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ORIGINAL RESEARCH

Association between iron deficiency and fertility

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Abstract

Introduction: This retrospective, observational cohort study investigated the association between treatment of iron deficiency with conception results and pregnancy outcomes in women with infertility and iron deficiency, before and after intravenous ferric carboxymaltose infusion.

Material and Methods: Data were collected from electronic health records from the Dextra Fertility Clinic (Helsinki, Finland) between 2015 and 2020. The cohort included 292 women (<43 years) with infertility and iron deficiency (s-ferritin ≤30 μg/L), treated with a ferric carboxymaltose infusion (Ferinject®, 500 mg i.v.). The main outcomes were live birth and miscarriage rates before and after treatment of iron deficiency. The main explanatory variable studied was the administered iron infusion.

Results: Mean s-ferritin levels increased from 16.2 ± 7.0 μg/L before to 81.5 ± 49.8 μg/L after iron infusion. The proportion of patients who conceived increased from 65% before to 77% after treatment of iron deficiency ($p < 0.001$). Of the study population, 28% of patients experienced miscarriages and 26% gave a live birth before iron infusion, and 13% and 51% after treatment of iron deficiency ($p < 0.001$). In the model adjusted for age, use of preimplantation genetic testing for aneuploidy, and repeated iron infusions, treatment of iron deficiency with iron infusion was associated with a higher live birth rate (OR = 3.19; 95% CI = 2.21–4.66; $p < 0.001$). In the model adjusted for age, reason for infertility, and total number of pregnancies, treatment of iron deficiency was associated with lower miscarriage rates (OR = 0.32; 95% CI = 0.20–0.52; $p < 0.001$).

Conclusions: Filling of depleted iron stores was positively associated with conception results (higher number of pregnancies) and pregnancy outcomes (higher live birth rates and lower miscarriage rates), regardless of the assisted reproductive technology method used. Screening of iron status seems to be important in patients seeking help for infertility problems.

KEYWORDS
ferritin, infertility, iron deficiency, miscarriage, pregnancy outcome

Abbreviations: AFC, Antral Follicle Count; AMH, Anti-Müllerian Hormone; ART, Assisted Reproductive Technology; BMI, Body Mass Index; CI, Confidence Interval; ET, Embryo Transfer; FET, Frozen Embryo Transfer; Findata, The Finnish Social and Health Data Permit Authority; IVF, In Vitro Fertilization; LBR, Live Birth Rate; OR, Odds Ratio; PGT-A, Preimplantation Genetic Testing for Aneuploidy; SD, Standard Deviation; SE, Standard Error; s-ferritin, Ferritin In Serum; s-Hb, Hemoglobin In Serum.

1 | INTRODUCTION

Previous estimates of infertility prevalence vary between 48.5 million couples to 186 million ever-married women in developed countries alone.[1,2] Currently, estimates show that approximately one in six people have experienced infertility at some stage in their lives, and the estimated lifetime prevalence of infertility was 17.5% in 2022.[3] In approximately 15% of cases, standard testing does not provide an obvious cause for infertility, that is, the infertility is unexplained.[4] In 1991, Rushton and co-workers observed a relationship between iron deficiency and infertility as a side finding in a study with premenopausal women treated with oral iron and vitamin C. The study was the first to suggest that conception may be prevented in women with depleted iron stores.[5]

Anemia is a major health problem with an age-standardized point prevalence estimated at 23% worldwide in 2019. In women, it is defined as a serum hemoglobin (s-Hb) level of <117 g/L. Although the pathophysiology of anemia is diverse, iron deficiency is the most common single cause of it, comprising approximately 50% and 25% of cases in developing and industrialized countries, respectively.[6]

Serum ferritin (s-ferritin) is a more sensitive indicator of iron stores than s-Hb concentration and thus, it is widely used to detect iron deficiency. Scandinavian studies have demonstrated that among fertile, non-pregnant women, approximately 40% had small or absent iron stores based on s-ferritin levels.[7] Iron deficiency during pregnancy has been shown to be associated with various adverse maternal and fetal outcomes.[8,9]

