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Open-label study of the efficacy and safety of Intravenous Ferric Carboxymaltose in pregnant women with Restless Legs Syndrome

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Abbreviations

AE	Adverse event
BP	Blood pressure
CI	Confidence interval
ESS	Epworth Sleepiness Scale
FCM	Ferric carboxymaltose
FSS	Fatigue Severity Scale
Hb	Hemoglobin
IRLS	International Restless Legs Syndrome
IV	Intravenous
PLM	Periodic limb movements
PSQI	Pittsburgh Sleep Quality Index
RLS	Restless legs syndrome
SAE	Serious adverse event
SD	Standard deviation

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Abstract

Objective: To test the efficacy and safety of intravenous ferric carboxymaltose (FCM) in pregnant women with Restless legs syndrome (RLS) and iron deficiency or anemia. The open-label pilot study (exploratory) was performed at the University Hospital of Zürich and Neurocenter of Southern Switzerland (Lugano).

Patient and Methods: Nineteen women in the third trimester of pregnancy with moderate-to-severe RLS and serum ferritin levels <35 µg/L or hemoglobin (Hb) <11.0 g/dl were included in the study. RLS was graded according to the International Restless Legs Syndrome (IRLS) Study Group rating scale. All participants had a score of ≥20 or had RLS ≥3 times/week. Depending on Hb levels, 500 or 700 mg of FCM was administered over 20 min. The primary endpoint was a ≥50% reduction in the mean IRLS score 1 week after FCM infusion. Secondary endpoints included periodic limb movements (PLMs; assessed using nocturnal foot actigraphy), sleep quality (assessed using the Pittsburgh Sleep Quality Index), and safety.

Results: The IRLS score decreased from 23 ± 7 (baseline) to 13 ± 7 ($P < 0.01$), whereas the PLM index decreased from 35 ± 26 (baseline) to 25 ± 20 ($P < 0.001$). Significant improvement in sleep quality was also reported ($P < 0.029$), and treatment was well tolerated. Three serious adverse events were reported but were considered unrelated to treatment.

Conclusions: These data provides promising evidence of the safety and efficacy of FCM for moderate-to-severe RLS in pregnant women with iron deficiency or anemia. A future placebo-controlled study is therefore warranted.

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Keywords

1. Restless Legs syndrome 2. anemia 3. pregnancy 4. ferric carboxymaltose 5. actigraphy

Introduction

Restless legs syndrome (RLS) is characterized by an urge to move the legs; it worsens at rest, predominantly in the evening or at night, and is relieved by movement[1,2]. The majority of patients with RLS also present with periodic limb movements (PLMs) during sleep, insomnia, and a significant reduction in their quality of life[3].

Pregnancy was first described as a risk factor for RLS by Ekbom[4] in 1945. Subsequently, several epidemiological studies have confirmed an increased prevalence of RLS during pregnancy, with rates of 10%–30% that peak in the third trimester[5-8]. Notably, although the symptoms tend to resolve after delivery, the recurrence rate in subsequent pregnancies range from 30% to 60%[7], and women who experience RLS during pregnancy have a three- to four-fold increased risk of developing idiopathic RLS in later life compared with those who had no symptoms during pregnancy. When assessed by the International Restless Legs Syndrome (IRLS) Study Group rating scale, severe symptoms have been reported in 45% and 54% of pregnant women in two recent studies[8,9]. Genetic, metabolic, and hormonal factors, such as iron deficiency and elevated estradiol levels, have all been proposed as determinants of pregnancy-related RLS. However, the current literature remains controversial, providing no clear explanation of the underlying mechanisms[7,8].

Pregnancy is the second most important cause of iron deficiency in women after menorrhagia. The World Health Organization recommends oral iron supplementation for pregnant women with anemia (Hb <10.5 g/dl) and for non-anemic women with iron deficiency (ferritin <30 µg/L), while recommending parenteral iron only for women who fail to respond to oral iron[10]. In Switzerland, parenteral ferric carboxymaltose (FCM) is

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approved for the treatment of iron deficiency and/or anemia from the second trimester of pregnancy onward. Moreover, it seems that FCM does not cross the placenta[11].

