



**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 Randomized Controlled 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 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.

1  
2 **Trial registration:** Australia and New Zealand Clinical Trial Registry under:  
3  
4 <http://www.ANZCTR.org.au> under ACTRN 12609000177257 and in the World Health Organization  
5  
6  
7 website under: [www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202](http://www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202).  
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10  
11 **Funding:** This research received a grant from the Clifford Craig Medical Research Trust, Launceston,  
12  
13 Tasmania, Australia.  
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15  
16 **Key words:** Quality of life assessment, iron deficiency anaemia, oral iron, intravenous iron,  
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18 pregnancy, long-term effect.  
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## 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,<sup>1-3</sup> IDA is a potential risk factor for preterm delivery and subsequent low birth weight and may be associated with inferior neonatal health.<sup>3-4</sup> 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.<sup>5-9</sup> 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.<sup>10,11</sup> 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.<sup>3,10,11</sup> 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.<sup>10,11</sup> Furthermore, the presence of chronic bowel disease can affect the absorption of iron, minimising the benefit received from oral iron therapy.<sup>11</sup>

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

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.<sup>14</sup> 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

1  
2 questionnaire, the effect of iron therapy on breastfeeding rates and on the general wellbeing of the  
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4 babies born to these women as measured by child growth charts set by the Australasian Paediatric  
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6 Endocrine Group (APEG).  
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## 10 11 **PATIENTS AND METHODS**

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14 The initial prospective randomised-controlled trial was conducted between March 2007 and January  
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16 2009 at the Launceston General Hospital (LGH), a tertiary referral centre for Northern Tasmania,  
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18 Australia. This follow-up study took place between January 2010 and January 2011. An informed  
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20 consent form was obtained from all participants according to the Code of Ethics. The trial was  
21  
22 approved by the Tasmanian Human Research Ethics Committee and registered in the Australia New  
23  
24 Zealand Clinical Trials Registry under trial No: ACTRN12609000177257 with web addresses of the  
25  
26 trial as follow: <http://www.ANZCTR.org.au/ACTRN12609000177257.aspx> and the World Health  
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28 Organization website under: [www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202](http://www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202).  
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### 35 **Participants**

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37 Pregnant women aged 18 years or above who presented to the LGH with IDA between 2007 and 2009  
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39 were invited to participate. In the original study, two hundred Caucasian pregnant women aged 18  
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41 years or above were identified with moderate IDA, defined as Hb  $\leq$ 115 g/L (reference range (RR)  
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43 120-160 g/L) and low iron stores based on a serum ferritin level  $<$ 30  $\mu$ g/L (RR 30-440  $\mu$ g/L).  
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46 Of the original 196 pregnant Caucasian women randomised to receive oral iron or a single intravenous  
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48 iron polymaltose infusion, 126 women completed the QoL follow-up study. The median age was 29  
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50 years at enrolment (range, 21 to 43); and the median follow up period was 32 months (range, 26 to 42)  
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53 post-delivery.  
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3 **Randomisation and interventions:** Informed consent was obtained by a research midwife.  
4 Treatment arm was randomised in blocks of 10 and assignment was performed by the LGH Pharmacy  
5 Department in order to avoid possible bias. The oral-only treatment arm comprised iron sulphate 250  
6 mg tablets, (elemental iron 80 mg, Abbott, Australasia Pty Ltd) to be taken daily within two days after  
7 booking until delivery. The IV arm required a single intravenous infusion of iron polymaltose  
8 (Ferrosig, Sigma Pharmaceuticals, Australia) within 1 week after booking followed by oral iron  
9 identical to the other arm. Pre-enrolment, there were no significant differences in the dietary iron  
10 intake or supplement intake between the two groups based on a specially-designed questionnaire  
11 addressing these issues. Patients assigned to IV iron polymaltose received a 100 mg test-dose  
12 dissolved in 50 ml normal saline infused over 30 minutes. Clinical observation and vital signs were  
13 assessed initially and every 15 min from the start of the infusion. After the test-dose was tolerated, the  
14 remainder of iron polymaltose dose was infused. The total dose of IV iron polymaltose was calculated  
15 according to the patient's body weight at their first antenatal visit and entry Hb level according to the  
16 product guidelines; iron dose in mg (50 mg per 1 ml) = body weight (maximum 90) in kg x target Hb  
17 (120 g/L) - actual Hb in g/L) x constant factor (0.24) + iron depot (500).<sup>14</sup>  
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37 **Outcome measurement:** Two Health-Related Quality of Life (HRQoL) questionnaires were  
38 administered during the initial and follow-up studies: Firstly, a clinical questionnaire was completed  
39 prospectively by trained midwives at 4 weeks after initiation of treatment, at 28 and 34 weeks  
40 gestation, and then post delivery. This questionnaire assessed four aspects of energy levels, activity,  
41 tolerance and side effects of treatment, and was used to guide individual patient clinical decision-  
42 making as well as providing a safety audit of the trial treatments.<sup>14</sup> Secondly, a retrospective survey  
43 was conducted between June and October 2010 by trained research personnel via phone interview  
44 using a modified version of the SF-36 questionnaire.<sup>16,17</sup> These modifications included: (1) use of  
45 eleven of the 36 questions (Table 1); and (2) the women were asked to recall their response to each of  
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2 the questions for four time points, pre-trial prior to commencement of iron therapy during the  
3 pregnancy, four weeks after starting iron therapy, one week after delivery, and the last four weeks  
4 prior to the telephone questionnaire contact (Table 1). In order to validate the retrospective use of the  
5 modified SF-36 to assess the women's HRQoL during and after pregnancy, the associations of the  
6 physical activity component of the prospective monitoring questionnaire following entry into the trial  
7 with the Physical Component Scales values of the modified SF-36 at each of the time points were  
8 estimated. We hypothesized that the association would be greatest at 4 weeks compared to trial entry,  
9 time of delivery or at the time of questionnaire completion. In addition, data regarding breastfeeding  
10 and the health of the woman's child were collected from the baby growth booklet. This included  
11 breastfeeding duration, baby gender, age, weight, and previous hospitalization, if any, in addition to  
12 the baby's sleep quality since birth and specific growth data for the children as set by the Australasian  
13 Paediatric Endocrine Group (APEG). Haemoglobin and ferritin levels for participants at delivery were  
14 available for all participants, however no further testing was performed during the follow up. The  
15 principal investigators including the statistician evaluated the questionnaire results data.

### 36 **Statistical methods**

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38 The HRQoL scores that form the raw data for this analysis are rank-order in nature. Means and  
39 standard deviations of the scores were estimated using generalized estimating equations for illustrative  
40 purposes only. Physical and mental composite scores were calculated in the modified SF36 according  
41 to the SF-12 scoring guidelines.<sup>16,17</sup> Group comparison and covariate effect size calculation, odds  
42 ratios (OR with 95% confidence intervals and P values) were estimated using repeated measures of  
43 ordinal logistic regression, with covariates selected for inclusion by backward stepwise regression (P  
44 for exclusion 0.22) from maternal age, haemoglobin, ferritin, Socio-Economic Indexes for Areas  
45 (SEIFA; based on the Collector District of residence of mothers), quality of sleep, use and duration of  
46 breast-feeding, hospitalization of baby, baby gender and mode of delivery. When iron status was  
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2 selected for inclusion in the model, the association between iron status (ferritin) and HRQoL was  
3 reported independently of trial treatment group. P values were corrected for multiple comparisons  
4 where necessary by the Holm method. The effect of IV iron versus oral iron on time of cessation of  
5 breastfeeding was compared by estimation of hazard ratio (HR; 95% confidence intervals and P-  
6 values) by Cox proportional hazards regression adjusted for covariates selected for inclusion by  
7 backward stepwise regression (P for exclusion 0.22). Neonatal growth in the treatment groups was  
8 compared by multivariate third-order polynomial regression as an approximation to APEG growth  
9 assessment. All HRQoL statistical analyses were performed using Stata SE for Windows 11.1  
10 (StataCorp, College Station, Tx USA).  
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## 27 RESULTS

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29 Of the original 196 patients randomised to receive the trial medications (98 received IV plus oral iron;  
30 98 received oral iron only), 183 patients completed the trial by the collection of blood for iron status  
31 estimation at the time of delivery. Data of HRQoL were collected from 126 women, representing 69%  
32 of the cohort who completed the trial, while 31% of patients were uncontactable or did not respond to  
33 the researcher messages (see Figure 1 for description of patient flow). Basic demographic data of  
34 those patients included in the follow-up study showed that the median age was 29 years at enrolment  
35 (range, 21 to 43); and the median follow up was 32 months (range, 26 to 42) post-delivery. There  
36 were no significant differences in demographic or iron status measurements between any of the  
37 groups of women recruited to the trial.  
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51 As reported in the original study, at delivery the proportion of women with lower than normal ferritin  
52 levels was 79% for women who were treated with oral iron as compared to 4.5% for women who  
53 received IV iron ( $p < 0.001$ ).<sup>14</sup> Furthermore, the percentage of women at delivery with Hb level  $< 116$   
54 g/L was 29% in the oral iron group versus 16% in the IV iron group ( $p = 0.04$ ).<sup>14</sup> This indicates that the  
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2 IV iron application was associated with a significantly higher percentage of treated women with  
3 normal ferritin levels and accordingly Hb. The HRQoL Physical Component Scale (OR 1.84; 95% CI  
4 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  
5 improved in the IV compared to the oral iron group, but these differences became less apparent at  
6 subsequent assessment time points (Figure 2a and b).  
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10 Furthermore, there were strong associations between the level of iron status, independent of how that  
11 iron status was achieved, and a number of the HRQoL scales (Figure 2): notably improved General  
12 Health (OR 1.49; 95% CI 1.09 to 2.03; P=0.021), improved Physical Energy (OR 1.36; 95% CI 1.06  
13 to 1.74; P=0.016), less Psychological Downheartedness (OR 1.57; 95% CI 1.14 to 2.15; P=0.005), less  
14 Clinical Depression (OR 2.05; 95% CI 1.27 to 3.32; P=0.003), and overall improved Mental  
15 Component Scale (OR 1.55; 95% CI 1.23 to 1.97; P<0.001). In addition, there was a mild trend  
16 towards a positive association between higher socioeconomic status and improved Mental Component  
17 Scale scores (p=0.17).  
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34 There was an increased duration of breastfeeding (HR for cessation was 0.70; 95% CI 0.50 to 0.99;  
35 p=0.046) in women in the IV iron group (Figure 3) where older women were more likely to breast  
36 feed longer (OR 0.76; 95% CI 1.00 to 1.52; P=0.006) (Table 2). Earlier cessation of breastfeeding was  
37 associated with downheartedness (OR 1.23; 95% CI 1.00 to 1.52; P=0.06). There was no difference  
38 between the oral iron or IV plus oral iron groups in the weight of the baby at birth (p=0.64), and no  
39 difference in the rate of weight gain (p=0.90).  
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48 The association between the physical symptom questions index from the clinical monitoring  
49 questionnaire and the Physical Component Scale of the HRQoL for the four time periods is shown in  
50 Table 3. There was significant association between the physical symptom questions index at 4 weeks  
51 after trial entry and each of the HRQoL recall time points, and that the association was strongest for  
52 the 4 weeks recall (OR 3.18; 2.14 to 4.74; P<0.001). An unanticipated finding of this study was an  
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2 association between male gender babies and an unfavourable mental health component outcome for  
3 participant women across the two groups. Of the seven component questions, two showed a  
4 significant association, with women who had male babies less likely to be calm and peaceful  
5 (OR=0.55, 0.32-0.97, p=0.039) and more likely to have accomplished less than they would have liked  
6 to as a result of their emotional state (OR=1.33, 1.05-1.69, p=0.018).  
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## 14 **DISCUSSION**

15  
16 We report on 126 patients in a follow up study of the effect of IV iron versus oral iron therapy during  
17 pregnancy on long-term HRQoL. There are no data available studying the effects of both IV and oral  
18 iron on post-delivery psychological and physical welfare of the mother, the quality of the bonding to  
19 her baby and the rate of developmental progress of the baby. Our study demonstrates that there was an  
20 improvement in the self-assessed feeling of general health in both treatment groups from the pre-  
21 labour period to all subsequent periods. Although the improvement was significantly greater in the IV  
22 iron group 4 weeks after commencement of trial treatment (p=0.02), at subsequent measurement  
23 periods the difference persisted at a lesser magnitude that did not achieve a statistical significance.  
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36 Regardless of treatment and regardless of which period was being considered, higher haemoglobin  
37 and higher ferritin levels were associated with better baby sleep quality and the mother breastfeeding  
38 as well as higher assessment of general health.  
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43 The HRQoL questionnaire includes many useful relevant aspects regarding general health, activities,  
44 level of energy and depression. There was a substantial improvement of iron status in women who  
45 received IV iron as demonstrated during the trial analysis. Criticism may arise due to the modified  
46 questionnaire being a retrospective HR-QoL evaluation which should ideally have been conducted  
47 within a shorter period of time, even though the opportunity for a prospective evaluation had been  
48 missed in our study. Therefore in order to overcome a possible recall bias, the number of retrospective  
49 questions would be needed to be abbreviated, since the women were asked to recall their responses to  
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2 each question at four different time points, so the full SF-36 was impractical and may be judged to be  
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4 an excessive burden on the women. Thus, we attempted to provide a retrospective form of validation  
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6 by showing that the clinical HR-QoL questions in the physical domain, recorded prospectively at  
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8 week 4 after trial, were most strongly associated with the Physical Component Scales of the recall of  
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10 modified SF-36 at week 4 compared to the other time points. This indicates that the retrospective  
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12 methodology was able to provide an acceptable degree of accuracy in the differentiation of HR-QoL  
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14 levels at different time points despite the concerns that may have arisen with this issue. The  
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16 assumption being made is that the way those patients will judge their physical and mental condition  
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18 will be relatively stable over time,<sup>18</sup> an assumption with which we agree that may occur in patients  
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20 with chronic diseases. However, this assumption may not hold for women during and after pregnancy.  
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22 The expectations by the woman about how she should be feeling at the different stages of pregnancy,  
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24 around the time of delivery, and when she is caring for one or more young infant and child may differ  
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26 substantially at those different time points. At least in our analysis the judgment the woman is making  
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28 about how to answer the questions is likely to be the same for each time point, since she had made that  
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30 judgment at one point in time: the repeated measures analysis compares each woman with herself,  
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32 thus substantially reducing the impact of variation between women in this judgment. Thus, for the  
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34 purpose of generating a hypothesis concerning iron status and quality of life, we believe that our  
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36 methodology has been adequate. Despite of the relative small number of women studied, it is  
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38 worthwhile publishing our study due to lack of researches that address HRQoL during and after  
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40 pregnancy, particularly, in view of the emerging novel association between iron status and postnatal  
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42 clinical depression as well as breastfeeding duration in our cohort of patients.  
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51 Regarding the incidental findings of unfavourable mental health component outcomes for women with  
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53 male babies, there is only a single report in the literature addressing this issue with similar findings.<sup>19</sup>  
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56 Perhaps this may be explained with the observation that male babies are usually more active and this  
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2 may be associated with post natal depression.<sup>19</sup> However, due to lack of data, this issue should be  
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4 addressed separately and studied thoroughly in future research.  
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10 In summary, there was a significant improvement in the general health of women who received IV  
11 iron ( $p=0.02$ ), but this effect was found directly after the IV iron treatment. The duration of breast-  
12 feeding was longer ( $p=0.04$ ) in those women who had received IV iron. Women with better iron status  
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14 were less downhearted ( $p=0.005$ ) and less likely to develop postnatal clinical depression ( $p=0.003$ ).  
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18 Our results would indicate that it is worthwhile considering Hb and iron status as a surrogate marker  
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20 for assessment of women's wellbeing, not only during pregnancy, but also during the postnatal period.  
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24 Further studies are warranted to confirm and extend our findings, and to determine outcomes in  
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26 different populations with IDA in order to improve the estimates of the magnitude of the benefits of  
27  
28 intravenous iron for the management of iron deficiency anaemia.  
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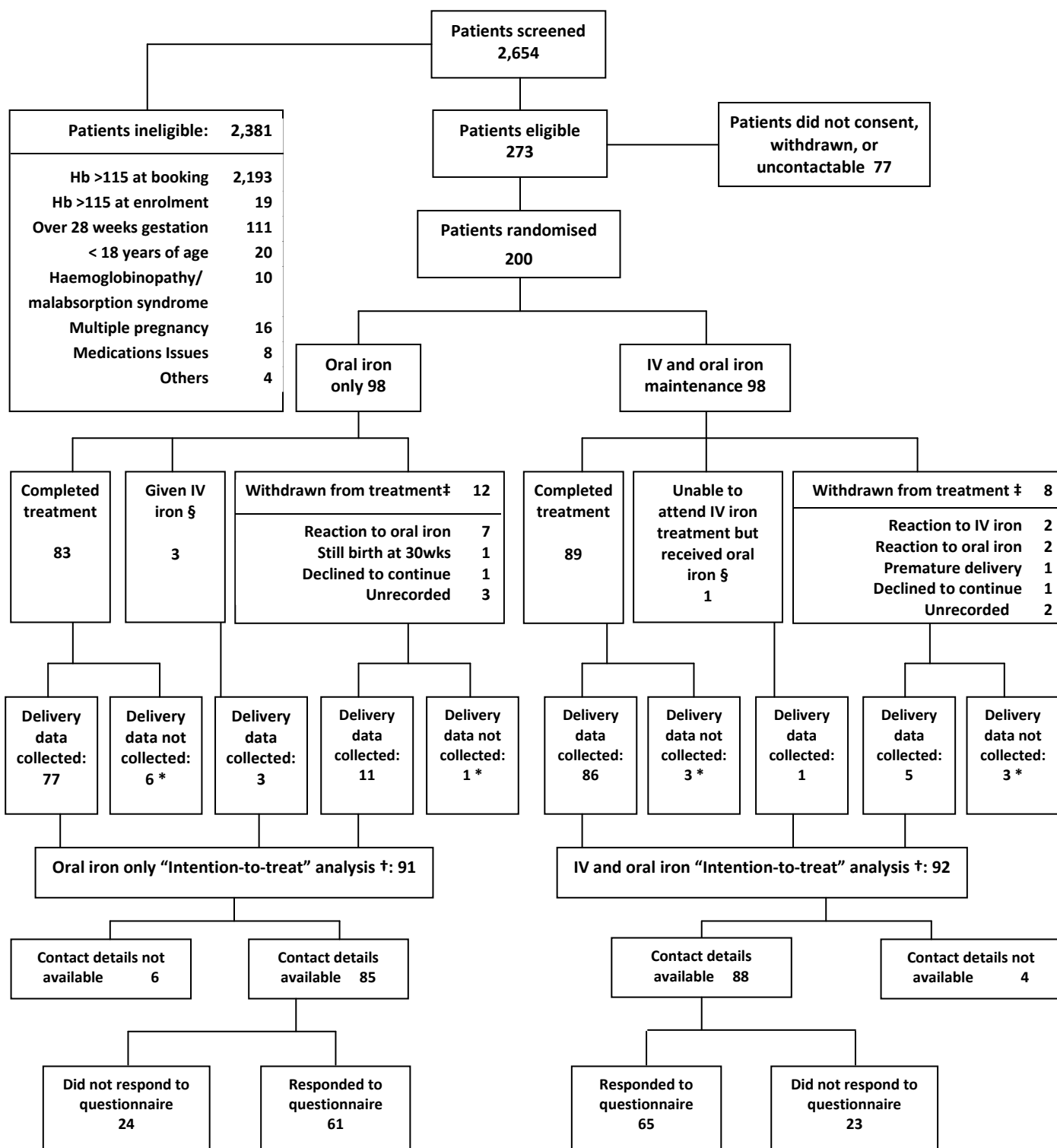
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Figure 1. Trial flow diagram: disposition of study participants by treatment assignment.



