 12 months, about 2 months longer {75th centile difference 2.25 months; 95% CI -2.79 to 7.30; P=0.38}), and particularly in the top 10% (who breast-feed for at least 15 months, about 6 months longer {90th percentile difference 6.22 months; 95% CI 0.36 to 12.1; P=0.038}).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page
Title and abstract	1	(*a*) The title is informative regarding the study design	1
		(*b*) Abstract was formulated as background and aims of the study, Patients and methods, results and conclusion.	3
Introduction			
Background/rationale	2	Scientific background and the rationale for the study were stated	5,6
Objectives	3	Aims and objective were mentioned	6
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	The setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	The outcomes, exposures, predictors, potential confounders, and effect modifiers are clearly mentioned.	8
Data sources/ measurement	8*	Each variable of interest data and details of methods of measurement was given. Comparability of assessment methods were explained	7,8
Bias	9	The authors declare no conflict of interest in relation with this study	1
Study size	10	The study size was explained	9
Quantitative variables	11	Variables were explained in the analyses	8,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Numbers of individuals at each stage of study were mentioned	9,10

		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10,11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-11
Discussion			
Key results	18	Key results with reference to study objectives were summarised	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**:1453-7