Recent European guidelines continue to support dopaminergic agents as the first-line therapy for RLS[12]. However, dopaminergic agents are not approved for use during pregnancy because of their potential to cause fetal malformations, and they are unsuitable for use during lactation because they can inhibit prolactin secretion. Alpha-2-delta ligands (pregabalin, gabapentin) are also unapproved, although information on their teratogenicity is inconclusive. In animal studies, increased indices of fetal structural abnormalities of the nervous system have been observed with pregabalin. In addition, Koo et al.[133] found higher rates for congenital oral malformation with gabapentin therapy. However, in a report of 44 live births, gabapentin exposure during pregnancy was not associated with an increased risk of adverse fetal events[144]. However, at present, most first-line therapies appear unsuitable for use in pregnancy.

Iron (FCM) is approved as a category C drug by the Food and Drug Administration for use in pregnancy and is indicated as a third-line therapy for RLS and iron deficiency. Despite this, there are only limited data and few clinical studies using FCM in pregnant women. In an observational study of 65 anemic pregnant women receiving FCM, 20% reported minor side effects such as hypotension, headache, nausea, and pruritus, without serious adverse events (SAEs)[15]. However, there have been no well-controlled trials for the treatment of pregnancy-related RLS, which remains without an approved treatment option[16].

Iron supplementation has been shown to be effective for idiopathic RLS in some studies. Although studies with oral dosing are limited, a study by Wang et al.[17] demonstrated significant improvement in patients with low ferritin levels. Of the studies using intravenous (IV) iron for RLS, there have been conflicting results[18]. On the one hand, Davis et al.[19] did not find any significant improvement with IV therapy. On the other hand,

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although Ondo et al.[20] found IV treatment with iron sucrose to be ineffective, they reported that IV treatment with iron dextran led to a significant improvement in severe, refractory RLS. In addition, Picchietti et al.[21] reported complete remission of RLS symptoms until 5 months postpartum in a 23-year-old woman treated with IV iron before pregnancy. A case report from 2013 also reported two patients who were treated with IV iron sucrose; they experienced a significant reduction or remission in RLS symptoms[22].

The objective of this open-label pilot study was to explore the efficacy and safety of an iron infusion with FCM during the third trimester of pregnancy in women with RLS and iron deficiency.

Methods

Design and setting

This was a prospective, uncontrolled, open-label, multicenter pilot study, conducted at the Departments of Neurology and Obstetrics, University Hospital of Zurich, and at the Sleep Center and Department of Obstetrics, Neurocenter of Southern Switzerland, Civic Hospital of Lugano between 2010 and 2013. Participants included in the study received no remuneration. Ethical approval was obtained from the Independent Ethics Committees of Zurich and Bellinzona, consistent with the principles of the Declaration of Helsinki. The clinical trial registration number is NCT01245777.

Participants

Screening (Visit 1)

Pregnant women were screened for RLS symptoms over the phone, using the standard diagnostic criteria of the International RLS Study Group[8]. All women with symptoms of RLS were interviewed face-to-face by an experienced neurologist to confirm their diagnosis. The personal and family histories of RLS, sleep habits, and medical histories

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were then recorded. Clinical assessments were completed and comprised general and neurological examinations, vital signs, body weight, and leg circumference measurements to assess leg edema. Blood tests [full blood count, Hb, ferritin, iron, transferrin, C-reactive protein (CRP), electrolytes, liver and kidney enzymes, glucose, vitamin B12, folic acid, thyroid-stimulating hormone, and estradiol levels] were performed to exclude secondary causes of RLS. We used the following standardized questionnaires to evaluate the severity of RLS: the IRLS score[23], the Fatigue Severity Scale (FSS)[24], the Epworth Sleepiness Scale (ESS)[25], and the Pittsburgh Sleep Quality Index (PSQI)[26].

The inclusion criteria were as follows: met all the essential criteria of the IRLS Study Group, in the third trimester of pregnancy; age older than 18 years, moderate-to-severe RLS (i.e., an IRLS score ≥20 and/or RLS occurring ≥3 times/per week), and iron deficiency (ferritin <35 µg/L) and/or anemia (Hb <11.0 g/dl).