**Footnotes to Figure 1. Patients Flow Chart.**

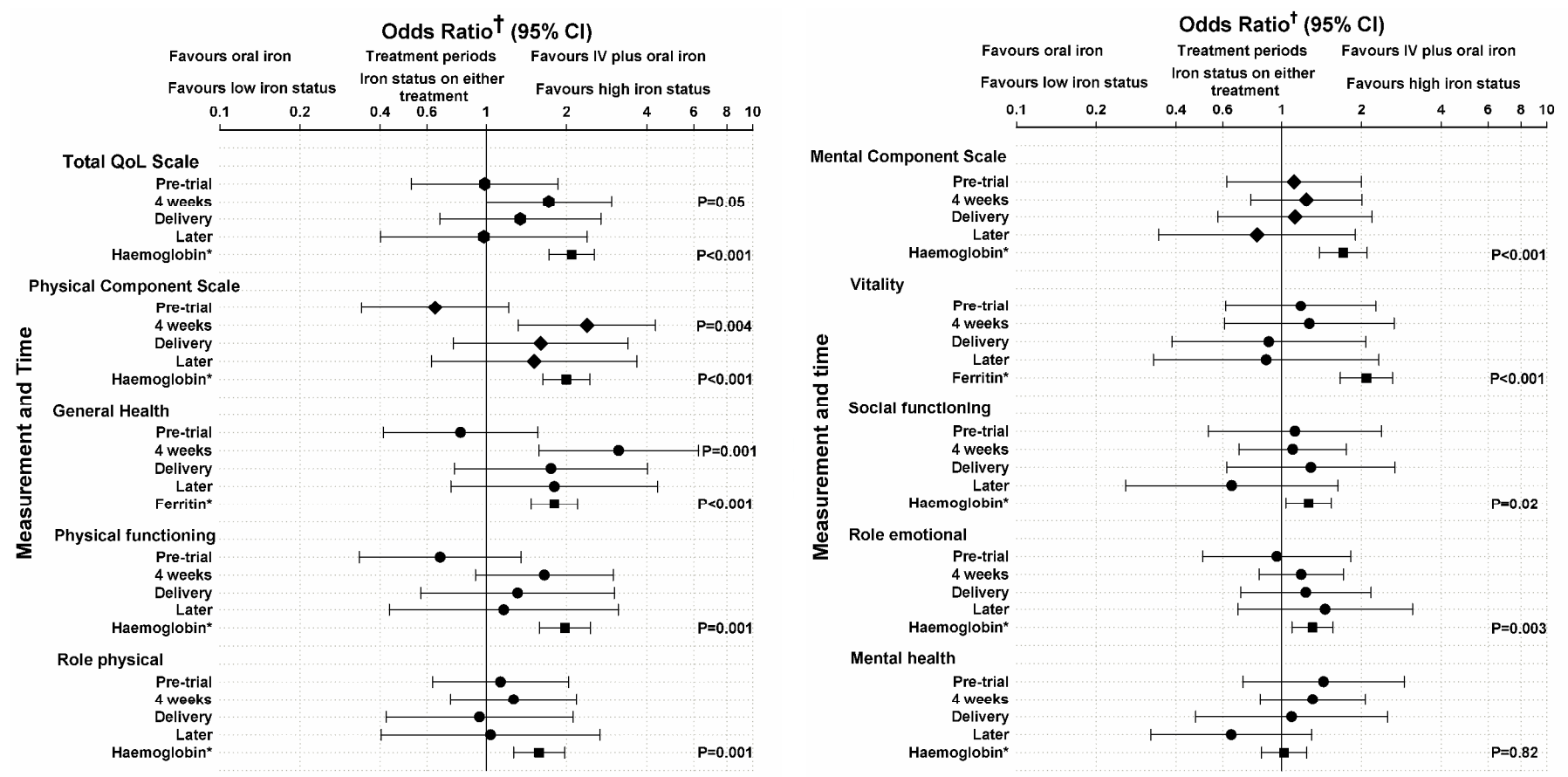
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4 \* Fourteen patients were admitted late in labour, and no blood samples were taken before delivery  
5 † The primary hypothesis examined the change in haemoglobin levels between the time of booking and immediately prior to  
6 delivery; an “intention-to-treat” analysis was performed according to original randomization group on those patients who  
7 had blood samples taken before delivery, whether or not the treatment was completed as per protocol  
8 ‡ Twenty one patients withdrew from the trial treatments, and all but one of these patients agreed to continued collection of  
9 haematological and other trial data; eight patients gave no reason for withdrawal  
10 § Five patients did not complete the intended treatments, but did not themselves choose to withdraw; three patients in the  
11 oral iron group were treated with IV iron when their haemoglobin was judged not to have responded adequately to oral  
12 iron, whilst one patient was unable to attend for IV iron treatment  
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**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
<b>Question: stem and detailed item</b>	<b>Response and Question number:</b>	<b>Response and Question number:</b>
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 <sup>1</sup>	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

<sup>1</sup> 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.

<sup>2</sup> Abbreviations: NVD – normal vaginal delivery; LSCS – lower segment caesarean section

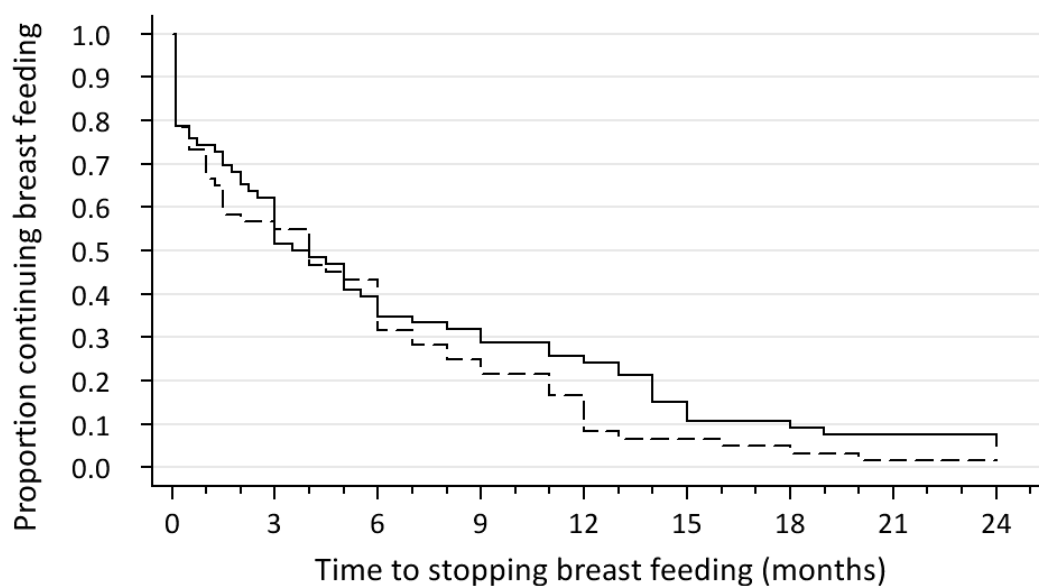
**Table 3.** Association between the physical symptom questions<sup>3</sup> in from the prospective clinical monitoring questionnaire and the Physical Component Scale of the retrospective HRQoL for the four time periods.

Time	Slope (SD) <sup>1</sup>	OR <sup>2a</sup>	95%CI	P-value	OR <sup>2b</sup>	95%CI	P-value
Pre-trial	2.67 (13.0) <sup>1</sup>	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

<sup>1</sup> 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).

<sup>2</sup> The strength of that <sup>a)</sup> absolute association at each time point, and <sup>b)</sup> 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).

<sup>3</sup> 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

Number at risk

IV plus oral	66	41	26	21	17	10	7	4	3
Oral	60	34	26	15	10	4	3	1	1

———— IV plus oral      - - - - - Oral

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}).



**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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<b>Primary Subject Heading</b>:	Reproductive medicine, obstetrics and gynaecology
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Keywords:	Anaemia < HAEMATOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Maternal medicine < OBSTETRICS, QUALITATIVE RESEARCH
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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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**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 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 2<sup>nd</sup> and 3<sup>rd</sup> 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.

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4 **Trial registration:** Australia and New Zealand Clinical Trial Registry under:  
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6 <http://www.ANZCTR.org.au> under ACTRN 12609000177257 and in the World Health Organization  
7  
8 website under: [www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202](http://www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202).  
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11  
12 **Funding:** This research received a grant from the Clifford Craig Medical Research Trust, Launceston,  
13  
14 Tasmania, Australia.  
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17  
18 **Key words:** Quality of life assessment, iron deficiency anaemia, oral iron, intravenous iron,  
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20 pregnancy, long-term effect.  
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## 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,<sup>1-3</sup> IDA is a potential risk factor for preterm delivery and subsequent low birth weight and may be associated with inferior neonatal health.<sup>3-4</sup> 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.<sup>5-9</sup> 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.<sup>10,11</sup> 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.<sup>3,10,11</sup> 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.<sup>10,11</sup> Furthermore, the presence of chronic bowel disease can affect the absorption of iron, minimising the benefit received from oral iron therapy.<sup>11</sup>

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

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

1  
2 therapies on the perceived health-related quality of life (HRQoL) as measured by a modified SF36  
3 questionnaire as well as the effect of iron therapy on breastfeeding rates and on the general wellbeing  
4 of the babies born to these women as measured by child growth charts set by the Australasian  
5 Paediatric Endocrine Group (APEG).  
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### 11 **Rationale and objectives**

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

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47 The initial prospective randomised-controlled trial was conducted between March 2007 and January  
48 2009 at the Launceston General Hospital (LGH), a tertiary referral centre for Northern Tasmania,  
49 Australia. This follow-up study took place between January 2010 and January 2011. An informed  
50 consent form was obtained from all participants according to the Code of Ethics. The original and the  
51 follow-up studies were approved by the Tasmanian Human Research Ethics Committee and registered  
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2 in the Australia New Zealand Clinical Trials Registry under trial No: ACTRN12609000177257 with  
3  
4 web addresses of the trial as follow: <http://www.ANZCTR.org.au/ACTRN12609000177257.aspx> and  
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7 the World Health Organization website under:  
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9 [www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202](http://www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202).

## 14 Participants

15  
16 Pregnant women aged 18 years or above who presented to the LGH with IDA between 2007 and 2009  
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18 were invited to participate. In the original study, two hundred Caucasian pregnant women aged 18  
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20 years or above were identified with moderate IDA, defined as Hb  $\leq$ 115 g/L (reference range (RR)  
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22 120-160 g/L) and low iron stores based on a serum ferritin level  $<$ 30  $\mu$ g/L (RR 30-440  $\mu$ g/L).  
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26 Of the original evaluable 183 pregnant Caucasian women randomised to receive oral iron or a single  
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28 intravenous iron polymaltose infusion, 126 women completed the QoL follow-up study (Table 1). The  
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30 median age was 29 years at enrolment (range, 21 to 43); and the median follow up period was 32  
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32 months (range, 26 to 42) post-delivery.  
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37 **Randomisation and interventions:** Informed consent was obtained by a research midwife.  
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39 Treatment arm was randomised in blocks of 10 and assignment was performed by the LGH Pharmacy  
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41 Department in order to avoid any possible bias. The oral-only treatment arm comprised iron sulphate  
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43 250 mg tablets, (elemental iron 80 mg, Abbott, Australasia Pty Ltd) to be taken daily within two days  
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45 after booking until delivery. The IV arm required a single intravenous infusion of iron polymaltose  
46  
47 (Ferrosig, Sigma Pharmaceuticals, Australia) within 1 week after booking followed by oral iron  
48  
49 identical to the other arm. Pre-enrolment, there were no significant differences in the dietary iron  
50  
51 intake or supplement intake between the two groups based on a specially-designed questionnaire  
52  
53 addressing these issues. Patients assigned to IV iron polymaltose received a 100 mg test-dose  
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1  
2 dissolved in 50 ml normal saline infused over 30 minutes. Clinical observation and vital signs were  
3  
4 assessed initially and every 15 min from the start of the infusion. After the test-dose was tolerated, the  
5  
6 remainder of iron polymaltose dose was infused. The total dose of IV iron polymaltose was calculated  
7  
8 according to the patient's body weight at their first antenatal visit and entry Hb level according to the  
9  
10 product guidelines; iron dose in mg (50 mg per 1 ml) = body weight (maximum 90) in kg x target Hb  
11  
12 (120 g/L) - actual Hb in g/L) x constant factor (0.24) + iron depot (500).<sup>14</sup>  
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16 **Outcome measurement:** Two Health-Related Quality of Life (HRQoL) questionnaires were  
17  
18 administered during the initial and follow-up studies: Firstly, a clinical questionnaire was completed  
19  
20 prospectively by trained midwives at 4 weeks after initiation of treatment, at 28 and 34 weeks  
21  
22 gestation, and then 6-8 weeks post delivery. This questionnaire assessed four aspects of energy levels,  
23  
24 activity, tolerance and side effects of treatment, and was used to guide individual patient clinical  
25  
26 decision-making as well as providing a safety audit of the trial treatments.<sup>14</sup> Secondly, a prospective/  
27  
28 retrospective survey was conducted between June and October 2010 by trained research personnel via  
29  
30 phone interview using a modified version of the SF-36 questionnaire.<sup>16,17</sup> These modifications  
31  
32 included: (1) use of eleven of the 36 questions (Table 2); and (2) the women were asked to recall their  
33  
34 response to each of the questions for four time points, pre-trial prior to commencement of iron therapy  
35  
36 during the pregnancy, four weeks after starting iron therapy, one week after delivery, and the last four  
37  
38 weeks prior to the telephone questionnaire contact (Table 2). This has been compared to the same  
39  
40 questions answered prospectively by the participants. In order to validate the retrospective use of the  
41  
42 modified SF-36 to assess the women's HRQoL during and after pregnancy, the associations of the  
43  
44 physical activity component of the prospective monitoring questionnaire following entry into the trial  
45  
46 with the Physical Component Scales values of the modified SF-36 at each of the time points were  
47  
48 estimated. We hypothesized that the association would be greatest at 4 weeks compared to trial entry,  
49  
50 time of delivery or at the time of questionnaire completion. In addition, data regarding breastfeeding  
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1  
2 and the health of the woman's child were collected from the baby growth booklet. This included  
3  
4 breastfeeding duration, baby gender, age, weight, and previous hospitalization, if any, in addition to  
5  
6 the baby's sleep quality since birth and specific growth data for the children as set by the Australasian  
7  
8 Paediatric Endocrine Group (APEG). Haemoglobin and ferritin levels for participants at delivery were  
9  
10 available for all participants, however no further testing was performed during the follow up. The  
11  
12 principal investigators including the statistician evaluated the questionnaire results data.  
13  
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15