The association between iron deficiency, anemia, and infertility is not well understood, and the available literature reports differing findings. In a recent study by Georgsen et al., women with a history of recurrent pregnancy loss had significantly lower median s-ferritin levels compared with the control group, suggesting an association between low s-ferritin levels (iron deficiency) and higher miscarriage rates.[10] Moreover, Holzer et al. have found that ferritin levels <30 μg/L were associated with unexplained infertility.[11] In another study, a U-shaped association between hemoglobin levels and miscarriage was observed, where miscarriages had a lower incidence in women with optimal hemoglobin levels of 120–130 g/L, and a higher miscarriage incidence at Hb levels below 110 g/dL and above 140 g/dL.[12] In contrast, while the use of iron-containing nutritional supplements has shown to positively impact fertility in women with a history of infertility and risk of ovulatory infertility,[13–15] it has also been reported that dietary intake of iron and fecundability were not consistently associated, although some evidence pointed toward a positive association among women with risk factors for iron deficiency.[16] Another report suggested that in women seeking fertility care, iron intake was inversely associated with antral follicle count.[17]

Although oral iron is the first-line treatment of iron deficiency, it is often poorly tolerated, and it commonly takes 3–6 months to reach an adequate ferritin level in serum.[18] Intravenous ferric carboxymaltose is indicated for the treatment of iron deficiency when oral iron preparations are ineffective or cannot be used and there is a clinical need to deliver iron rapidly. A single-dose infusion has been shown to be a well-tolerated and efficient treatment for iron deficiency in individuals with and without anemia.[19,20]

Key message

This study shows that treatment of iron deficiency was positively associated with conception results and pregnancy outcomes, suggesting the need for screening of iron status for patients seeking help for infertility.

In our clinical practice, we have observed many women with low ferritin levels (≤30 μg/L) seeking fertility care. Moreover, to our knowledge, the association between treatment of iron deficiency, infertility treatment, and pregnancy outcomes has not been assessed. Based on the available evidence and the unclear role of iron deficiency treatment with iron infusion in women with low s-ferritin levels and a history of infertility, here we sought to investigate whether treating iron deficiency with iron infusion would be associated with improved conception rates and pregnancy outcomes. The aim of this retrospective, observational cohort study was to assess the association between iron infusion treatment with conception results and pregnancy outcomes in women with a history of infertility and iron deficiency, before and after treatment of iron deficiency. The primary outcomes were live birth (LBR) and miscarriage rates before and after iron infusion.

2 | MATERIAL AND METHODS

2.1 | Study cohort and data collection

This was a retrospective, observational cohort study based on the data collected from electronic health records from the Dextra Fertility Clinic (Helsinki, Finland). We identified 444 women <43 years of age who had low iron deposits (s-ferritin ≤30 μg/L) and a history of infertility (primary or secondary; defined as the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse, as per World Health Organization definition[21]). In total, 152 patients were excluded from the analysis, and the reasons for the exclusion of patients are presented in Table S1. Altogether, the study cohort included women who had a heterogenous background of infertility treatments: some patients had no previous assisted reproductive technology (ART) treatments, other women had several failed cycles. In the analyses, only patients ($n = 292$) for whom iron deficiency was treated with ferric carboxymaltose (Ferinject®[22]) infusion in the treatment planning phase (before steps concerning stimulation, retrieval, and transfer) (500 mg iv., henceforth iron infusion) between December 31, 2015, and December 31, 2020, were included. During that period, a total of 523 iron infusions were performed. The first date of iron infusion was defined as the index date for the patients (Figure S1).

All patients were followed up between January 31, 2015, and December 31, 2020. The patient follow-up period was divided into two periods: before the index date (pre-iron treatment period) and after the index date (post-iron treatment period) (Figure S1).

2.2 | Outcome Measures

The main outcome measures were LBR and miscarriage rate in the pre- and post-iron treatment periods. Pregnancy outcomes were analyzed for the most recent pregnancy before and after the index date (multiple treatments [both the fresh in vitro fertilization (IVF) treatment and all the frozen embryo transfers] may have been included to the point of a pregnancy). The explorative outcomes included characterization of: (1) demographic factors [age, body mass index (BMI)]; (2) factors related to fertility/infertility [anti-müllerian hormone (AMH) levels, antral follicle count (AFC), preimplantation genetic testing for aneuploidy (PGT-A)]; (3) laboratory measures related to iron deficiency (s-ferritin and s-Hb); (4) reasons for infertility; (5) duration of infertility; (6) given treatments for infertility and number of cycles of each treatment, and (7) factors related to conception, miscarriage, and LBR before and after iron infusion.