The exclusion criteria were as follows: age <18 years, current or past (last 3 months before treatment) IV iron therapy, twin/multiple pregnancies, severe pre-existing illnesses, secondary RLS not due to iron deficiency (e.g., peripheral neuropathy, chronic kidney disease, chronic pain syndrome), any disorders of iron metabolism, vitamin B12 or folic acid deficiency, significant blood loss (defined as a decrease in Hb levels to <2.0 g/dl), pregnancy weight <35 kg, any other pharmacological treatment, and excessive intake of alcohol or coffee. All participants gave oral and written informed consent.

Intervention (Visit 2)

Each participant received 500 mg of IV FCM approximately 3–6 days after screening. All anemic patients with an Hb below 11 g/dl received a second infusion (200 mg IV) 7 days after the first infusion. Vital signs were measured at 10-min intervals before, during, and after the infusion; the IRLS score was recorded at the end of each infusion.

Ferinject® contains FCM for i.v. application. One vial with 10 ml solution contains 500 mg iron as iron carboxymaltose. Additional ingredients are sodiumhydroxid, hydrochloric acid,

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H2O. One vial of Ferinject (500mg of FCM) was diluted with 250ml of sterile saline (sterile 0.9% NaCl) solution. It was administered over a period of 15min i.v.

Outcome and follow up (visits 3–8)

Treatment effects were evaluated using questionnaires (IRLS, FSS, ESS), blood tests (iron, ferritin, CRP, estrogen), vital sign measurements, and leg circumference measurements on days 3 (visit 3), 7 (visit 4), 14 (visit 5), and 28 (visit 6) after therapy. In addition, the PSQI was completed during visits 6 and 8. A telephone interview was conducted 14 days postpartum (visit 7) to determine the IRLS score. The final visit (visit 8) was in the obstetrics department at 60 days postpartum and included general and neurological examinations, vital sign measurements, leg circumference measurements, questionnaire completion, and blood tests (Hb, ferritin, CRP, estrogen) .

Foot actigraphy was performed for three nights before and 7 days after therapy to evaluate the evolution of PLM per hour of sleep (i.e., the PLM index), as described by King et al.[27] When patients required two doses of FCM, the subsequent measurements were counted from infusion 1. Treatment responders were defined as patients with ≥50% reduction in the mean IRLS score after 14 days. Non-responders were defined as those with a <50% reduction in the IRLS score from baseline.

Safety assessment

Safety data for all patients were included in the analysis. Adverse events (AEs) and SAEs were documented by an investigator at each visit, and clinically significant changes in clinical assessments and laboratory measurements were recorded.

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Statistical analysis

The primary endpoint of this study was a ≥50% reduction in the mean IRLS score from baseline at visit 5. The study was not powered but exploratory in design. One-way analysis of variance with linear mixed-model analysis was performed. For the primary analysis, a two-sided paired *t*-test with linear mixed-model analysis was performed to assess the changes in the ESS, FSS, and PSQI. A *P*-value of less than 0.05 was considered statistically significant. For the secondary analysis, a non-parametric Mann–Whitney *U* test was conducted to detect any reduction in the PLM index from baseline to after therapy. Spearman's rank correlation was used to evaluate the correlation between different variables. Baseline differences between responders and non-responders were evaluated using Welch two-sample *t*-tests. The Statistical Package for the Social Sciences (BM SPSS Statistics 22; 1989; 2013) was used for all statistical analyses. Descriptive data are presented as mean ± standard deviation, unless stated otherwise.

Results

Participants

We enrolled 20 pregnant women with moderate-to-severe RLS and iron deficiency according to the inclusion/exclusion criteria. One participant discontinued the study before receiving any treatment. Overall, 19 women (age, 34 ± 4 years; range, 26–41 years) completed the study.

Before pregnancy, 8/19 (42%) of women reported having already experienced RLS unrelated to pregnancy. During pregnancy, none of the patients consumed alcohol; however, 16% were smokers (3–7 cigarettes/week), 63% were taking vitamins, and 37% were taking magnesium supplements. One patient received a vitamin B12 injection 3 weeks before screening. Oral iron therapy was stopped 5 days before study inclusion

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(Table 1). All participants had ferritin levels <35 μg/L and two were anemic (Hb, 10.8 ± 1 g/dl), requiring a second FCM infusion.