### 16 17 **Statistical methods**

18  
19 The HRQoL scores that form the raw data for this analysis are rank-order in nature. Means and  
20  
21 standard deviations of the scores were estimated using generalized estimating equations for illustrative  
22  
23 purposes only. Physical and mental composite scores were calculated in the modified SF36 according  
24  
25 to the SF-12 scoring guidelines.<sup>16,17</sup> Group comparison and covariate effect size calculation, odds  
26  
27 ratios (OR with 95% confidence intervals and P values) were estimated using repeated measures of  
28  
29 ordinal logistic regression, with covariates selected for inclusion by backward stepwise regression (P  
30  
31 for exclusion 0.22) from maternal age, haemoglobin, ferritin, Socio-Economic Indexes for Areas  
32  
33 (SEIFA; based on the Collector District of residence of mothers), quality of sleep, use and duration of  
34  
35 breast-feeding, hospitalization of baby, baby gender and mode of delivery. **This included**  
36  
37 **randomization group covariate interactions in the starting model with exclusion of those**  
38  
39 **interactions using the above criteria.** When iron status was selected for inclusion in the model, the  
40  
41 association between iron status (ferritin) and HRQoL was reported independently of trial treatment  
42  
43 group. P values were corrected for multiple comparisons where necessary by the Holm method. The  
44  
45 effect of IV iron versus oral iron on time of cessation of breastfeeding was compared by estimation of  
46  
47 hazard ratio (HR; 95% confidence intervals and P-values) by Cox proportional hazards regression  
48  
49 adjusted for covariates selected for inclusion by backward stepwise regression (P for exclusion 0.22).  
50  
51 **The time to cessation of breast-feeding was taken from the subject's baby growth booklet for all**  
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1  
2 **participants.** Neonatal growth in the treatment groups was compared by multivariate third-order  
3  
4 polynomial regression as an approximation to APEG growth assessment. All HRQoL statistical  
5  
6 analyses were performed using Stata SE for Windows 11.1 (StataCorp, College Station, Tx USA).  
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## 10 11 12 **RESULTS**

13  
14 Of the original 196 patients randomised to receive the trial medications (98 received IV plus oral iron;  
15  
16 98 received oral iron only), 183 patients completed the trial by the collection of blood for iron status  
17  
18 estimation at the time of delivery. Data of HRQoL were collected from 126 **of the 183** women who  
19  
20 completed the original trial, representing 69% of the cohort who completed the trial, while **57** (31%)  
21  
22 **of the 183** patients were moved away, uncontactable or did not respond to the researcher messages  
23  
24 (see Figure 1 for description of patient flow). Basic demographic data of those patients included in the  
25  
26 follow-up study showed that the median age was 29 years at enrolment (range, 21 to 43); and the  
27  
28 median follow up was 32 months (range, 26 to 42) post-delivery. There were no significant  
29  
30 differences in demographic or iron status measurements between any of the groups of women  
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32 recruited to the trial.  
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40 As reported in the original study, at delivery the proportion of women with lower than normal ferritin  
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42 levels was **53 of 67** (79%) for women **with analysable iron status measurements** who were treated  
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44 with oral iron as compared to **3 of 66** (4.5%) for women who received IV iron (**Fisher's exact**  
45  
46  $p < 0.001$ ).<sup>14</sup> Furthermore, the percentage of women at delivery with Hb level  $< 116$  g/L was 29% (**25**  
47  
48 **of 85**) in the oral iron group versus 16% (**14 of 87**) in the IV iron group ( $p = 0.04$ ).<sup>14</sup> This indicates that  
49  
50 the IV iron application was associated with a significantly higher percentage of treated women with  
51  
52 normal ferritin levels and accordingly Hb. **The HRQoL Physical Component Scale (difference**  
53  
54 **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**  
55  
56 **(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**  
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1  
2 were improved in the IV compared to the oral iron group, but these differences became less  
3  
4 apparent at subsequent assessment time points (Figure 2a and b).

5  
6  
7 Furthermore, there were strong associations between the level of iron status, independent of  
8  
9 how that iron status was achieved, and a number of the HRQoL scales (Figure 2): notably  
10 improved General Health (slope {1SD log.-ferritin} 10.0; 7.2 to 12.7; P<0.001; OR 1.49; 95% CI  
11 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  
12 2.09; 95% CI 1.66 to 2.62; P<0.001), less Psychological Downheartedness ({1SD haemoglobin}  
13 OR 1.57; 95% CI 1.14 to 2.15; P=0.005), less Clinical Depression ({1SD log.-ferritin} OR 2.05;  
14 95% CI 1.27 to 3.32; P=0.003), and overall improved Mental Component Scale (slope {1SD  
15 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  
16 Downheartedness and Clinical Depression analysis used raw scores rather than 100-point  
17 scales).

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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,

1  
2 were most strongly associated with the Physical Component Scales of the recall of modified SF-36 at  
3  
4 week 4 compared to the other time points. This indicates that the retrospective methodology was able  
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6 to provide an acceptable degree of accuracy in the differentiation of HRQoL levels at different time  
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8 points despite the concerns that may have arisen with this issue. The assumption being made is that  
9  
10 the way those patients will judge their physical and mental condition will be relatively stable over  
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12 time,<sup>18</sup> an assumption with which we agree that may occur in patients with chronic diseases. However,  
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14 this assumption may not hold for women during and after pregnancy. The expectations by the woman  
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16 about how she should be feeling at the different stages of pregnancy, around the time of delivery, and  
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18 when she is caring for one or more young infant and child may differ substantially at those different  
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20 time points. At least in our analysis the judgment the woman is making about how to answer the  
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22 questions is likely to be the same for each time point, since she had made that judgment at one point in  
23  
24 time: the repeated measures analysis compares each woman with herself, thus substantially reducing  
25  
26 the impact of variation between women in this judgment. Thus, for the purpose of generating a  
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28 hypothesis concerning iron status and quality of life, we believe that our methodology has been  
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30 adequate. Other limitations of our study include a relatively small number of women studied.  
31  
32 However, it is worthwhile publishing our study due to lack of researches that address HRQoL during  
33  
34 and after pregnancy, particularly, in view of the emerging novel association between iron status and  
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36 postnatal clinical depression as well as breastfeeding duration in our cohort of patients.  
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39  
40 Regarding the incidental findings of the trend for unfavourable mental health component outcomes for  
41  
42 women with male babies, there is only a single report in the literature addressing this issue with  
43  
44 similar findings.<sup>19</sup> Perhaps this may be explained with the observation that male babies are usually  
45  
46 more active and this may be associated with post natal depression.<sup>19</sup> However, due to lack of data, this  
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48 issue should be addressed separately and studied thoroughly in future research.  
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**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.<sup>20</sup> 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.<sup>20</sup> The study focused on patients HRQoL recovery after both delivery interventions. In this study<sup>20</sup>, 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.

1  
2 Further studies are warranted to confirm and extend our findings, and to determine outcomes in  
3  
4 different populations with IDA in order to improve the estimates of the magnitude of the benefits of  
5  
6 intravenous iron for the management of iron deficiency anaemia.  
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### 10 11 **Acknowledgements:**

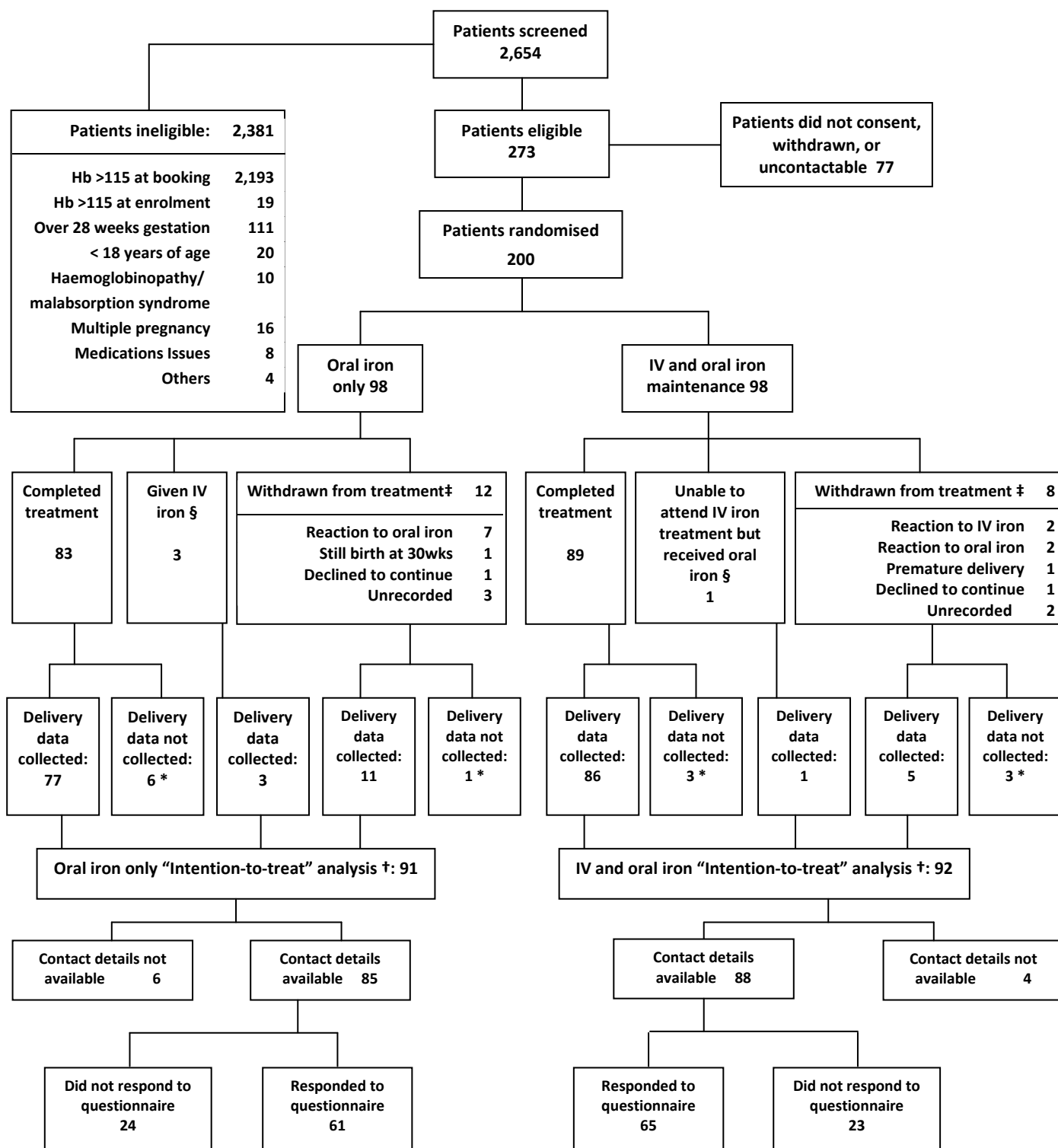
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**Figure 1.** Trial flow diagram: disposition of study participants by treatment assignment.





**Footnotes to Figure 1. Patients Flow Chart.**

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4 \* Fourteen patients were admitted late in labour, and no blood samples were taken before delivery  
5 † The primary hypothesis examined the change in haemoglobin levels between the time of booking and immediately prior to  
6 delivery; an “intention-to-treat” analysis was performed according to original randomization group on those patients who  
7 had blood samples taken before delivery, whether or not the treatment was completed as per protocol  
8 ‡ Twenty one patients withdrew from the trial treatments, and all but one of these patients agreed to continued collection of  
9 haematological and other trial data; eight patients gave no reason for withdrawal  
10 § Five patients did not complete the intended treatments, but did not themselves choose to withdraw; three patients in the  
11 oral iron group were treated with IV iron when their haemoglobin was judged not to have responded adequately to oral  
12 iron, whilst one patient was unable to attend for IV iron treatment  
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**Table 1.** Patients Characteristics

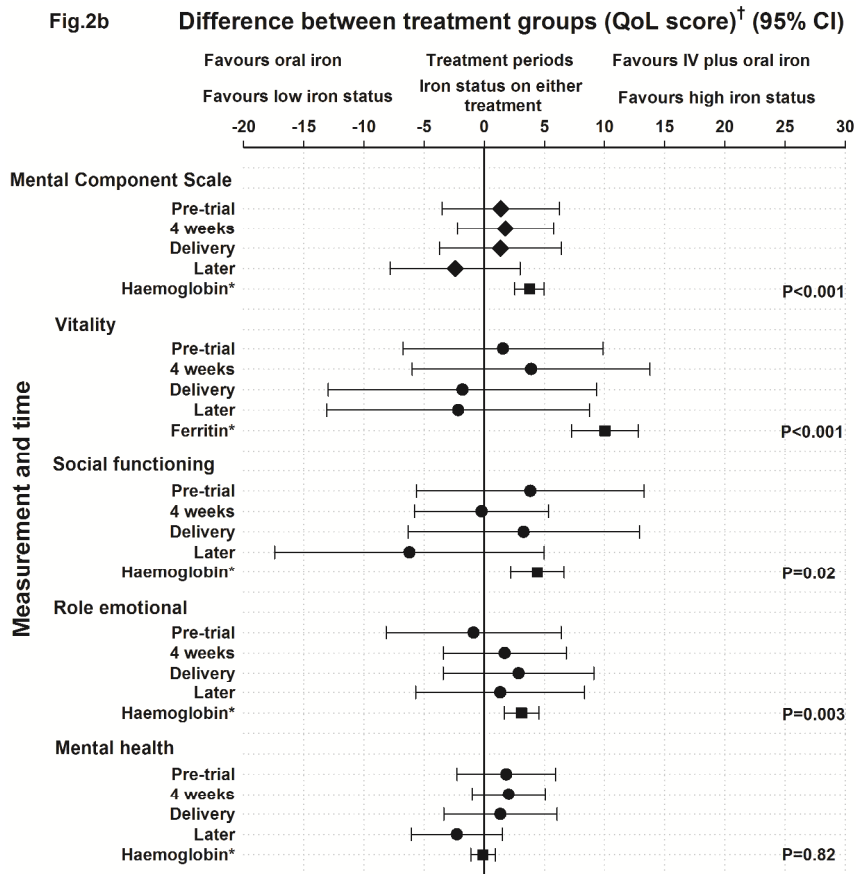
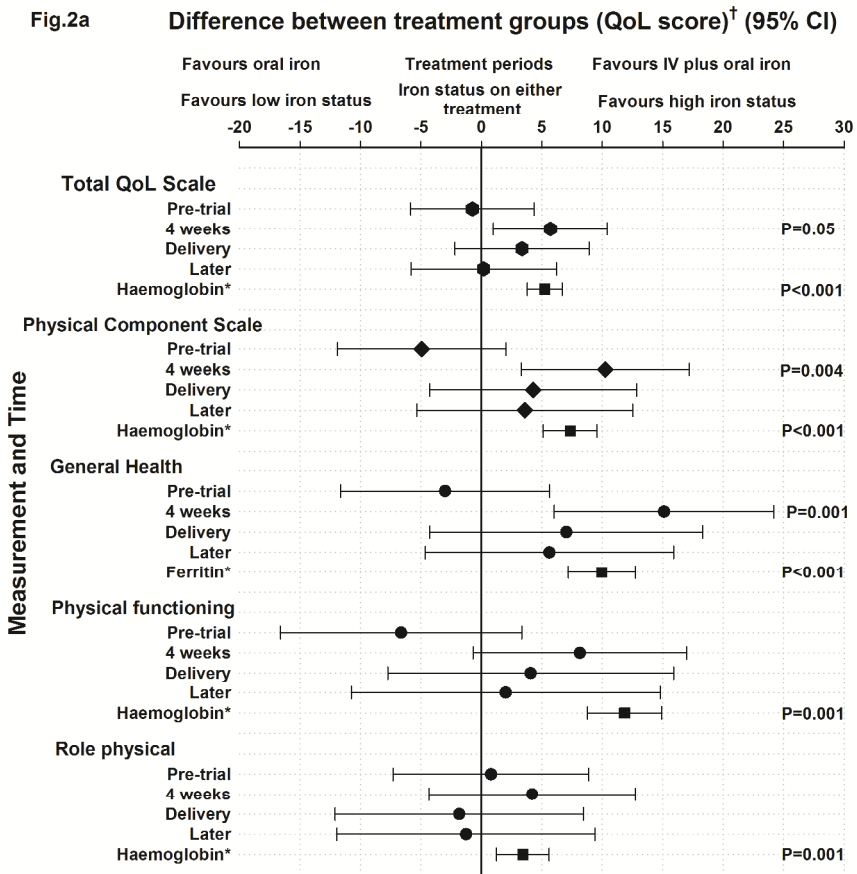
	<b>IV iron group</b>	<b>Oral iron group</b>
No of patients	64	62
Vaginal delivery	45	46
Caesarean section	19	16
Median age in years	28 years (range; 21-43)	28.5 years (Range; 22-42)
Mean age in years	27.5 years	28
Median time between trial intervention and delivery in months	2.7 months ( range; 2.6-6)	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
<b>Question: stem and detailed item</b>	<b>Response and Question number:</b>	<b>Response and Question number:</b>
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 <sup>1</sup>	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

<sup>1</sup> **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 ( $\{\text{mother's age} - \text{group mean age}\} / \text{group standard deviation of age}$ ): mean age  $28.1 \pm 5.6$  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.**

<sup>2</sup> Abbreviations: NVD – normal vaginal delivery; LSCS – lower segment caesarean section

**Table 4.** Association between the physical symptom questions<sup>3</sup> in from the prospective clinical monitoring questionnaire and the Physical Component Scale of the retrospective HRQoL for the four time periods.