The main explanatory variable studied was the treatment of iron deposits with iron infusion. Other variables studied with respect to the main outcome measures were age, number of ART treatment cycles, total number of pregnancies, donated cells, PGT-A, BMI, AFC, duration of infertility, and reason for infertility.

2.3 | Clinical examinations and infertility treatments

S-ferritin was measured by a chemiluminescent microparticle immunoassay (CMIA) within 30 days before and on average 110 days after iron infusion. S-Hb was measured using a photometric assay within 30 days before infusion and AMH was measured by electrochemiluminescent immunoassay (ECLIA) with Roche Elecsys®, both by Synlab (Helsinki, Finland). AFC was counted at a vaginal ultrasound scan before infertility treatments. PGT-A was performed at Eurofins Genoma laboratory (Rome, Italy). Standard diagnostic and clinical practices were used for the characterization of the various reasons for infertility (Table 1). The infertility treatments (Table 1) were performed according to standard clinical practices. A miscarriage was defined as an ultrasound-verified clinical pregnancy (at least a visible amniotic sac) that miscarried before pregnancy week 22, thus including both early and late miscarriages, but excluding biochemical pregnancies.

2.4 | Statistical analyses

Patient baseline demographic characteristics and clinical characteristics were analyzed with descriptive statistics. All comparisons were performed with an individual in the pre-iron period vs post-iron treatment period (Figure S1). As the response variables were binary, generalized linear models were used, assuming binomial error distribution. In the models, the main explanatory variable was iron infusion. Adjusting variables were selected based on univariate tests (Table S2); the model for live births was adjusted with patient age, PGT-A, and whether the patient received repeated infusions or not, while the model for miscarriages was adjusted with patient age, reason for infertility, and the total number of pregnancies. The resulting *p*-values were corrected for multiple testing using the false discovery rate method, as implemented in the "adjust *p*-value" function in rstatix package in R.[23] All statistical analyses were conducted using R version 4.0.3.[24] All *p*-values were two-tailed and $p < 0.05$ was considered statistically significant; *p*-values between 0.05 and 0.1 were treated as suggestive. From the models, point estimates and 95% confidence intervals were presented.

Continuous background variables that contained a <20% proportion of missing values were categorized to introduce a "missing" category. This procedure was applied to AFC (low, AFC <10; medium, 10 ≤AFC <20; high, AFC≥20), BMI (normal, BMI <25; overweight, 25 ≤BMI <30; obesity, BMI≥30), and duration of infertility (1 year, <12 months; 2 years, 12–23 months; 3 years, 24–35 months; 4 years, 36–47 months; 5+ years, >47 months).

For modeling the probability of live births and miscarriages (including the last pregnancy before and the first pregnancy after iron infusion), all patients with no recorded pregnancies or with missing values in outcome variables were excluded.

3 | RESULTS

3.1 | Demographic and clinical characteristics of the study population

The study population consisted of 292 females with a history of infertility and treated with iron infusion (Figure S1). The demographic and clinical characteristics of the patients before iron infusion are presented in Table 2. The mean age of the patients was 36.3 ± 4.1 years at the time of iron infusion. The mean BMI was within the normal range (23.9 ± 4.5 kg/m^2), as was the mean AMH level (2.2 ± 2.2 μg/L). The mean AFC was 15.7 ± 10.5. The mean duration of infertility at the time of iron infusion was 3.4 years (40.8 ± 32.7 months).