Primary outcome

The IRLS score decreased from 23 ± 7 (baseline) to 13 ± 7 (P < 0.01) by 7 days after treatment. Two weeks after FCM infusion, the IRLS score decreased further to 10 ± 8 (compared with baseline; 95% confidence interval (CI), 8.21–18.63; P < 0.0005). Ten women (52%) were considered responders based on a >50% reduction in the IRLS score at visit 5 (14 days after infusion; Fig. 1). Responders reported a mean improvement in the IRLS score of 82% (compared with 30% for the nine non-responders). There were no significant differences between responders and non-responders with respect to age (P = 0.49), serum ferritin (P = 0.81), Hb level (P = 0.93), ESS (P = 0.35), FSS (P = 0.88), PSQI (P = 0.81), or PLM index (P = 0.43). Four weeks after the FCM infusion, the IRLS score was 8 ± 5 (compared to baseline; 95% CI, 9.58–20; P < 0.0005; Fig. 1). Two weeks after delivery, the mean IRLS score was 3 ± 4, with seven women (36%) still reporting RLS symptoms; of these, four had already suffered from RLS before pregnancy.

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Secondary outcomes

The PLM index before treatment was higher than 10 for 14 patients. One week after FCM infusion, the PLM index decreased from 35 ± 26 at baseline to 25 ± 20 (95% CI, 2.0–17.4; $P < 0.001$; Fig. 2).

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Baseline serum iron levels were below normal at 18 ± 8 μmol/L, with a transferrin saturation of 16% ± 6% and serum transferrin levels of 46 ± 7 μmol/L. Ferritin levels increased significantly from 15 ± 8 μg/L to a maximum of 315 ± 119 μg/L by 7 days after treatment and declined to 70 ± 27 μg/L by 4 weeks after therapy (Table 2). After treatment, the Hb levels increased slowly (but not significantly) over time from 12.0 ± 0.9 g/dl to 12.5 ± 0.8 g/dl. After delivery, the ferritin levels were comparable with those at visit 6.

Neither daytime sleepiness (ESS) nor fatigue (FSS) showed significant improvement, whereas sleep quality according to the PSQI score improved significantly from 11 ± 4 to 8 ± 3 (95% CI, 0.25–4.38; $P < 0.029$; Table 2). There was a significant

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correlation between sleep quality (PSQI) and the IRLS score (r = 0.77; n = 14/19; P < 0.002) measured 28 days after therapy. There were no significant correlations between the IRLS score and the ESS score, FSS score, Hb levels, ferritin levels, age, weight, or PLM index.

The systolic blood pressure (BP) decreased during the infusion by 8 ± 11 mmHg but increased again to 108 ± 14 mmHg 60 min after the infusion. In contrast, the heart rate remained stable at 90 ± 13 beats/minute during the infusion. Body weight increased from 72 ± 10 to 75 ± 11 kg 4 weeks after the FCM infusion. Leg circumference, as assessed before therapy and at every visit, did not change significantly over the course of the study.

Adverse advents

A decrease in the BP by 8 ± 11 mmHg was observed during the infusion in 55% of patients. In addition, headache and dizziness (10% of patients) were considered medication related. Infections (10% with viral gastroenteritis without sepsis) were not considered treatment related. In addition, the nausea and nocturia presented in 26% of women were also considered pregnancy related and unrelated to the medication because they were present before treatment. There were no reports of local injection site reactions or allergic reactions. No extravasation occurred at administration site. The decrease in BP could be associated to the infusion rate, although the solution was administered according to the swiss agency for therapeutic products (500mg/15min).

The three following SAEs occurred during the study: one patient suffered from an hour-long episode of vaginal bleeding of unknown etiology; one patient was hospitalized for 12 h because of periodic uterine contractions in the 38th week of pregnancy; and one patient suffered from pre-eclampsia in the 40th week of pregnancy. We determined that these events were unrelated to FCM treatment.

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All AEs resolved before the end of the study. All babies were born healthy, with six being delivered before visit 6 (i.e., 4 weeks after the FCM infusion).

Discussion

RLS occurs in 10%–30% of pregnant women and can have detrimental effects on sleep quality and overall wellbeing. Currently, no treatment has been approved for RLS during pregnancy. To our knowledge, this pilot study is the first to assess IV iron therapy in pregnant women with RLS. Our findings indicate that treatment with FCM is safe and may be effective in improving moderate-to-severe RLS in pregnant women with iron deficiency or anemia.