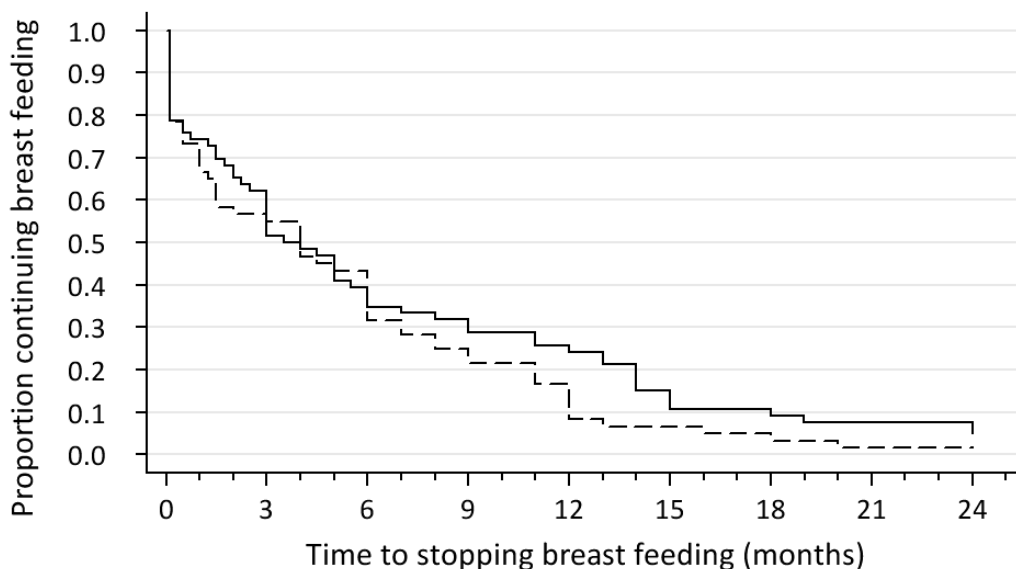
Time	Slope (SD) <sup>1</sup>	OR <sup>2a</sup>	95%CI	P-value	OR <sup>2b</sup>	95%CI	P-value
Pre-trial	2.67 (13.0) <sup>1</sup>	1.46	(1.01 to 2.11)	0.043	1.00		
4 weeks	8.07 (18.6)	3.18	(2.11 to 4.80)	<0.001	2.18	(1.44 to 3.28)	<0.001
Delivery	4.91 (12.2)	2.14	(1.37 to 3.35)	<0.001	1.46	(0.94 to 2.29)	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

<sup>1</sup> 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).

<sup>2</sup> The strength of that <sup>a)</sup> absolute association at each time point, and <sup>b)</sup> 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).

<sup>3</sup> 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



Number at risk		0	3	6	9	12	15	18	21	24
IV plus oral	65	41	26	21	17	10	7	4	3	
Oral	61	34	26	15	10	4	3	1	1	

IV plus oral    
  Oral

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
<b>Title and abstract</b>	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
<b>Introduction</b>			
Background/rationale	2	Scientific background and the rationale for the study were stated	5,6
Objectives	3	Aims and objective were mentioned	6
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6-8
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	9
		(e) Describe any sensitivity analyses	Not applicable
<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	10,11
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	Not applicable
		<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://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-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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<b>Primary Subject Heading</b>:	Reproductive medicine, obstetrics and gynaecology
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
<p>Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.</p> <p>Suppl_Tables.docm</p>	

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## 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 2<sup>nd</sup> and 3<sup>rd</sup> 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.

1  
2  
3 **Trial registration:** Australia and New Zealand Clinical Trial Registry under:  
4 <http://www.ANZCTR.org.au> under ACTRN 12609000177257 and in the World Health Organization  
5 website under: [www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202](http://www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202).  
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11 **Funding:** This research received a grant from the Clifford Craig Medical Research Trust, Launceston,  
12 Tasmania, Australia.  
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16 **Key words:** Quality of life assessment, iron deficiency anaemia, oral iron, intravenous iron,  
17 pregnancy, long-term effect.  
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## 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,<sup>1-3</sup> IDA is a potential risk factor for preterm delivery and subsequent low birth weight and may be associated with inferior neonatal health.<sup>3-4</sup> 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.<sup>5-9</sup> 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.<sup>10,11</sup> 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.<sup>3,10,11</sup>

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

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}).<sup>14</sup> 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



1  
2 the World Health Organization website under:  
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4 [www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202](http://www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202).  
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## 9 **Participants**

10 Pregnant women aged 18 years or above who presented to the LGH with IDA between 2007 and 2009  
11 were invited to participate. In the original study (Figure 1), two hundred Caucasian pregnant women  
12 aged 18 years or above were identified with moderate IDA, defined as Hb  $\leq$ 115 g/L (reference range  
13 (RR) 120-160 g/L) and low iron stores based on a serum ferritin level  $<$ 30  $\mu$ g/L (RR 30-440  $\mu$ g/L).  
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19 Of the original evaluable 183 pregnant Caucasian women randomised to receive oral iron or a single  
20 intravenous iron polymaltose infusion, 126 women completed the QoL follow-up study (Table 1). The  
21 median age was 29 years at enrolment (range, 21 to 43); and the median follow up period was 32  
22 months (range, 26 to 42) with an average follow-up period of 36 months post-delivery.  
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## 33 **Randomisation and interventions**

34 Informed consent was obtained by a research midwife. Treatment arm was randomised in blocks of 10  
35 and assignment was performed by the LGH Pharmacy Department in order to avoid any possible bias.  
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37 The oral-only treatment arm comprised iron sulphate 250 mg tablets, (elemental iron 80 mg, Abbott,  
38 Australasia Pty Ltd) to be taken daily within two days after booking until delivery. The IV arm  
39 required a single intravenous infusion of iron polymaltose (Ferrosig, Sigma Pharmaceuticals,  
40 Australia) within 1 week after booking followed by oral iron identical to the other arm. Pre-enrolment,  
41 there were no significant differences in the dietary iron intake or supplement intake between the two  
42 groups based on a specially-designed questionnaire addressing these issues. Patients assigned to IV  
43 iron polymaltose received a 100 mg test-dose dissolved in 50 ml normal saline infused over 30  
44 minutes. Clinical observation and vital signs were assessed initially and every 15 min from the start of  
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2 the infusion. After the test-dose was tolerated, the remaining of iron polymaltose dose was infused.  
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4 The total dose of IV iron polymaltose was calculated according to the patient's body weight at their  
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6 first antenatal visit and entry Hb level according to the product guidelines; iron dose in mg (50 mg per  
7  
8 1 ml) = body weight (maximum 90) in kg x target Hb (120 g/L) - actual Hb in g/L) x constant factor  
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10 (0.24) + iron depot (500).<sup>14</sup>  
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### 14 15 16 17 **Outcome measurement**

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20 Two Health-Related Quality of Life (HRQoL) questionnaires were administered during the initial and  
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22 follow-up studies: Firstly, a clinical questionnaire was completed prospectively by trained midwives  
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24 at 4 weeks after initiation of treatment, at 28 and 34 weeks gestation, and then 6-8 weeks post  
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26 delivery. This questionnaire assessed four aspects; energy levels, activity, tolerance and side effects of  
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28 treatment, and was used to guide individual patient clinical decision-making as well as providing a  
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30 safety audit of the trial treatments.<sup>14</sup> Secondly, a prospective/retrospective survey was conducted  
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32 between June and October 2010 by trained research personnel via phone interview using a modified  
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34 version of the SF-36 questionnaire.<sup>16,17</sup> These modifications included: (1) use of eleven of the 36  
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36 questions (Table 2); and (2) the women were asked to recall their response to each of the questions for  
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38 four time points, pre-trial prior to commencement of iron therapy during the pregnancy, four weeks  
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40 after starting iron therapy, one week after delivery, and the last four weeks prior to the telephone  
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42 questionnaire contact (Table 2). This has been compared in retrospect to the same questions answered  
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44 prospectively by the participants at these different times. In order to validate the retrospective use of  
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46 the modified SF-36 to assess the women's HRQoL during and after pregnancy, the associations of the  
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48 physical activity component of the prospective monitoring questionnaire following entry into the trial  
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50 with the Physical Component Scale values of the modified SF-36 at each of the time points were  
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52 estimated. We hypothesized that the association would be greatest at 4 weeks compared to trial entry,  
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2 time of delivery or at the time of questionnaire completion. In addition, data regarding breastfeeding  
3 and the health of the woman's child were collected from the baby's growth booklet. This included  
4 breastfeeding duration, baby gender, age, weight, and previous hospitalization, if any, in addition to  
5  
6 the baby's sleep quality since birth and specific growth data for the children as set by the Australasian  
7 Paediatric Endocrine Group (APEG). Haemoglobin and ferritin levels for participants at delivery were  
8 available for all participants, however no further testing was performed during the follow up. The  
9 principal investigators, including the statistician, evaluated the questionnaire results data.  
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### 19 **Statistical methods**

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21 The HRQoL scores that form the raw data for this analysis are rank-order in nature. Means and  
22 standard deviations of the scores were estimated using generalized estimating equations for illustrative  
23 purposes only. Physical and mental composite scores were calculated in the modified SF36 according  
24 to the SF-12 scoring guidelines.<sup>16,17</sup> Group comparison and covariate effect size calculation, odds  
25 ratios (OR with 95% confidence intervals and P values) were estimated using repeated measures of  
26 ordinal logistic regression, with covariates selected for inclusion by backward stepwise regression (P  
27 for exclusion 0.22) from maternal age, haemoglobin, ferritin, Socio-Economic Indexes for Areas  
28 (SEIFA; based on the Collector District of residence of mothers), quality of sleep, use and duration of  
29 breast-feeding, hospitalization of baby, baby gender and mode of delivery. This included  
30 randomization group covariate interactions in the starting model with exclusion of those interactions  
31 using the above criteria. When iron status was selected for inclusion in the model, the association  
32 between iron status (ferritin) and HRQoL was reported independently of trial treatment group. P  
33 values were corrected for multiple comparisons where necessary by the Holm method. The effect of  
34 IV iron versus oral iron on time of cessation of breastfeeding was compared by estimation of hazard  
35 ratio (HR; 95% confidence intervals and P-values) by Cox proportional hazards regression adjusted  
36 for covariates selected for inclusion by backward stepwise regression (P for exclusion 0.22). The time  
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2 to cessation of breast-feeding was taken from the subject's baby growth booklet for all participants.  
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4 Neonatal growth in the treatment groups was compared by multivariate third-order polynomial  
5  
6 regression as an approximation to APEG growth assessment. All HRQoL statistical analyses were  
7  
8 performed using Stata SE for Windows 11.1 (StataCorp, College Station, Tx USA).  
9  
10

## 11 12 13 14 **RESULTS**

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17 Of the original 196 patients randomised to receive the trial medications (98 received IV plus oral iron;  
18  
19 98 received oral iron only), 183 patients completed the trial by the collection of blood for iron status  
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21 estimation at the time of delivery. Data of HRQoL were collected from 126 of the 183 women who  
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23 completed the original trial, representing 69% of the cohort who completed the trial, while 57 (31%)  
24  
25 of the 183 patients had moved away, were uncontactable or did not respond to the researcher  
26  
27 messages (see Figure 1 for description of patient flow). Basic demographic data of those patients  
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29 included in the follow-up study showed that the median age was 29 years at enrolment (range, 21 to  
30  
31 43); and the median follow up was 32 months (range, 26 to 42) post-delivery. There were no  
32  
33 significant differences in demographic or iron status measurements between any of the groups of  
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35 women recruited to the trial. All pregnant women recruited in this study were Caucasians.  
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40  
41 As reported in the original study (PMID: 20546462), at delivery the proportion of women with lower  
42  
43 than normal ferritin levels was 53 of 67 (79%) for women with analysable iron status measurements  
44  
45 who were treated with oral iron as compared to 3 of 66 (4.5%) for women who received IV iron  
46  
47 (Fisher's exact  $p < 0.001$ ). The pre-treatment mean serum ferritin levels were low in both groups at 17  
48  
49  $\mu\text{g/L}$ . However, the serum ferritin of those in the IV iron group increased markedly within four weeks  
50  
51 of the IV therapy with 222  $\mu\text{g/L}$ ; 95% CI 194 to 249  $\mu\text{g/L}$  ( $p < 0.001$ ). This substantial improvement  
52  
53 was maintained after delivery with an increase of 108  $\mu\text{g/L}$ ; 95% CI 43 to 209  $\mu\text{g/L}$  ( $p < 0.001$ ).<sup>14</sup> On  
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55 the other hand the ferritin level did not show a significant increase in the oral iron group through  
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1 pregnancy and after delivery. Furthermore, the percentage of women at delivery with Hb level <116  
2 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)  
3  
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6  
7 incidence rate ratio 0.55 (95% CI 0.31 to 0.98; p=0.043). After delivery, the mean Hb levels declined  
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9  
10 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  
11  
12 continuing favourable effect of IV iron therapy of 5.8 g/L (95% CI 2.5 to 9.1; p=0.004) despite the  
13  
14 blood loss of delivery.<sup>14</sup>

15  
16 There were no significant differences in the birth weights of the babies in the two treatment groups  
17  
18 with an average birth weight of 3.42 kg in both groups with a difference of 0.03 kg (p=0.77). There  
19  
20 were also no differences in the gestational age at delivery in both treatment groups with mean of 39.1  
21  
22 weeks in the oral iron versus 38.9 weeks with only a slight difference of 0.2 weeks (p=0.74). There  
23  
24 were no significant differences in placental cord Hb or ferritin levels in both treatment groups. The  
25  
26 mean cord Hb was 165g/L (SD 9.6) in the oral iron group versus 157g/L (SD 14.1) in the IV iron  
27  
28 group (difference -7; 95% CI -18 to 3; p=0.17). In the meantime the ferritin levels were 142 µg/L (SD  
29  
30 86) and 185 µg/L (SD 101) respectively (difference 43; 95% CI -59 to 145; p=0.41).  
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38 The HRQoL Physical Component Scale (difference 10.3; 95% CI 3.3 to 17.2; P=0.27; OR 2.39; 95%  
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40 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;  
41  
42 95% CI 1.57 to 6.26; P=0.001) responses were improved in the IV compared to the oral iron group,  
43  
44 but these differences became less apparent at subsequent assessment time points (Figure 2a and b).

45  
46 Furthermore, there were strong associations between the level of iron status, independent of how that  
47  
48 iron status was achieved, and a number of the HRQoL scales (Figure 2): notably improved General  
49  
50 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),  
51  
52 improved Vitality (slope {1SD log.-ferritin} 10.0; 7.3 to 12.8; P<0.001; OR 2.09; 95% CI 1.66 to  
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54 2.62; P<0.001), less Psychological Downheartedness ({1SD haemoglobin} OR 1.57; 95% CI 1.14 to  
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2 2.15; P=0.005), less Clinical Depression ( $\{1SD \log\text{-ferritin}\}$  OR 2.05; 95% CI 1.27 to 3.32;  
3  
4 P=0.003), and overall improved Mental Component Scale (slope  $\{1SD \text{ haemoglobin}\}$  3.8; 2.5 to 5.0;  
5  
6 P<0.001; OR 1.71; 95% CI 1.39 to 2.10; P<0.001)(Psychological Downheartedness and Clinical  
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8 Depression analysis used raw scores rather than 100-point scales).  
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14 There was an increased duration of breastfeeding (HR for cessation was 0.70; 95% CI 0.50 to 0.99;  
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16 p=0.046) in women in the IV iron group (Figure 3) where older women were more likely to breast  
17  
18 feed longer (HR 0.76; 95% CI 1.00 to 1.52; P=0.006) (Table 3). Earlier cessation of breastfeeding was  
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20 associated with downheartedness (HR 1.23; 95% CI 1.00 to 1.52; P=0.06). There was no difference  
21  
22 between the oral iron or IV plus oral iron groups in the weight of the baby at birth (p=0.64), and no  
23  
24 difference in the rate of weight gain (p=0.90).  
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31 The association between the physical symptom questions index from the clinical monitoring  
32  
33 questionnaire and the Physical Component Scale of the HRQoL for the four time periods is shown in  
34  
35 Table 4. There was significant association between the physical symptom questions index at 4 weeks  
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37 after trial entry and each of the HRQoL recall time points, and that the association was strongest for  
38  
39 the 4 weeks recall (OR 3.18; 2.14 to 4.74; P<0.001).  
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## 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

1  
2 after trial, were most strongly associated with the Physical Component Scales of the recall of modified  
3 SF-36 at week 4 compared to the other time points. This indicates that the retrospective methodology  
4 was able to provide an acceptable degree of accuracy in the differentiation of HRQoL levels at  
5 different time points despite the concerns that may have arisen with this issue. The assumption being  
6 made is that the way those patients judge their physical and mental condition will be relatively stable  
7 over time,<sup>18</sup> an assumption with which we agree may occur in patients with chronic diseases.  
8 However, this assumption may not hold for women during and after pregnancy. The expectations by  
9 the woman about how she should be feeling at the different stages of pregnancy, around the time of  
10 delivery, and when she is caring for one or more young infant or child may differ substantially at  
11 those different time points. At least in our analysis the judgment the woman is making about how to  
12 answer the questions is likely to be the same for each time point, since she had made that judgment at  
13 one point in time: the repeated measures analysis compares each woman with herself, thus  
14 substantially reducing the impact of variation between women in this judgment. Thus, for the purpose  
15 of generating a hypothesis concerning iron status and quality of life, we believe that our methodology  
16 has been adequate. Another limitation of our study was the relatively small number of women studied.  
17 However, it is worthwhile publishing our study due to lack of research that addresses HRQoL during  
18 and after pregnancy, particularly, in view of the emerging novel association between iron status and  
19 postnatal clinical depression as well as breastfeeding duration in our cohort of patients.  
20  
21 Regarding the incidental findings of the trend for unfavourable mental health component outcomes for  
22 women with male babies, there is only a single report in the literature addressing this issue with  
23 similar findings.<sup>19</sup> Perhaps this may be explained with the observation that male babies are usually  
24 more active and this may be associated with post natal depression.<sup>19</sup> However, due to lack of data, this  
25 issue should be addressed separately and studied thoroughly in future research.  
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2 Due to paucity of data regarding HRQoL during and after pregnancy, there are only very limited data  
3 available. Jansen *et al* studied the effect of delivery and postpartum changes on the HRQoL.<sup>20</sup> A  
4 cohort of 141 pregnant women were included in that study. HRQoL questionnaires were measuring  
5 the immediate effect of delivery on the quality of life. The HRQoL questionnaires were conducted  
6 less than 1 day after vaginal delivery and less than two days after delivery by caesarean section and  
7 compared to 3-6 weeks post delivery for both groups.<sup>20</sup> The study focused on patient's HRQoL  
8 recovery after both delivery interventions. In this study<sup>20</sup>, the different time-points of conduction of  
9 the questionnaire may not necessarily reflect the HRQoL during pregnancy and subsequently after the  
10 postpartum period. Furthermore, the immediate questionnaire after delivery and 3-6 weeks time  
11 during the post-partum period may be at least, in theory, influenced by the event of delivery, in  
12 particular if complications occur, as well as the possible emotional and hormonal fluctuations during  
13 this period. It is worthwhile noting that the same study did not show association with Hb and QoL,  
14 however it did not investigate a possible effect of iron status on perceived HRQoL in conjunction with  
15 breastfeeding. This highlights our novel finding of the correlation between iron status and improved  
16 HRQoL during and after pregnancy.  
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39 In summary, there was a significant improvement in the general health of women who received IV  
40 iron ( $p < 0.001$ ), but this effect was found prominently 4 weeks after the IV iron treatment. The  
41 duration of breast-feeding was longer ( $p = 0.04$ ) in those women who had received IV iron. Women  
42 with better iron status were less downhearted ( $p = 0.005$ ) and less likely to develop postnatal clinical  
43 depression ( $p = 0.003$ ).  
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50 Our results would indicate that it is worthwhile considering Hb and iron status as a surrogate marker  
51 for assessment of women's wellbeing, not only during pregnancy, but also during the postnatal period.  
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2 Further studies are warranted to confirm and extend our findings, and to determine outcomes in  
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4 different populations with IDA in order to improve the estimates of the magnitude of the benefits of  
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6 intravenous iron for the management of iron deficiency anaemia.  
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### 10 11 **Acknowledgements:**