S-ferritin levels were measured for all patients ($n = 292$) within <30 days before iron infusion and for 53% ($n = 154$) of the patients after the infusion (Table 2). Before iron infusion, the mean s-ferritin level was 16.2 ± 7.0 μg/L. All patients had mean s-ferritin levels ≤ 30 μg/L before iron infusion, and 44% ($n = 128$) had s-ferritin levels <15 μg/L. Measured on average 110 days after iron infusion, the mean s-ferritin level in the 154 patients was 81.5 ± 49.8 μg/L. At this stage, 14% ($n = 21$) and 2% ($n = 5$) of the patients had s-ferritin levels of ≤30 μg/L and <15 μg/L, respectively. The mean s-Hb level, measured before iron infusion at the same time as the first s-ferritin

TABLE 1 Reasons for infertility and the respective duration of infertility. The number and proportion of patients who have received different infertility treatments/analyses and the mean treatment cycle count before and after the i.v. iron infusion ($n=292$).

		Duration of infertility (months)		
Reason for infertility	***n* (%)**	**Mean**	**Median**	**SD**
Tubal	15 (5)	28.6	20.5	24.8
Female hormonal	23 (8)	33.4	35.5	19.4
Endometriosis	24 (8)	50.0	59.5	40.8
Female other	46 (16)	43.0	36.0	32.1
Male	29 (10)	49.0	35.0	39.0
Multiple	25 (9)	54.0	51.0	31.2
Unexplained	118 (40)	36.0	26.5	30.7
Habitual abortions	11 (4)	37.6	20.0	38.8

	Before infusion				After infusion			
Treatment	***n* (%)**	**Mean**	**Median**	**SD**	***n* (%)**	**Mean**	**Median**	**SD**
IUI, IVF/fresh ET, or IVF /FET	169 (58)	n.d.	n.d.	n.d.	242 (83)	n.d.	n.d.	n.d.
IVF/ fresh ET, or IVF/FET	141 (48)	n.d.	n.d.	n.d.	210 (72)	n.d.	n.d.	n.d.
IUI	90 (31)	0.8	0	1.5	55 (19)	0.5	0	1.2
IVF/fresh ET	134 (46)	1.7	0	2.7	182 (63)	1.5	1	1.9
IVF/FET	105 (36)	1.0	0	1.9	176 (60)	1.3	1	1.7
PGT-A	17 (6)	n.d.	n.d.	n.d.	49 (16)	n.d.	n.d.	n.d.
Donor sperm	51 (18)	n.d.	n.d.	n.d.	65 (22)	n.d.	n.d.	n.d.
Donor oocytes	5 (2)	n.d.	n.d.	n.d.	27 (10)	n.d.	n.d.	n.d.
ERA	24 (8)	n.d.	n.d.	n.d.	99 (34)	n.d.	n.d.	n.d.

Note: The number of patients (*n*) and proportion (%) of the total study population, as well as the mean, median, and standard deviation (SD) for the duration of infertility are presented for each variable. For each treatment, the number of patients (*n*) and % of the total study population before and after the iron infusion are presented. Mean, median, and standard deviation represent the treatment cycle count before and after the iron infusion.

Abbreviations: ERA, endometrial receptivity array; ET, embryo transfer; FET, frozen embryo transfer; IUI, intrauterine insemination; IVF, in vitro fertilization; PGT-A, preimplantation genetic testing for aneuploidy; SD, standard deviation.

TABLE 2 Demographic and clinical characteristics of patients ($n=292$) before or after the i.v. iron infusion.

Variable	Time point	*n* (%)	Mean	Median	SD	SE
Age (years)	Before	292 (100)	36.3	37.0	4.1	0.2
BMI (kg/m^2)	Before	252 (86)	23.9	23.0	4.5	0.3
AMH (μg/L)	Before	209 (72)	2.2	1.6	2.2	0.1
AFC (number)	Before	272 (93)	15.7	13.0	10.5	0.6
Duration of infertility (months)	Before	269 (92)	40.8	33.0	32.7	1.9
Hemoglobin (g/L)	Before	154 (53)	130.3	130.0	10.9	0.6
Ferritin (μg/L)	Before	292 (100)	16.2	16.0	7.0	0.4
Ferritin (μg/L)	After	154 (53)	81.5	69.5	49.8	2.9

Note: For each variable, the time point (before or after the iron infusion), number (*n*), and proportion (%) of patients with available records, mean, median, SD, and SE are presented.