Although the placebo effect is quite high in studies of RLS, two key observations in this report suggest that iron infusion had a valid therapeutic effect beyond the placebo effect. First, improvement in RLS (mean reduction in the IRLS score of 14 points; remission rate, 52%) was similar to the improvement reported during treatment with dopamine agonists[28,29]. Second, PLM, which is an objective marker of RLS, also improved significantly, although this was to a lesser extent than that generally observed with dopaminergic drugs. However, it is important to note that the effect on PLM may be less relevant because some patients with RLS do not experience PLM and because the exact relationship between improvement in RLS and PLM is unclear[3]. Furthermore, the limited effect observed on PLM could be due to the large data variance and the fact that actigraphy was performed before the full treatment effect on RLS had been achieved. Our data are consistent with some reports of improvement in idiopathic RLS and PLM after iron infusion[30-32].

Apart from the placebo effect, other factors such as administration route (oral versus IV) and the type of iron may play a role in the effectiveness of therapy. Although oral iron therapy has been shown to be effective in the treatment of RLS[17], ferritin levels

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increase slowly with oral treatment, leading to a delay in the treatment response by a few months[33]. Bypassing the gastrointestinal–blood barrier with IV iron leads to a more rapid increase in ferritin levels and a rapid resolution of symptoms[31]. Nevertheless, it is not clear whether IV iron results in a sustained improvement in RLS for a few months without the need for other RLS medications[31].

Concerning the type of iron, studies have demonstrated iron sucrose to be ineffective, whereas other studies have reported improvements in idiopathic RLS after iron dextran and FCM[20,32,34]. A possible explanation for the different treatment responses could be differences in the pharmacokinetics of the iron formulations. Iron dextran and FCM have high molecular weights and high structural homogeneity, whereas iron sucrose complexes are semi-robust and release larger amounts of weakly bound iron into the blood. These iron complexes are then taken up by macrophages via endocytosis and stored as ferritin. A higher concentration and longer bioavailability of iron may therefore play a key role in treatment efficacy[32]. The evidence is less consistent for iron dextran between FCM and iron dextran, suggesting that FCM is probably the treatment of choice.

In this study, the treatment response was not predicted by patient demographics, ESS score, FSS score, PLM index, Hb levels, or ferritin levels. The mechanisms leading to improvements in RLS after iron infusions during pregnancy remain speculative. We believe that iron supplementation exerts a direct effect. In fact, a reduction in brain iron concentrations has been reported in patients with idiopathic RLS, even in those with normal blood ferritin levels; moreover, this reduction can improve with iron infusions[30,35].

In developed countries, pregnancy represents the second most common cause of iron deficiency after menorrhagia. The high demand for iron by the fetus can lead to a rapid decline in maternal iron stores and low ferritin levels. For the biological plausibility of iron therapy, iron is needed as a cofactor in the synthesis of dopamine[36]. Hence, dopamine synthesis may be reduced if iron levels are low[36], which could explain the

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increase in RLS severity during pregnancy. However, other effects that are related to iron infusions, but not directly related to blood iron or ferritin levels, may play a role. This is supported by the observation in the present study that the extent and duration of treatment response was not strictly linked to blood ferritin levels (Table 2). Furthermore, RLS improved after delivery in all patients, including those not responding to iron infusions, as reported previously[8]. After delivery, RLS symptoms were still reported in seven patients (36%) but with an average decline in the IRLS score of 53% when compared with the initial symptoms. There was no subsequent treatment provided within the protocol.

Hormonal changes have been suggested to play a role in idiopathic RLS and in RLS during pregnancy[77,37]. In fact, estradiol, prolactin, and progesterone levels increase physiologically during pregnancy, reaching their highest levels during the third trimester. After delivery, estradiol and progesterone levels decline, while prolactin is released in a pulsatile manner. However, in a recent study, we found no differences in estradiol levels between patients with and without RLS[8].

In this study, treatment was generally well tolerated, with just two adverse effects considered medication related. A decrease in the systolic BP was observed in 10 patients during the infusion, and two patients reported dizziness after the infusion. The decrease in BP could be associated to the infusion rate, although the solution was administered according to the swiss agency for therapeutic products (500mg/15min). Although three patients suffered SAEs (vaginal bleeding, pre-eclampsia, and periodic contractions), none was considered treatment related and all babies were born healthy.