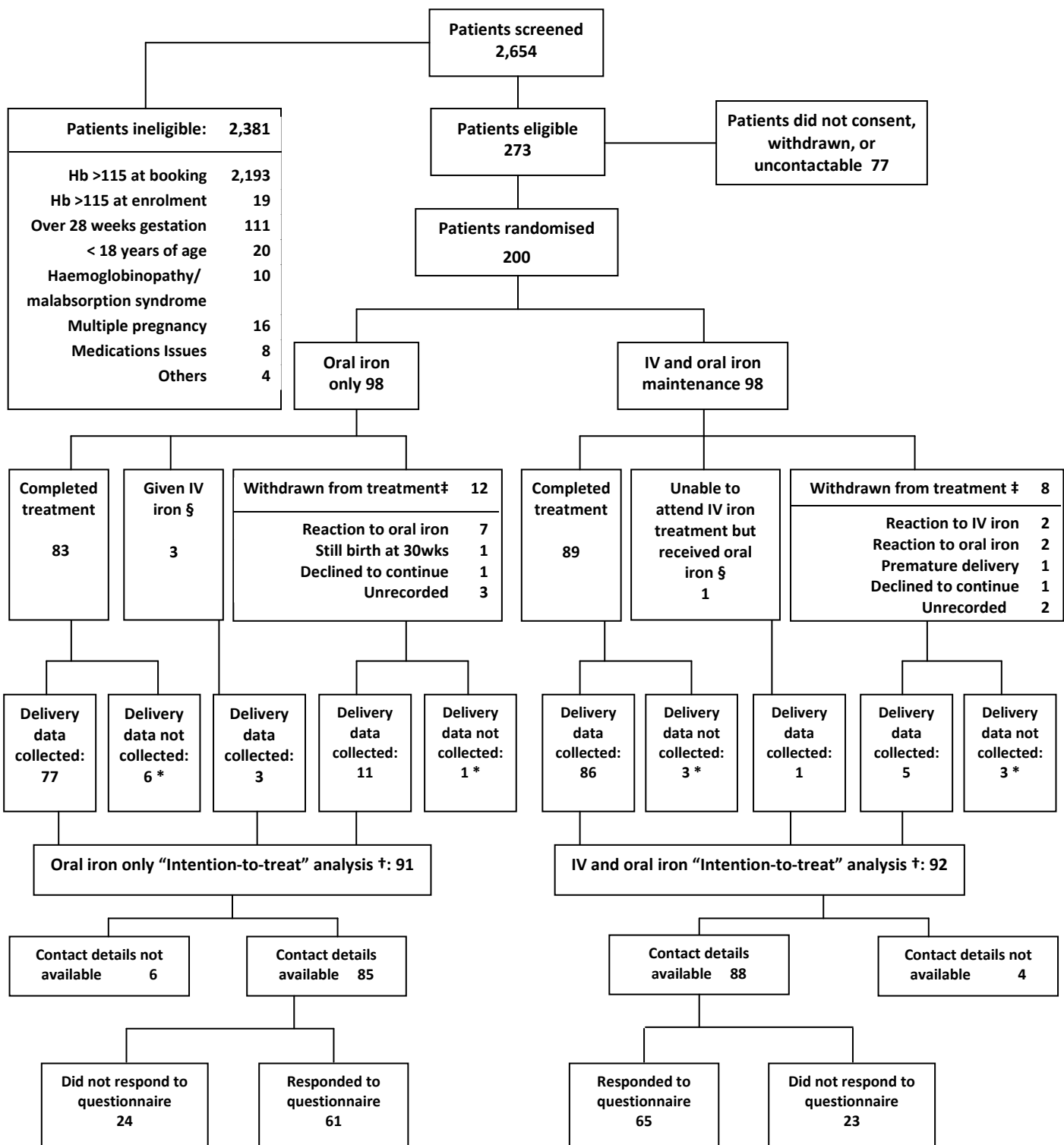
12 This research received a grant from the Clifford Craig Medical Research Trust, Launceston,  
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**Figure 1.** Trial flow diagram: disposition of study participants by treatment assignment.



**Footnotes to Figure 1. Patients Flow Chart.**

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4 \* Fourteen patients were admitted late in labour, and no blood samples were taken before delivery  
5 † The primary hypothesis examined the change in haemoglobin levels between the time of booking and immediately prior to  
6 delivery; an “intention-to-treat” analysis was performed according to original randomization group on those patients who  
7 had blood samples taken before delivery, whether or not the treatment was completed as per protocol  
8 ‡ Twenty one patients withdrew from the trial treatments, and all but one of these patients agreed to continued collection of  
9 haematological and other trial data; eight patients gave no reason for withdrawal  
10 § Five patients did not complete the intended treatments, but did not themselves choose to withdraw; three patients in the  
11 oral iron group were treated with IV iron when their haemoglobin was judged not to have responded adequately to oral  
12 iron, whilst one patient was unable to attend for IV iron treatment  
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**Table 1.** Patients Characteristics

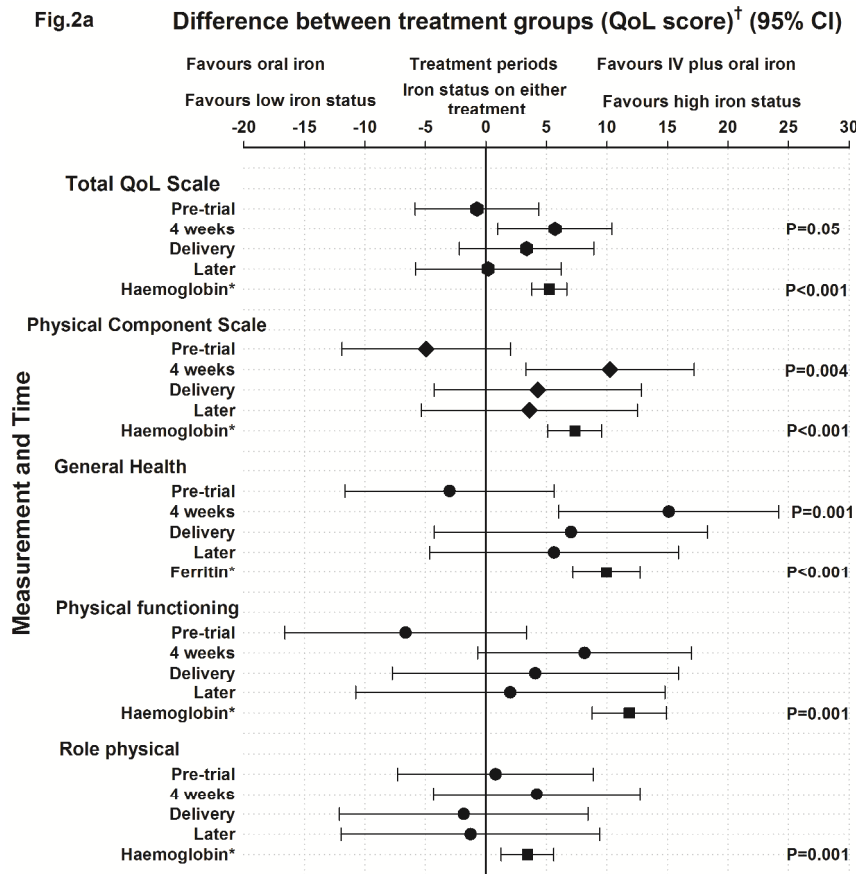
	<b>IV iron group</b>	<b>Oral iron group</b>
No of patients	64	62
Vaginal delivery	45	46
Caesarean section	19	16
Median age in years	28 years (range; 21-43)	28.5 years (Range; 22-42)
Mean age in years	27.5 years	28
Median time between trial intervention and delivery in months	2.7 months ( range; 2.6-6)	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
<b>Question: stem and detailed item</b>	<b>Response and Question number:</b>	<b>Response and Question number:</b>
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

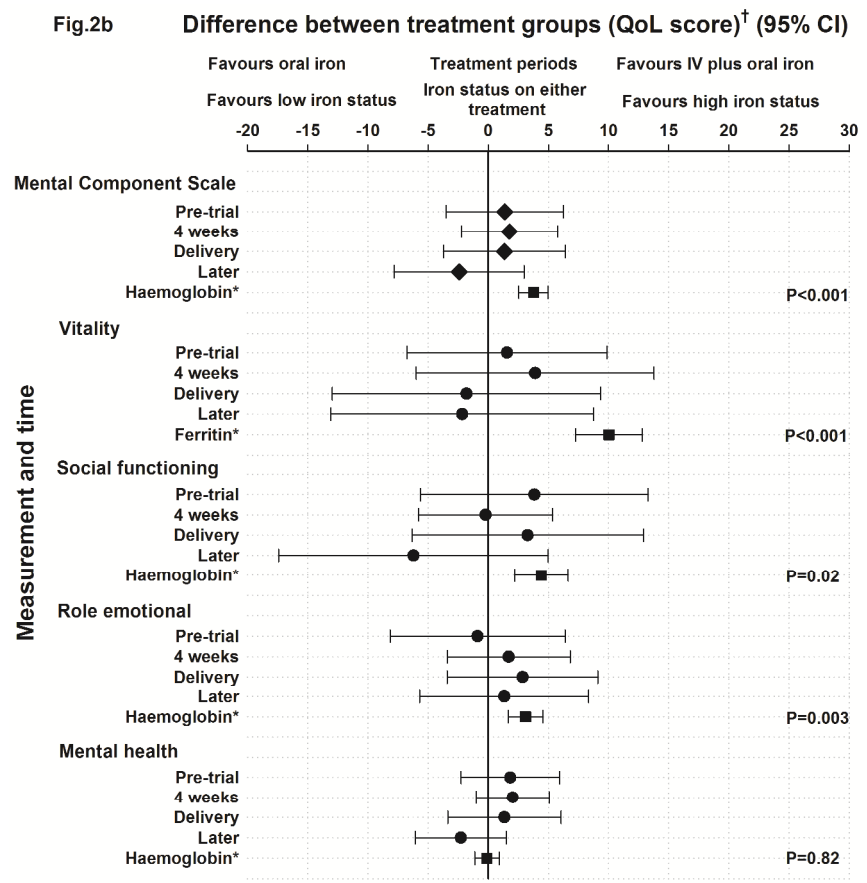
**\* Not all of the original SF-36 questions are included in this list. All the questions shown in this list, except for the last original SF-36 question about pain, were included in the questionnaire administered in this study. Where the questionnaire response was the same this is indicated, and where 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



only





† 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 <sup>1</sup>	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

<sup>1</sup> **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 ( $\{\text{mother's age} - \text{group mean age}\} / \text{group standard deviation of age}$ ): mean age  $28.1 \pm 5.6$  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.**

<sup>2</sup> Abbreviations: NVD – normal vaginal delivery; LSCS – lower segment caesarean section

**Table 4.** Association between the physical symptom questions<sup>3</sup> in from the prospective clinical monitoring questionnaire and the Physical Component Scale of the retrospective HRQoL for the four time periods.

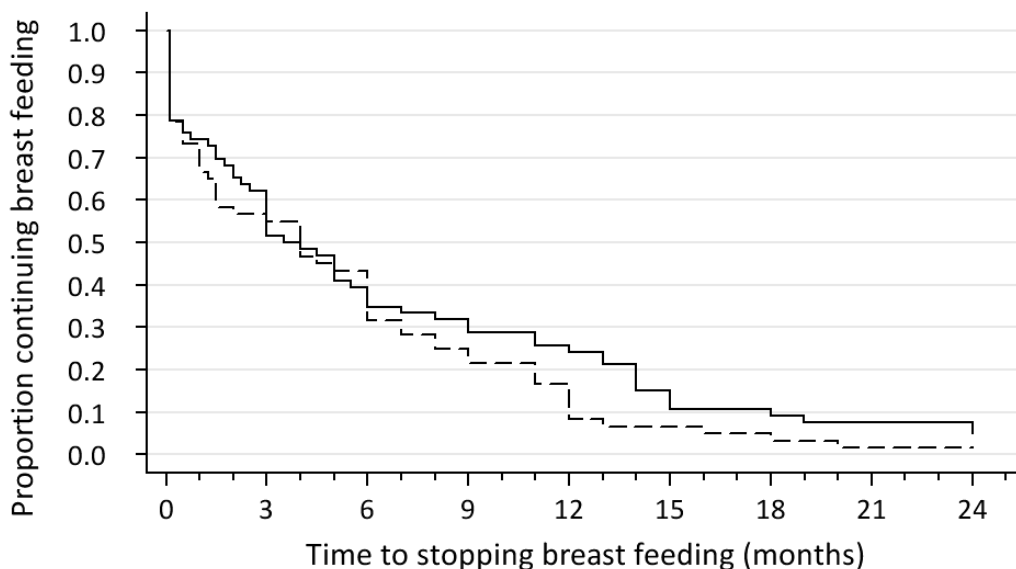
Time	Slope (SD) <sup>1</sup>	OR <sup>2a</sup>	95%CI	P-value	OR <sup>2b</sup>	95%CI	P-value
Pre-trial	2.67 (13.0) <sup>1</sup>	1.46	(1.01 to 2.11)	0.043	1.00		
4 weeks	8.07 (18.6)	3.18	(2.11 to 4.80)	<0.001	2.18	(1.44 to 3.28)	<0.001
Delivery	4.91 (12.2)	2.14	(1.37 to 3.35)	<0.001	1.46	(0.94 to 2.29)	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

<sup>1</sup> 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).

<sup>2</sup> The strength of that <sup>a)</sup> absolute association at each time point, and <sup>b)</sup> 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).

<sup>3</sup> 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



Number at risk		0	3	6	9	12	15	18	21	24
IV plus oral	65	41	26	21	17	10	7	4	3	
Oral	61	34	26	15	10	4	3	1	1	

IV plus oral    
  Oral

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
<b>Title and abstract</b>	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
<b>Introduction</b>			
Background/rationale	2	Scientific background and the rationale for the study were stated	5,6
Objectives	3	Aims and objective were mentioned	6
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6-8
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	9
		(e) Describe any sensitivity analyses	Not applicable
<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	10,11
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	Not applicable
		<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://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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<b>Primary Subject Heading</b>:	Obstetrics and gynaecology
Secondary Subject Heading:	Haematology (incl blood transfusion), Public health
Keywords:	Anaemia < HAEMATOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Maternal medicine < OBSTETRICS, QUALITATIVE RESEARCH
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	
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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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**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 (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.

1  
2  
3 **Trial registration:** Australian New Zealand Clinical Trial Registry (<http://www.ANZCTR.org.au>) under  
4 ACTRN 12609000177257 and in the World Health Organization Clinical Trials Registry  
5 (<http://www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202>).  
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8

9  
10  
11 **Funding:** This research received a grant from the Clifford Craig Medical Research Trust, Launceston,  
12 Tasmania, Australia.  
13

14  
15  
16 **Key words:** Quality of life assessment, iron deficiency anaemia, oral iron, intravenous iron,  
17 pregnancy, long-term effect.  
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21  
22 **Short title:** Quality of life in pregnancy  
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## 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,<sup>1-3</sup> IDA is a potential risk factor for preterm delivery and subsequent low birth weight, and may be associated with inferior neonatal health.<sup>3-4</sup> 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.<sup>5-9</sup> 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.<sup>10,11</sup> 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.<sup>3,10,11</sup>

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

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.<sup>14</sup> 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.<sup>14</sup> 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

1  
2 breastfeeding rates and on the general wellbeing of the babies born to these women was measured by  
3  
4 child growth charts set by the Australasian Paediatric Endocrine Group (APEG).  
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8

## 9 PATIENTS AND METHODS

### 10 Rationale and objectives

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13  
14 An initial prospective randomised controlled trial was conducted between March 2007 and  
15  
16 January 2009 at the Launceston General Hospital (LGH), a tertiary referral centre for Northern  
17  
18 Tasmania, Australia. The initial study assessed haemoglobin and serum ferritin levels after IV  
19  
20 followed by oral iron therapy versus oral iron therapy only. The current study constitutes a follow-up  
21  
22 on the earlier one and took place between January 2010 and January 2011 and focussed on HRQoL,  
23  
24 breastfeeding duration and child health. Informed consent was obtained from all participants in  
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26 accordance with the Declaration of Helsinki. The original and the follow-up studies were approved by  
27  
28 the Tasmanian Human Research Ethics Committee and registered in the Australian New Zealand  
29  
30 Clinical Trials Registry (<http://www.ANZCTR.org.au/ACTRN12609000177257.aspx>) and the World  
31  
32 Health Organization Clinical Trials Registry  
33  
34 (<http://www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202>).  
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42 In the original study, we prospectively assessed HRQoL at baseline prior to treatment in the  
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44 second trimester, 4 weeks after initiation of treatment, in the third trimester before delivery, and at 6-8  
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46 weeks post delivery. In the follow-up study, a HRQoL questionnaire was completed that incorporated  
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48 the original questionnaire plus additional parameters such as the length of the breastfeeding period  
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50 and occurrence of postnatal depression as well as child growth data. This was performed at a median  
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52 of 32 months post intervention in order to assess the long-term effects of both treatment types on  
53  
54 mothers' HRQoL in relation to data from the earlier study. This questionnaire, although completed  
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1  
2 prospectively, had a retrospective component that asked the participating mothers the same questions  
3  
4 again that they had previously answered prospectively. These data were compared with the mothers'  
5  
6 original prospective QoL data for validation purposes.  
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9

## 10 11 **Participants**

12  
13 Pregnant women aged 18 years or above who presented to the LGH with IDA between 2007 and 2009  
14  
15 were invited to participate. In the original study (Figure 1), 196 Caucasian pregnant women aged 18  
16  
17 years or above were identified who had moderate IDA, defined as haemoglobin (Hb)  $\leq 115$  g/L  
18  
19 (reference range (RR) 120-160 g/L), and low iron stores, based on serum ferritin levels  $< 30$   $\mu\text{g/L}$  (RR  
20  
21 30-440  $\mu\text{g/L}$ ).  
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26 Of the original evaluable 183 pregnant Caucasian women randomised to receive oral iron or a single  
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28 intravenous iron polymaltose infusion, 126 women completed the QoL follow-up study (Table 1). The  
29  
30 median age was 29 years at enrolment (range, 21 to 43); and the median follow-up period was 32  
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32 months (range, 26 to 42) with an average follow-up period of 36 months post delivery.  
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## 38 **Randomisation and interventions**

39  
40 Informed consent was obtained from all patients. Treatment arms were allocated in blocks of 10 by  
41  
42 computer-generated random assignment, and allocation was done by concealed envelopes. This was  
43  
44 done by the LGH Pharmacy Department in order to avoid possible bias. The oral-only treatment arm  
45  
46 comprised iron sulphate 250 mg tablets once daily, (elemental iron 80 mg, Abbott, Australasia Pty  
47  
48 Ltd) to be taken daily within two days after booking until delivery. The IV arm required a single  
49  
50 intravenous infusion of iron polymaltose (Ferrosig, Sigma Pharmaceuticals, Australia) within 1 week  
51  
52 after first antenatal visit followed by oral iron identical to the other arm. Pre-enrolment, there were no  
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54 significant differences in the dietary iron intake or supplement intake between the two groups based  
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2 on a specially-designed questionnaire addressing these issues.<sup>14</sup> Patients assigned to IV iron  
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4 polymaltose received a 100 mg test dose dissolved in 50-100 mL normal saline infused over 30  
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6 minutes. Clinical observation and vital signs were assessed initially and every 15 min from the start of  
7  
8 the infusion. After the test-dose was tolerated, the remainder of the iron polymaltose dose was  
9  
10 infused. The total dose of IV iron polymaltose was calculated according to the patients' body weight  
11  
12 at their first antenatal visit and entry Hb level according to the product guidelines; iron dose in mg (50  
13  
14 mg per 1 mL) = body weight (maximum 90) in kg x target Hb (120 g/L) - actual Hb (in g/L) x  
15  
16 constant factor (0.24) + iron depot (500).<sup>14</sup>  
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## 24 **Outcome measurement**

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27 Two Health-Related Quality of Life (HRQoL) questionnaires were administered during the initial and  
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29 follow-up studies. First, a clinical questionnaire was completed prospectively by trained midwives at 4  
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31 weeks after initiation of treatment, at 28 and 34 weeks gestation, and then 6-8 weeks post delivery.  
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33 This questionnaire assessed four aspects: energy levels, activity, tolerance and side effects of the  
34  
35 treatment. This was used to guide individual patient clinical decision-making as well as to provide a  
36  
37 safety audit of the trial treatments.<sup>14</sup> Second, a prospective/retrospective survey was conducted  
38  
39 between June and October 2010 by trained research personnel via phone interview using a modified  
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41 version of the SF-36 HRQoL questionnaire, similar to a version published previously.<sup>16,17</sup> Additional  
42  
43 modifications for this study included: (1) use of eleven of the 36 questions (Table 2), and (2) the  
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45 women were asked to recall their response to each of the questions at four timepoints, pre-trial prior to  
46  
47 commencement of iron therapy during the pregnancy, four weeks after the start of iron therapy, one  
48  
49 week after delivery, and the last four weeks prior to the telephone questionnaire contact (Table 2).  
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51 This was compared in a retrospective fashion to the same questions answered earlier prospectively by  
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53 the participants at these different timepoints. In order to validate the retrospective use of the modified  
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2 SF-36 questionnaire to assess the women's HRQoL during and after pregnancy, we estimated the  
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4 associations of the physical activity component of the prospective monitoring questionnaire following  
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6 entry into the trial with the Physical Component Scale values of the modified SF-36 at each of the  
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8 timepoints. We hypothesized that the association would be greatest at 4 weeks after enrolment  
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10 compared to trial entry, time of delivery or at the time of questionnaire completion. In addition, data  
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12 concerning breastfeeding and the health of the child were collected from the baby's growth booklet.  
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14 This included breastfeeding duration, baby gender, age, weight and previous hospitalisation, if any, in  
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16 addition to the baby's sleep quality since birth and specific growth data for the children as set by the  
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18 Australasian Paediatric Endocrine Group (APEG). Haemoglobin and ferritin levels for participants at  
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20 delivery were available for all participants; however no further testing was performed during the  
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22 follow up. The principal investigators, including the statistician, evaluated the questionnaire results  
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24 data.  
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### 31 **Statistical methods**

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33 The HRQoL scores that form the raw data for this analysis are rank-order in nature. Means and  
34  
35 standard deviations of the scores were estimated using generalised estimating equations for illustrative  
36  
37 purposes only. Physical and mental composite scores were calculated in the modified SF-36 according  
38  
39 to the SF-12 scoring guidelines.<sup>16,17</sup> Group comparison and covariate effect size calculation, odds  
40  
41 ratios (OR with 95% confidence intervals and P values) were estimated using repeated measures of  
42  
43 ordinal logistic regression, with covariates selected for inclusion by backward stepwise regression (P  
44  
45 for exclusion 0.22) from maternal age, haemoglobin, ferritin, Socio-Economic Indexes for Areas  
46  
47 (SEIFA; based on the Collector District of residence of mothers), quality of sleep, use and duration of  
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49 breastfeeding, hospitalization of the baby, baby gender and mode of delivery. This included  
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51 randomisation group covariate interactions in the starting model with exclusion of those interactions  
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53 using the above criteria. When iron status was selected for inclusion in the model, the association  
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2 between iron status (ferritin) and HRQoL was reported independently of trial treatment group. P  
3 values were corrected for multiple comparisons where necessary by the Holm method. The effect of  
4 IV iron versus oral iron on time of cessation of breastfeeding was compared by estimation of hazard  
5 ratio (HR) with 95% confidence intervals and P-values by Cox proportional hazards regression  
6 adjusted for covariates selected for inclusion by backward stepwise regression (P for exclusion 0.22).  
7 The time to cessation of breast-feeding was taken from the subject's baby growth booklet for all  
8 participants. Neonatal growth in the treatment groups was compared by multivariate third-order  
9 polynomial regression as an approximation to APEG growth assessment. The iron status variables  
10 used in the multivariate regression models were selected by stepwise regression. All HRQoL  
11 statistical analyses were performed using Stata SE for Windows 11.1 (StataCorp, College Station, Tx  
12 USA).

## 31 RESULTS

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

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2 As reported in the original study,<sup>14</sup> at delivery the proportion of women with lower than normal  
3 ferritin levels was 53 of 67 (79%) for women with analysable iron status measurements who were  
4 treated with oral iron as compared to 3 of 66 (4.5%) for women who received IV iron (Fisher's exact  
5  $p < 0.001$ ). The pretreatment mean serum ferritin levels were low in both groups at 17  $\mu\text{g/L}$ . However,  
6 the serum ferritin of those in the IV iron group increased markedly within four weeks of the IV  
7 therapy with a mean level of 222  $\mu\text{g/L}$ ; 95% CI 194 to 249  $\mu\text{g/L}$  ( $p < 0.001$ ). This substantial  
8 improvement was maintained after delivery with a mean level of 108  $\mu\text{g/L}$ ; 95% CI 43 to 209  $\mu\text{g/L}$   
9 ( $p < 0.001$ ).<sup>14</sup> On the other hand, ferritin levels did not show a significant increase in the oral iron group  
10 through pregnancy and after delivery. Furthermore, the percentage of women at delivery with Hb  
11 levels  $< 116$  g/L was 29% (25 of 85) in the oral iron group versus 16% (14 of 87) in the IV iron group  
12 ( $p = 0.04$ ) incidence rate ratio 0.55 (95% CI 0.31 to 0.98;  $p = 0.043$ ). After delivery, the mean Hb levels  
13 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  
14 showed a continuing favourable effect of IV iron therapy (95% CI 2.5 to 9.1;  $p = 0.004$ ) despite the loss  
15 of blood at delivery.<sup>14</sup>

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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  $\mu\text{g/L}$  (SD 86) and 185  $\mu\text{g/L}$  (SD 101) respectively (difference 43; 95% CI -59 to 145;  $p = 0.41$ ).

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2 The HRQoL Physical Component Scale (difference 10.3; 95% CI 3.3 to 17.2; P=0.27; OR 2.39; 95%  
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4 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;  
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6 95% CI 1.57 to 6.26; P=0.001) responses were improved in the IV compared to the oral iron group,  
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8 but these differences became less apparent at subsequent assessment timepoints (Figure 2a and b).  
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10 Furthermore, there were strong associations between the level of iron status, independent of how that  
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12 iron status was achieved, and a number of the HRQoL scales (Figure 2): notably improved general  
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14 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),  
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16 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;  
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18 P<0.001), less psychological downheartedness ({1SD haemoglobin} OR 1.57; 95% CI 1.14 to 2.15;  
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20 P=0.005), less clinical depression ({1SD log.-ferritin} OR 2.05; 95% CI 1.27 to 3.32; P=0.003), and  
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22 overall improved mental component scale (slope {1SD haemoglobin} 3.8; 2.5 to 5.0; P<0.001; OR  
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24 1.71; 95% CI 1.39 to 2.10; P<0.001) (Psychological Downheartedness and Clinical Depression  
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26 analysis used raw scores rather than 100-point scales).  
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35 There was an increased duration of breastfeeding (HR for cessation was 0.70; 95% CI 0.50 to 0.99;  
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37 p=0.046) in women in the IV iron group (Figure 3), where higher maternal age was associated with  
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39 longer breastfeeding (HR 0.76; 95% CI 1.00 to 1.52; P=0.006) (Table 3). Earlier cessation of  
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41 breastfeeding was associated with downheartedness (HR 1.23; 95% CI 1.00 to 1.52; P=0.06). There  
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43 was no difference between the oral iron or IV plus oral iron groups in the weight of the baby at birth  
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45 (p=0.64), and no difference in the rate of weight gain (p=0.90).  
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52 The correlation between the prospective physical symptom questions index from the clinical  
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54 monitoring questionnaire and the Physical Component Scale of the retrospective HRQoL for the four  
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56 time periods is shown in Table 4. There was a significant association between the physical symptom  
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2 questions index at 4 weeks after trial entry and each of the HRQoL recall timepoints, and the  
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4 correlation was strongest for the 4 weeks recall (OR 3.18; 2.14 to 4.74;  $P<0.001$ ).  
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9 Another finding of our study was an association between male gender babies and an unfavourable  
10 mental health component outcome for participant women across the two groups. Of the seven  
11 component questions, two showed a significant association, with women who had male babies less  
12 likely to be calm and peaceful (OR=0.55, 0.32-0.97,  $p=0.039$ ). There were no statistical differences in  
13 terms of HRQoL assessment regarding the method of delivery between women who delivered  
14 normally and those who had caesarean section.  
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## 27 DISCUSSION

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29 Prior to our study, there were no data available concerning the effects of either IV or oral iron  
30 supplementation for anaemia on post-delivery psychological and physical welfare of mothers, the  
31 quality of the bonding to the baby and the rate of developmental progress of the baby. We are  
32 reporting on 126 patients in a follow up study of the effect of IV iron versus oral iron therapy on  
33 HRQoL during and after pregnancy. Our study demonstrates that there was an improvement in the  
34 self-assessed feeling of general health in both treatment groups from the pre-labour period to all  
35 subsequent periods. Although the improvement was significantly greater during pregnancy in the IV  
36 iron group 4 weeks after commencement of trial treatment ( $p=0.001$ ), the difference persisted in the  
37 subsequent measurement periods at a lesser magnitude that did not achieve statistical significance.  
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51 Regardless of treatment and regardless of which period was being considered, higher haemoglobin  
52 and higher ferritin levels were associated with better baby sleep quality, a longer period of  
53 breastfeeding and a higher level of mothers' general health.  
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2 The modified HRQoL questionnaire used in our study includes many useful and relevant aspects  
3 regarding general health, daily activities, levels of energy and depression. There was a substantial  
4 improvement of iron status in women who received IV iron compared to oral iron as demonstrated  
5 during the trial analysis ( $p < 0.001$ ). Limitations of our study include the modified questionnaire being  
6 in part a retrospective HRQoL evaluation which should ideally have been conducted within a shorter  
7 period of time. However, a correlation to a prospective evaluation of the studied subjects has been  
8 made in our study in order to overcome a possible recall bias. Therefore, we were able to minimise the  
9 number of retrospective questions, since the women were asked to recall their responses to each  
10 question at four different timepoints. The full SF-36 was impractical and may have been judged to be  
11 an excessive burden on the women. Thus, we attempted to provide a retrospective form of validation  
12 by showing that the clinical HRQoL questions in the physical domain, recorded prospectively at week  
13 4 after trial, were most strongly associated with the Physical Component Scales of the recall of  
14 modified SF-36 at week 4 compared to the other timepoints. This indicates that the retrospective  
15 methodology was able to provide an acceptable degree of accuracy in the differentiation of HRQoL  
16 levels at different timepoints despite the concerns that may have arisen with this issue. The  
17 assumption being made is that the way those patients judge their physical and mental condition will be  
18 relatively stable over time,<sup>18</sup> an assumption with which we agree may occur in patients with chronic  
19 diseases. However, this assumption may not hold for women during and after pregnancy. The  
20 expectations by the woman about how she should be feeling at the different stages of pregnancy,  
21 around the time of delivery, and when she is caring for one or more young infant or child may differ  
22 substantially at those different timepoints. At least in our analysis, the judgment the woman is making  
23 about how to answer the questions is likely to be the same for each timepoint, since she had made that  
24 judgment at one point in time: the repeated measures analysis compares each woman with herself,  
25 thus substantially reducing the impact of variation between women in this judgment. Thus, for the  
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2 purpose of generating a hypothesis concerning iron status and quality of life, we believe that our  
3 methodology has been adequate. Another limitation of our study is the relatively small number of  
4 women studied. Nevertheless, prior to our study there was a lack of research that addressed HRQoL  
5 during and after pregnancy, and particularly the association between iron status and postnatal clinical  
6 depression as well as breastfeeding duration in our cohort of patients provides a novel finding and a  
7 basis for further research.  
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9  
10 An incidental finding of our study was a trend for unfavourable mental health component outcomes  
11 for women with male babies there is only a single report in the literature that addressed this issue and  
12 reported similar findings.<sup>19</sup> Perhaps this may be explained with the observation that male babies are  
13 usually more active, and this may be associated with post natal depression.<sup>19</sup> However, due to lack of  
14 more detailed data, this issue should be addressed separately and studied in future research.  
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17 Due to paucity of data regarding HRQoL during and after pregnancy, there are only limited data  
18 available from other studies. Jansen *et al* studied the effect of delivery and postpartum changes on the  
19 HRQoL.<sup>20</sup> A cohort of 141 pregnant women were included in that study. HRQoL questionnaires were  
20 measuring the immediate effect of delivery on the quality of life. The HRQoL questionnaires were  
21 conducted less than 1 day after vaginal delivery and less than two days after delivery by caesarean  
22 section and compared to 3-6 weeks post delivery for both groups.<sup>20</sup> The study focused on patients'  
23 HRQoL recovery after both delivery interventions. In that study,<sup>20</sup> the different timepoints of  
24 completion of the questionnaire (immediately post-delivery and 3-6 weeks thereafter) may not  
25 necessarily reflect the HRQoL during pregnancy and subsequently after the postpartum period.  
26 Furthermore, the immediate questionnaire after delivery and at 3-6 weeks time in the postpartum  
27 period may have been influenced, at least in theory, by the event of delivery, in particular when  
28 complications occurred, as well as by the possible emotional and hormonal fluctuations during this  
29 period. It is worthwhile to note that the same study did not show any association between Hb and  
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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 INTERESTS 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.**

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6 \* Fourteen patients were admitted late in labour, and no blood samples were taken before delivery.  
7 † The primary hypothesis examined the change in haemoglobin levels between the time of booking and immediately prior to  
8 delivery; an “intention-to-treat” analysis was performed according to original randomisation group on those patients who  
9 had blood samples taken before delivery, whether or not the treatment was completed as per protocol.  
10 ‡ Twenty-one patients withdrew from the trial treatments, and all but one of these patients agreed to continued collection of  
11 haematological and other trial data; eight patients gave no reason for withdrawal.  
12 § Five patients did not complete the intended treatments, but did not choose to withdraw themselves; three patients in the  
13 oral iron group were treated with IV iron when their haemoglobin was judged not to have responded adequately to oral  
14 iron, while one patient was unable to attend for IV iron treatment.  
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**Table 1.** Patient characteristics

	<b>IV iron group</b>	<b>Oral iron group</b>
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.