In conclusion, the results of the present pilot study are encouraging, thus providing evidence to indicate that treatment with FCM is safe and potentially effective for improving moderate-to-severe RLS in pregnant women with iron deficiency or anemia. The main limitations of this study were the absence of a control group treated with placebo and the small sample size. In addition the observed improvement in symptoms the night following

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the first infusion (with mean reduction in the IRLS score of 10 points) could be due to placebo effect.

In future studies, actigraphy or polysomnography should be performed for longer periods of time and at the time of maximal subjective RLS treatment response.

However, because the placebo effect is a significant issue in the treatment of RLS, the real value of the present investigation is to provide justification for structured, larger placebo-controlled trials in the future, which we believe are now warranted.

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Acknowledgments

Author contributions: C. Bassetti designed the study. A. Hübner and C. Baumann helped to implement the study. J. Schneider, A. Krafft, M. Manconi, and T. Gyr helped in data collection. J. Schneider, E. Werth, M. Manconi, and C. Bassetti performed statistical analyses. J. Schneider, M. Manconi, and C. Bassetti helped to interpret analyses and write the report. All authors had full access to all the data in the study. The authors take full responsibility for the integrity of the data and the accuracy of the data analysis.

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Table and figure legends

Figure 1. Decrease in mean International Restless Legs Study Group Rating Scale score from baseline over time (mean ± SE).

Figure 2. Decrease in mean periodic limb movements/hour ± SE before and after treatment with ferric carboxymaltose.

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Table 1: Demographic Data

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Characteristics	Mean ± SD (N = 19)	Range and %
Age, mean, years	34 ± 4	26 – 41
Weight, mean, Kg	72 ± 10	56 – 92
High, mean, cm	167 ± 5	158 – 177
BMI[a], mean	26 ± 3	22 – 31
Pregnancy		
Week of pregnancy	32 ± 3	28 – 37
Primagravida	10 / 19	52%
Multigravida	9 / 19	47%
Prior oral iron treatment	8 / 19	42%
Vitamins	12 / 19	63%
Magnesium	7 / 19	36%
RLS		
RLS[b] before pregnancy	8 / 19	42%
RLS in previous pregnancies	4 / 19	21%
Positive family history for RLS	8 / 19	42%
Positive family history for RLS and		
• RLS before pregnancy	3 / 19	16%
• RLS in previous pregnancies	2 / 19	10.5%
Prior oral iron treatment and:		
• RLS before pregnancy	3 / 19	16%
• RLS in previous pregnancies	2 / 19	10.5%
• Positive family history	3 / 19	16%
RLS moderate/RLS occurs >3 times/week (IRLS[c] score, 11–20 points)	5 / 19	26%
RLS severe (21–30)	14 /19	74%
RLS very severe (31–40)	3 / 19	16%

a: Body Mass Index
b: Restless Legs Syndrome
c: International Restless Legs Syndrome Study Group Rating Scale score

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Table 2: Secondary outcome

Time (days)	Screening (± 3days)	Iron	3 d	7 d	14 d	28d	60d	*P*-Value
Visit	V1	V2	V3	V4	V5	V6	V8	*(Screen vs. V5)*
IRLS[a]	23 ± 7		15 ± 7	13 ± 7	10 ± 8	8 ± 5	5 ± 7	0.001
Hb[b] g/dl	12 ± 1		12 ± 1	12 ± 1	12 ± 1	12 ± 1	14 ± 1	1.0
Ferritin µg/l	15 ± 8		413 ± 128	315 ± 119	175 ± 82	70 ± 27	72 ± 56	0.001
Estradiol pmol/l	49362			69565 ± 10792			218 ± 281	<0.01
ESS[c]	10 ± 5			8 ± 6	7 ± 3	7 ± 3	7 ± 4	0.44
FSS[d]	5 ± 1			4 ± 1	4 ± 1	4 ± 2	4 ± 2	0.15
PSQI[e]	11 ± 4					8 ± 3	6 ± 4	0.03
PLM[f]	35 ± 26			25 ± 20				0.04

SI conversion factors: To convert Hemoglobin to g/L, multiply values by 10
a: International Restless Legs Syndrome Study Group Rating Scale score
b: Hemoglobin
c: Epworth Sleepiness Scale
d: Fatigue Severity Scale
e: Pittsburgh Sleep Quality Index
f: periodic limb movements

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