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2 **Figure 2a and 2b.** Comparison of physical component scale of HRQoL scores in the IV plus oral iron versus the oral iron group, and  
3 separate association with iron status  
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8 † Comparison of the effect of IV plus oral iron versus oral iron on physical (**Figure 2a**) and mental (**Figure 2b**) components of the  
9 HRQoL scores at different time periods (before starting iron, 4 weeks after starting iron, at delivery and when the mother responded to  
10 questionnaire), estimated using ordinal logistic regression adjusted for significant demographic confounders but not including iron  
11 status, corrected for repeated measures and multiple comparisons (Holm method).  
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13 \* The effect of iron status on physical component and mental component scores was estimated separately without including treatment  
14 group in the analysis. The timepoint “Later” is referring to the post delivery follow-up assessment.  
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**Table 3.** Effect of IV iron versus oral iron on rate of cessation of breast feeding.

	HR <sup>1</sup>	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

<sup>1</sup> **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 ( $\{\text{mother's age} - \text{group mean age}\} / \text{group standard deviation of age}$ ): mean age  $28.1 \pm 5.6$  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.**

<sup>2</sup> Abbreviations: NVD – normal vaginal delivery; LSCS – lower segment caesarean section

**Table 4.** Correlation between the physical symptom questions<sup>3</sup> from the prospective clinical monitoring questionnaire and the Physical Component Scale of the retrospective HRQoL for the four time periods.

Time	Slope (SD) <sup>1</sup>	OR <sup>2a</sup>	95%CI	P-value	OR <sup>2b</sup>	95%CI	P-value
Pre-trial	2.67 (13.0) <sup>1</sup>	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

<sup>1</sup> 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).

<sup>2</sup> The strength of the <sup>a)</sup> absolute association at each timepoint, and <sup>b)</sup> 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).

<sup>3</sup> 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.



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**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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**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 (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.~~
- 
- 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.

1  
2 **Trial registration:** Australian New Zealand Clinical Trial Registry (<http://www.ANZCTR.org.au>) under  
3  
4 ACTRN 12609000177257 and in the World Health Organization Clinical Trials Registry  
5  
6 (<http://www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202>).  
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11 **Funding:** This research received a grant from the Clifford Craig Medical Research Trust, Launceston,  
12  
13 Tasmania, Australia.  
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15  
16 **Key words:** Quality of life assessment, iron deficiency anaemia, oral iron, intravenous iron,  
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18 pregnancy, long-term effect.  
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22 **Short title:** Quality of life in pregnancy  
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## INTRODUCTION

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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,<sup>1-3</sup> IDA is a potential risk factor for preterm delivery and subsequent low birth weight, and may be associated with inferior neonatal health.<sup>3-4</sup> 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.<sup>5-9</sup> 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.<sup>10,11</sup> 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.<sup>3,10,11</sup>

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

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.<sup>14</sup> 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.<sup>14</sup> 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

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

### 10 Rationale and objectives

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14 An initial prospective randomised controlled trial was conducted between March 2007 and  
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16 January 2009 at the Launceston General Hospital (LGH), a tertiary referral centre for Northern  
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18 Tasmania, Australia. The initial study assessed haemoglobin and serum ferritin levels after IV  
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20 followed by oral iron therapy versus oral iron therapy only. The current study constitutes a follow-  
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22 up on the earlier one and took place between January 2010 and January 2011 and focussed on  
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24 HRQoL, breastfeeding duration and child health. Informed consent was obtained from all  
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26 participants in accordance with the Declaration of Helsinki. The original and the follow-up studies  
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28 were approved by the Tasmanian Human Research Ethics Committee and registered in the Australian  
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30 New Zealand Clinical Trials Registry (<http://www.ANZCTR.org.au/ACTRN12609000177257.aspx>)  
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32 and the World Health Organization Clinical Trials Registry  
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34 (<http://www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202>).  
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43 In the original study, we prospectively assessed HRQoL at baseline prior to treatment in the  
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45 second trimester, 4 weeks after initiation of treatment, in the third trimester before delivery, and at 6-8  
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47 weeks post delivery. In the follow-up study, a HRQoL questionnaire was completed that incorporated  
48  
49 the original questionnaire plus additional parameters such as the length of the breastfeeding period  
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51 and occurrence of postnatal depression as well as child growth data. This was performed at a median  
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53 of 32 months post intervention in order to assess the long-term effects of both treatment types on  
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55 mothers' HRQoL in relation to data from the earlier study. This questionnaire, although completed  
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2 prospectively, had a retrospective component that asked the participating mothers the same questions  
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4 again that they had previously answered prospectively. These data were compared with the mothers'  
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6 original prospective QoL data for validation purposes.  
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## 10 11 **Participants**

12  
13 Pregnant women aged 18 years or above who presented to the LGH with IDA between 2007 and 2009  
14  
15 were invited to participate. In the original study (Figure 1), 196 Caucasian pregnant women aged 18  
16  
17 years or above were identified who had moderate IDA, defined as haemoglobin (Hb)  $\leq 115$  g/L  
18  
19 (reference range (RR) 120-160 g/L), and low iron stores, based on serum ferritin levels  $< 30$   $\mu\text{g/L}$  (RR  
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21 30-440  $\mu\text{g/L}$ ).  
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26 Of the original evaluable 183 pregnant Caucasian women randomised to receive oral iron or a single  
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28 intravenous iron polymaltose infusion, 126 women completed the QoL follow-up study (Table 1). The  
29  
30 median age was 29 years at enrolment (range, 21 to 43); and the median follow-up period was 32  
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32 months (range, 26 to 42) with an average follow-up period of 36 months post delivery.  
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## 38 **Randomisation and interventions**

39  
40 Informed consent was obtained from all patients. Treatment arms were allocated in blocks of 10 by  
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42 **computer-generated random assignment, and allocation was done by concealed envelopes. This was**  
43  
44 **done** by the LGH Pharmacy Department in order to avoid possible bias. The oral-only treatment arm  
45  
46 comprised iron sulphate 250 mg tablets once daily, (elemental iron 80 mg, Abbott, Australasia Pty  
47  
48 Ltd) to be taken daily within two days after booking until delivery. The IV arm required a single  
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50 intravenous infusion of iron polymaltose (Ferrosig, Sigma Pharmaceuticals, Australia) within 1 week  
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52 after first antenatal visit followed by oral iron identical to the other arm. Pre-enrolment, there were no  
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54 significant differences in the dietary iron intake or supplement intake between the two groups based  
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2 on a specially-designed questionnaire addressing these issues.<sup>14</sup> Patients assigned to IV iron  
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4 polymaltose received a 100 mg test dose dissolved in 50-100 mL normal saline infused over 30  
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6 minutes. Clinical observation and vital signs were assessed initially and every 15 min from the start of  
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8 the infusion. After the test-dose was tolerated, the remainder of the iron polymaltose dose was  
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10 infused. The total dose of IV iron polymaltose was calculated according to the patients' body weight  
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12 at their first antenatal visit and entry Hb level according to the product guidelines; iron dose in mg (50  
13  
14 mg per 1 mL) = body weight (maximum 90) in kg x target Hb (120 g/L) - actual Hb (in g/L) x  
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16 constant factor (0.24) + iron depot (500).<sup>14</sup>  
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## 24 Outcome measurement

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27 Two Health-Related Quality of Life (HRQoL) questionnaires were administered during the initial and  
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29 follow-up studies. **First**, a clinical questionnaire was completed prospectively by trained midwives at 4  
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31 weeks after initiation of treatment, at 28 and 34 weeks gestation, and then 6-8 weeks post delivery.  
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33 This questionnaire assessed four aspects: energy levels, activity, tolerance and side effects of the  
34  
35 treatment. This was used to guide individual patient clinical decision-making as well as to provide a  
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37 safety audit of the trial treatments.<sup>14</sup> **Second**, a prospective/retrospective survey was conducted  
38  
39 between June and October 2010 by trained research personnel via phone interview using a modified  
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41 version of the SF-36 HRQoL questionnaire, similar to a version published previously.<sup>16,17</sup> **Additional**  
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43 modifications **for this study** included: (1) use of eleven of the 36 questions (Table 2), and (2) the  
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45 women were asked to recall their response to each of the questions at four time points, pre-trial prior  
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47 to commencement of iron therapy during the pregnancy, four weeks after the start of iron therapy, one  
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49 week after delivery, and the last four weeks prior to the telephone questionnaire contact (Table 2).  
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51 This **was** compared in a retrospective fashion to the same questions answered earlier prospectively by  
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53 the participants at these different **timepoints**. In order to validate the retrospective use of the modified  
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2 SF-36 questionnaire to assess the women's HRQoL during and after pregnancy, **we estimated** the  
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4 associations of the physical activity component of the prospective monitoring questionnaire following  
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6 entry into the trial with the Physical Component Scale values of the modified SF-36 at each of the  
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8 **timepoints**. We hypothesized that the association would be greatest at 4 weeks **after enrolment**  
9  
10 **compared to trial entry**, time of delivery or at the time of questionnaire completion. In addition, data  
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12 concerning breastfeeding and the health of the child were collected from the baby's growth booklet.  
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14 This included breastfeeding duration, baby gender, age, weight and previous hospitalisation, if any, in  
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16 addition to the baby's sleep quality since birth and specific growth data for the children as set by the  
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18 Australasian Paediatric Endocrine Group (APEG). Haemoglobin and ferritin levels for participants at  
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20 delivery were available for all participants; however no further testing was performed during the  
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22 follow up. The principal investigators, including the statistician, evaluated the questionnaire results  
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24 data.  
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### 31 **Statistical methods**

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33 The HRQoL scores that form the raw data for this analysis are rank-order in nature. Means and  
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35 standard deviations of the scores were estimated using generalised estimating equations for illustrative  
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37 purposes only. Physical and mental composite scores were calculated in the modified SF-36 according  
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39 to the SF-12 scoring guidelines.<sup>16,17</sup> Group comparison and covariate effect size calculation, odds  
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41 ratios (OR with 95% confidence intervals and P values) were estimated using repeated measures of  
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43 ordinal logistic regression, with covariates selected for inclusion by backward stepwise regression (P  
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45 for exclusion 0.22) from maternal age, haemoglobin, ferritin, Socio-Economic Indexes for Areas  
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47 (SEIFA; based on the Collector District of residence of mothers), quality of sleep, use and duration of  
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49 breastfeeding, hospitalization of the baby, baby gender and mode of delivery. This included  
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51 randomisation group covariate interactions in the starting model with exclusion of those interactions  
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53 using the above criteria. When iron status was selected for inclusion in the model, the association  
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2 between iron status (ferritin) and HRQoL was reported independently of trial treatment group. P  
3 values were corrected for multiple comparisons where necessary by the Holm method. The effect of  
4 IV iron versus oral iron on time of cessation of breastfeeding was compared by estimation of hazard  
5 ratio (HR) with 95% confidence intervals and P-values by Cox proportional hazards regression  
6 adjusted for covariates selected for inclusion by backward stepwise regression (P for exclusion 0.22).  
7 The time to cessation of breast-feeding was taken from the subject's baby growth booklet for all  
8 participants. Neonatal growth in the treatment groups was compared by multivariate third-order  
9 polynomial regression as an approximation to APEG growth assessment. **The iron status variables**  
10 **used in the multivariate regression models were selected by stepwise regression.** All HRQoL  
11 statistical analyses were performed using Stata SE for Windows 11.1 (StataCorp, College Station, Tx  
12 USA).

## 31 RESULTS

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

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As reported in the original study,<sup>14</sup> 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  $\mu\text{g/L}$ . 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  $\mu\text{g/L}$ ; 95% CI 194 to 249  $\mu\text{g/L}$  ( $p < 0.001$ ). This substantial improvement was maintained after delivery with a mean level of 108  $\mu\text{g/L}$ ; 95% CI 43 to 209  $\mu\text{g/L}$  ( $p < 0.001$ ).<sup>14</sup> 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  $< 116 \text{ g/L}$  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  $\text{g/L}$  (SD 14.2) in the oral iron versus 115.5  $\text{g/L}$  (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.<sup>14</sup>

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 165  $\text{g/L}$  (SD 9.6) in the oral iron group versus 157  $\text{g/L}$  (SD 14.1) in the IV iron group (difference -7; 95% CI -18 to 3;  $p = 0.17$ ). The ferritin levels were 142  $\mu\text{g/L}$  (SD 86) and 185  $\mu\text{g/L}$  (SD 101) respectively (difference 43; 95% CI -59 to 145;  $p = 0.41$ ).

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2 The HRQoL Physical Component Scale (difference 10.3; 95% CI 3.3 to 17.2; P=0.27; OR 2.39; 95%  
3 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;  
4 95% CI 1.57 to 6.26; P=0.001) responses were improved in the IV compared to the oral iron group,  
5 but these differences became less apparent at subsequent assessment timepoints (Figure 2a and b).  
6  
7 Furthermore, there were strong associations between the level of iron status, independent of how that  
8 iron status was achieved, and a number of the HRQoL scales (Figure 2): notably improved general  
9 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),  
10 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;  
11 P<0.001), less psychological downheartedness ({1SD haemoglobin} OR 1.57; 95% CI 1.14 to 2.15;  
12 P=0.005), less clinical depression ({1SD log.-ferritin} OR 2.05; 95% CI 1.27 to 3.32; P=0.003), and  
13 overall improved mental component scale (slope {1SD haemoglobin} 3.8; 2.5 to 5.0; P<0.001; OR  
14 1.71; 95% CI 1.39 to 2.10; P<0.001) (Psychological Downheartedness and Clinical Depression  
15 analysis used raw scores rather than 100-point scales).  
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35 There was an increased duration of breastfeeding (HR for cessation was 0.70; 95% CI 0.50 to 0.99;  
36 p=0.046) in women in the IV iron group (Figure 3), where higher maternal age was associated with  
37 longer breastfeeding (HR 0.76; 95% CI 1.00 to 1.52; P=0.006) (Table 3). Earlier cessation of  
38 breastfeeding was associated with downheartedness (HR 1.23; 95% CI 1.00 to 1.52; P=0.06). There  
39 was no difference between the oral iron or IV plus oral iron groups in the weight of the baby at birth  
40 (p=0.64), and no difference in the rate of weight gain (p=0.90).  
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52 The **correlation** between the prospective physical symptom questions index from the clinical  
53 monitoring questionnaire and the Physical Component Scale of the retrospective HRQoL for the four  
54 time periods is shown in Table 4. There was a significant association between the physical symptom  
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2 questions index at 4 weeks after trial entry and each of the HRQoL recall time points, and the  
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4 correlation was strongest for the 4 weeks recall (OR 3.18; 2.14 to 4.74;  $P<0.001$ ).  
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9 Another finding of our study was an association between male gender babies and an unfavourable  
10 mental health component outcome for participant women across the two groups. Of the seven  
11 component questions, two showed a significant association, with women who had male babies less  
12 likely to be calm and peaceful (OR=0.55, 0.32-0.97,  $p=0.039$ ). There were no statistical differences in  
13 terms of HRQoL assessment regarding the method of delivery between women who delivered  
14 normally and those who had caesarean section.  
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## 27 DISCUSSION

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29 Prior to our study, there were no data available concerning the effects of either IV or oral iron  
30 supplementation for anaemia on post-delivery psychological and physical welfare of mothers, the  
31 quality of the bonding to the baby and the rate of developmental progress of the baby. We are  
32 reporting on 126 patients in a follow up study of the effect of IV iron versus oral iron therapy on  
33 HRQoL during and after pregnancy. Our study demonstrates that there was an improvement in the  
34 self-assessed feeling of general health in both treatment groups from the pre-labour period to all  
35 subsequent periods. Although the improvement was significantly greater during pregnancy in the IV  
36 iron group 4 weeks after commencement of trial treatment ( $p=0.001$ ), the difference persisted in the  
37 subsequent measurement periods at a lesser magnitude that did not achieve statistical significance.  
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51 Regardless of treatment and regardless of which period was being considered, higher haemoglobin  
52 and higher ferritin levels were associated with better baby sleep quality, a longer period of  
53 breastfeeding and a higher level of mothers' general health.  
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2 The modified HRQoL questionnaire used in our study includes many useful and relevant aspects  
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4 regarding general health, daily activities, levels of energy and depression. There was a substantial  
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6 improvement of iron status in women who received IV iron compared to oral iron as demonstrated  
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8 during the trial analysis ( $p < 0.001$ ). Limitations of our study include the modified questionnaire being  
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10 in part a retrospective HRQoL evaluation which should ideally have been conducted within a shorter  
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12 period of time. However, a correlation to a prospective evaluation of the studied subjects has been  
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14 made in our study in order to overcome a possible recall bias. Therefore, we were able to minimise the  
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16 number of retrospective questions, since the women were asked to recall their responses to each  
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18 question at four different time points. The full SF-36 was impractical and may have been judged to be  
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20 an excessive burden on the women. Thus, we attempted to provide a retrospective form of validation  
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22 by showing that the clinical HRQoL questions in the physical domain, recorded prospectively at week  
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24 4 after trial, were most strongly associated with the Physical Component Scales of the recall of  
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26 modified SF-36 at week 4 compared to the other time points. This indicates that the retrospective  
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28 methodology was able to provide an acceptable degree of accuracy in the differentiation of HRQoL  
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30 levels at different timepoints despite the concerns that may have arisen with this issue. The  
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32 assumption being made is that the way those patients judge their physical and mental condition will be  
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34 relatively stable over time,<sup>18</sup> an assumption with which we agree may occur in patients with chronic  
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36 diseases. However, this assumption may not hold for women during and after pregnancy. The  
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38 expectations by the woman about how she should be feeling at the different stages of pregnancy,  
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40 around the time of delivery, and when she is caring for one or more young infant or child may differ  
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42 substantially at those different time points. At least in our analysis, the judgment the woman is making  
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44 about how to answer the questions is likely to be the same for each time point, since she had made that  
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46 judgment at one point in time: the repeated measures analysis compares each woman with herself,  
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48 thus substantially reducing the impact of variation between women in this judgment. Thus, for the  
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2 purpose of generating a hypothesis concerning iron status and quality of life, we believe that our  
3 methodology has been adequate. Another limitation of our study is the relatively small number of  
4 women studied. Nevertheless, prior to our study there was a lack of research that addressed HRQoL  
5 during and after pregnancy, and particularly the association between iron status and postnatal clinical  
6 depression as well as breastfeeding duration in our cohort of patients provides a novel finding and a  
7 basis for further research.  
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16 **An incidental finding of our study was** a trend for unfavourable mental health component outcomes  
17 for women with male babies there is only a single report in the literature that addressed this issue and  
18 reported similar findings.<sup>19</sup> Perhaps this may be explained with the observation that male babies are  
19 usually more active, and this may be associated with post natal depression.<sup>19</sup> However, due to lack of  
20 more detailed data, this issue should be addressed separately and studied in future research.  
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29 Due to paucity of data regarding HRQoL during and after pregnancy, there are only limited data  
30 available from other studies. Jansen *et al* studied the effect of delivery and postpartum changes on the  
31 HRQoL.<sup>20</sup> A cohort of 141 pregnant women were included in that study. HRQoL questionnaires were  
32 measuring the immediate effect of delivery on the quality of life. The HRQoL questionnaires were  
33 conducted less than 1 day after vaginal delivery and less than two days after delivery by caesarean  
34 section and compared to 3-6 weeks post delivery for both groups.<sup>20</sup> The study focused on patients'  
35 HRQoL recovery after both delivery interventions. In that study,<sup>20</sup> the different time points of  
36 completion of the questionnaire (**immediately post-delivery and 3-6 weeks thereafter**) may not  
37 necessarily reflect the HRQoL during pregnancy and subsequently after the postpartum period.  
38  
39 Furthermore, the immediate questionnaire after delivery and at 3-6 weeks time in the postpartum  
40 period may **have been** influenced, at least in theory, by the event of delivery, in particular **when**  
41 complications **occurred**, as well as by the possible emotional and hormonal fluctuations during this  
42 period. It is worthwhile to note that the same study did not show any association between Hb and  
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2 QoL; however it did not investigate a possible effect of iron status on perceived HRQoL in  
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4 conjunction with breastfeeding. This highlights our novel finding of the correlation between iron  
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6 status and improved HRQoL during and after pregnancy.  
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10 In summary, **we found** a significant improvement in the general health of women who received IV  
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12 iron ( $p<0.001$ ), but this effect was found prominently 4 weeks after the IV iron treatment. The  
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14 duration of breast-feeding was longer ( $p=0.04$ ) in those women who had received IV iron. Women  
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16 with better iron status were less downhearted ( $p=0.005$ ) and less likely to develop postnatal clinical  
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18 depression ( $p=0.003$ ).  
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22 Our results indicate that it is worthwhile considering Hb and iron status as a surrogate marker for  
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24 assessment of women's wellbeing, not only during pregnancy, but also during the postnatal period.  
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28 Further studies are warranted to confirm and extend our findings, and to determine outcomes in  
29  
30 different populations with IDA in order to improve the estimates of the magnitude of the benefits of  
31  
32 intravenous iron for the management of iron deficiency anaemia.  
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38  
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40  
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43 Hospital, Singapore) for helpful comments on the manuscript. **The authors acknowledge the midwives  
44  
45 and the Pharmacy Department at the Launceston General Hospital for their help in conducting the  
46  
47 trial.**

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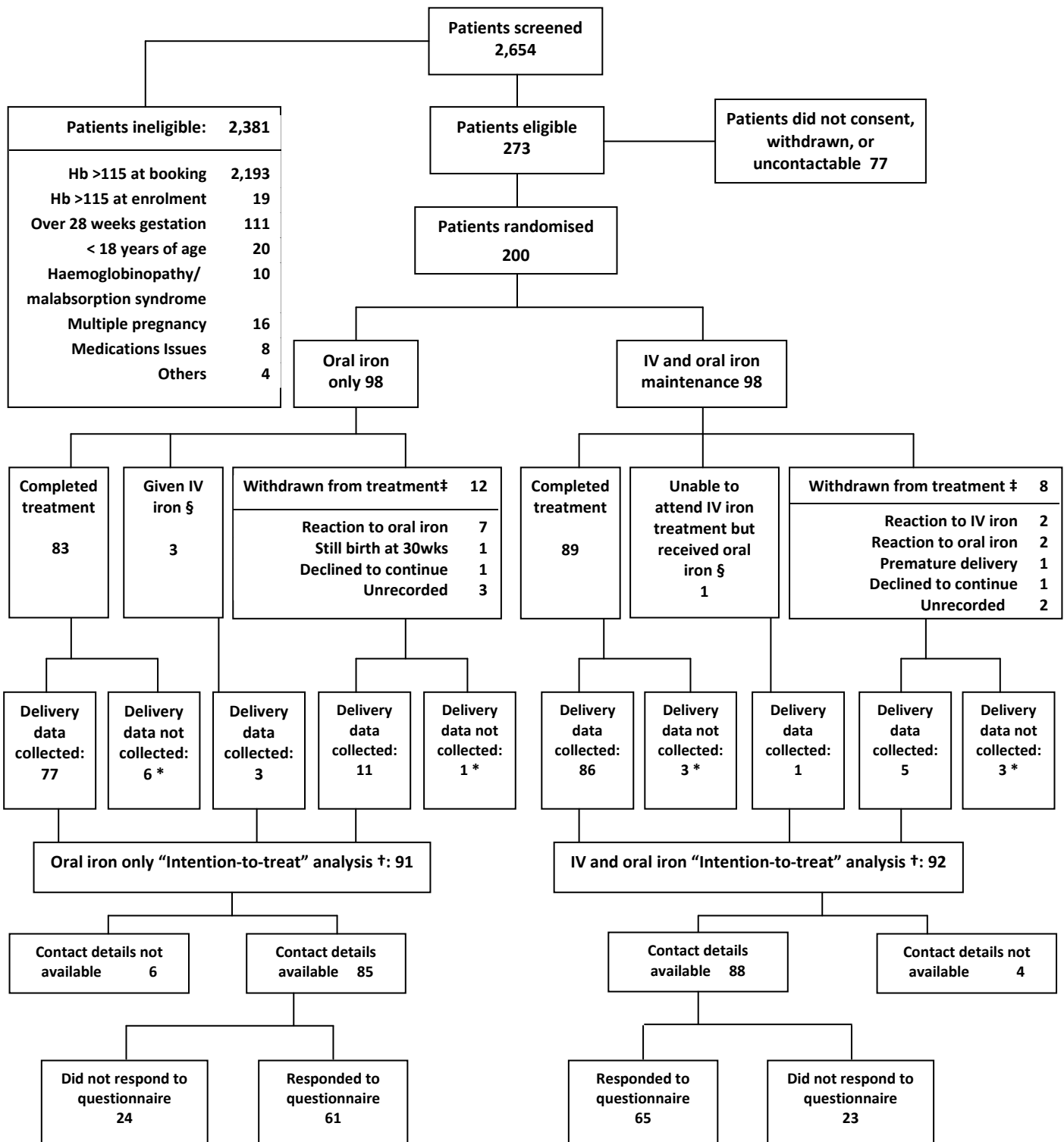
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**Figure 1.** Trial flow diagram: disposition of study participants by treatment assignment.



**Footnotes to Figure 1. Patients Flow Chart.**

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4 \* Fourteen patients were admitted late in labour, and no blood samples were taken before delivery.  
5 † The primary hypothesis examined the change in haemoglobin levels between the time of booking and immediately prior to  
6 delivery; an “intention-to-treat” analysis was performed according to original randomisation group on those patients who  
7 had blood samples taken before delivery, whether or not the treatment was completed as per protocol.  
8 ‡ Twenty-one patients withdrew from the trial treatments, and all but one of these patients agreed to continued collection of  
9 haematological and other trial data; eight patients gave no reason for withdrawal.  
10 § Five patients did not complete the intended treatments, but did not choose to withdraw themselves; three patients in the  
11 oral iron group were treated with IV iron when their haemoglobin was judged not to have responded adequately to oral  
12 iron, while one patient was unable to attend for IV iron treatment.  
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For peer review only

**Table 1.** Patient characteristics

	<b>IV iron group</b>	<b>Oral iron group</b>
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

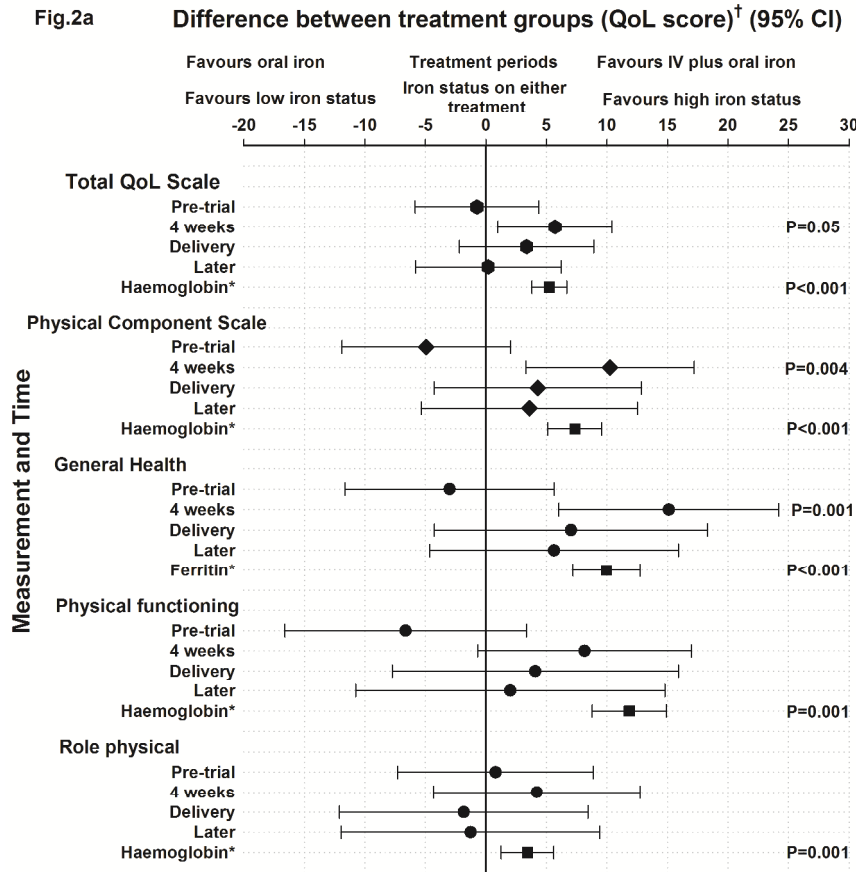
**Table 2.** Comparison of the questions in the SF-36 and the abbreviated HRQoL questionnaire used in this study.

*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

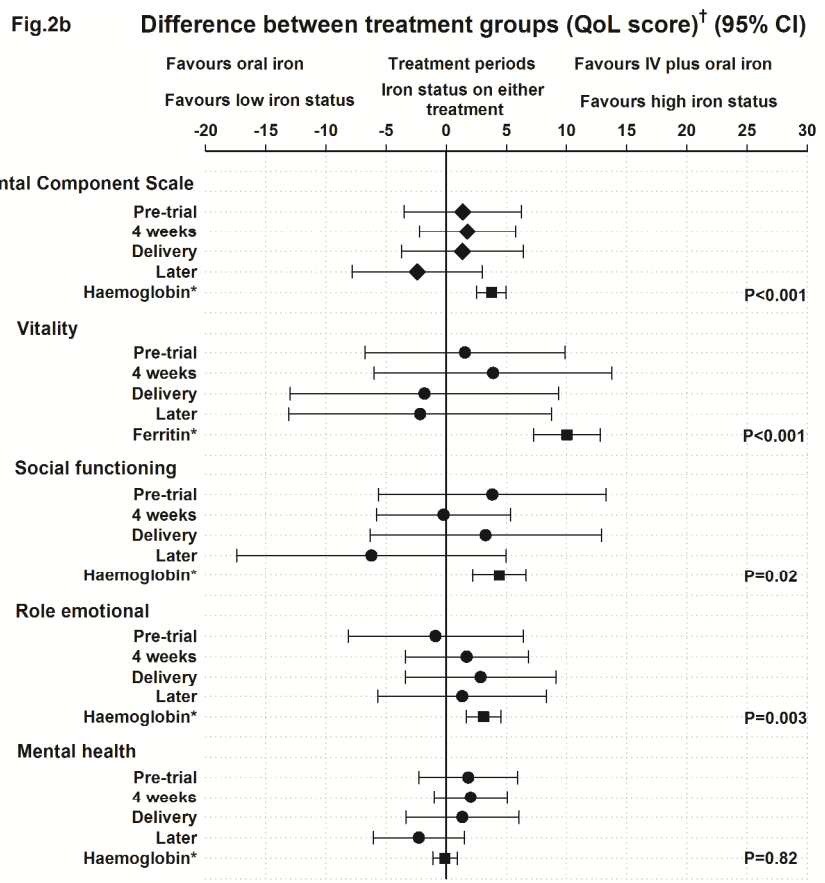
\* Not all of the original SF-36 questions are included in this list. All the questions shown in this list, except for the last original SF-36 question about pain, were included in the questionnaire administered in this study. Where the questionnaire response was the same this is indicated, and where 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



only



† 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 <sup>1</sup>	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

<sup>1</sup> **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 ( $\{\text{mother's age} - \text{group mean age}\} / \text{group standard deviation of age}$ ): mean age  $28.1 \pm 5.6$  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.**

<sup>2</sup> Abbreviations: NVD – normal vaginal delivery; LSCS – lower segment caesarean section

**Table 4. Correlation** between the physical symptom questions<sup>3</sup> from the prospective clinical monitoring questionnaire and the Physical Component Scale of the retrospective HRQoL for the four time periods.

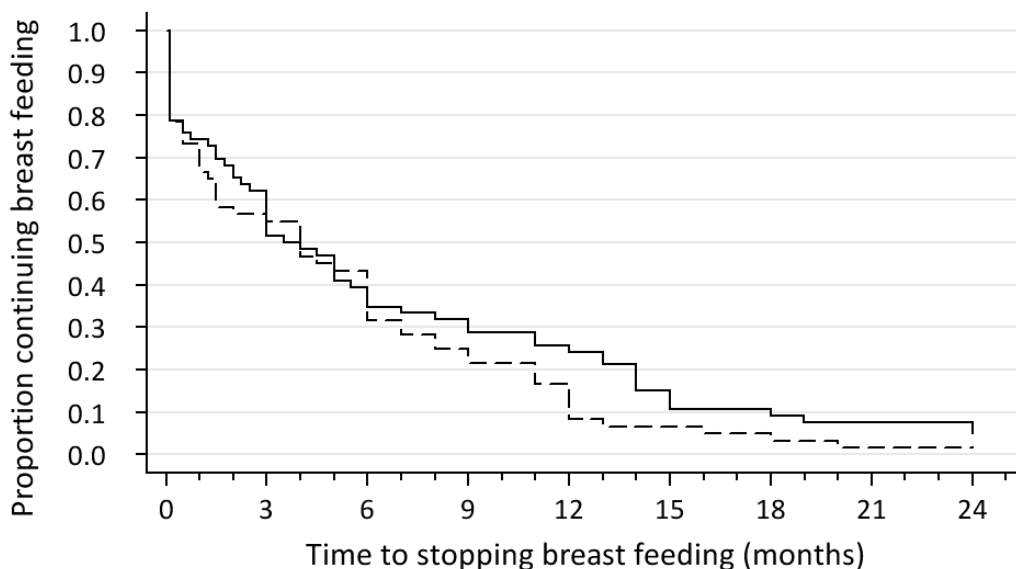
Time	Slope (SD) <sup>1</sup>	OR <sup>2a</sup>	95%CI	P-value	OR <sup>2b</sup>	95%CI	P-value
Pre-trial	2.67 (13.0) <sup>1</sup>	1.46	(1.01 to 2.11)	0.043	1.00		
4 weeks	8.07 (18.6)	3.18	(2.11 to 4.80)	<0.001	2.18	(1.44 to 3.28)	<0.001
Delivery	4.91 (12.2)	2.14	(1.37 to 3.35)	<0.001	1.46	(0.94 to 2.29)	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

<sup>1</sup> 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).

<sup>2</sup> The strength of the <sup>a)</sup> absolute association at each time point, and <sup>b)</sup> 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).

<sup>3</sup> 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.



Number at risk		0	3	6	9	12	15	18	21	24
IV plus oral	65	41	26	21	17	10	7	4	3	
Oral	61	34	26	15	10	4	3	1	1	

IV plus oral    
  Oral

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
<b>Title and abstract</b>	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
<b>Introduction</b>			
Background/rationale	2	Scientific background and the rationale for the study were stated	5,6
Objectives	3	Aims and objective were mentioned	6
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6-8
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	9
		(e) Describe any sensitivity analyses	Not applicable
<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	10,11
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	Not applicable
		<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://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