Abbreviations: AFC, antral follicle count; AMH, anti-Müllerian hormone; BMI, body mass index; SD, Standard deviation; SE, Standard error.

measurement, was 130.3 ± 10.9 g/L ($n=154$), considered to be within the normal range (117–155 g/L).

3.2 | Reasons and treatments for infertility

The reasons for and mean duration of infertility were characterized before iron infusion (Table 1). The most common reason was unexplained infertility, including single women and lesbian couples without any medical diagnosis (40%, $n=118$). Other reasons due to the female (such as primary ovarian insufficiency or premature ovarian failure) accounted for 16% of the cases ($n=46$).

Utilization of different infertility treatments before and after iron infusion, and the number of treatment cycles, are presented in Table 1. Before iron infusion, 58% ($n=169$) were treated with intrauterine insemination or IVF, while the proportion was 83% ($n=242$) after the iron infusion.

3.3 | Conception results and pregnancy outcomes before and after treatment of iron deficiency

Pregnancy outcomes were analyzed for the most recent pregnancy before and after iron infusion (Figure 1 and Tables S3 and S4). The proportion of patients who conceived increased from 64% ($n=188$) before to 77% ($n=225$) after iron infusion ($p<0.001$). Before iron infusion, 28% ($n=82$) had experienced miscarriages compared to 13% ($n=38$) after iron infusion ($p<0.001$). Accordingly, the LBR was 25% ($n=74$) before and increased to 51% ($n=148$) after iron infusion ($p<0.001$).

In patients with unexplained infertility ($n=118$), LBR was 23% ($n=27$) before iron infusion and 48% ($n=57$) after ($p<0.01$) (Figure 1). The proportion of patients who had a miscarriage decreased from 22% ($n=26$) to 8% ($n=9$) after ($p<0.001$).

3.4 | Association between treatment of iron deficiency and birth and miscarriage rates

First, the associations between each of several explanatory variables and the main outcomes (LBR and miscarriage) were analyzed independently (univariate analysis; Table S2). These analyses indicated that treatment of iron deficiency ($p<0.001$), age ($p=0.013$), PGT-A ($p=0.015$), and repeated iron infusions ($p=0.061$) were associated with the LBR, whereas treatment of iron deficiency ($p<0.001$), age ($p=0.017$), reason for infertility ($p<0.001$), and the total number of pregnancies ($p<0.001$) were associated with the probability of miscarriage.

Based on this analysis, age, PGT-A, and repeated iron infusions (no/yes) were used to adjust the effect of treatment of iron deficiency on the probability of live birth, while age, reason for infertility (using reason due to male as reference), and the total number of pregnancies were used to adjust the effect of treatment of iron deficiency on the probability of miscarriage. In the adjusted models, all patients with no recorded pregnancies ($n=26$), or missing values in outcome variables ($n=2$) were excluded. The remaining data consisted of 264 patients. Treatment of iron deficiency was associated with more than three times higher LBR (odds ratio [OR]=3.19; 95% confidence interval [CI]=2.21–4.66; $p<0.001$) and more than two-thirds lower miscarriage rates (OR=0.32; 95% CI=0.20–0.52; $p<0.001$) (Figure 2).

Considering the adjusting predictors, treatment of iron deficiency with repeated iron infusions was associated with 43% (OR=0.57; 95% CI=0.35–0.93; $p=0.046$), and increasing age by 1 year was associated with a 6% lower probability of live birth (OR=0.94; 95% CI=0.90–0.98; $p=0.012$). Also, the model provided suggestive evidence that PGT-A was associated with 1.7 times higher LBR (OR=1.71; 95% CI=0.97–3.01; $p=0.079$).

As a sensitivity analysis, the models were also fitted using a subsample of the data, containing only patients ($n=77$) who underwent in vitro fertilization (IVF) followed by embryo transfer (ET) or frozen embryo transfer (FET) both before and after iron infusion. After adjusting for multiple testing, treatment of iron deficiency remained a statistically significant predictor of live birth (OR=2.98; $p=0.018$), whereas for miscarriages, the effect of iron deficiency treatment was no longer significant (OR=0.52; $p=0.28$). Yet, treatment of iron deficiency still had a significant effect on total number of pregnancies. (OR=1.85; $p=0.0019$) (Figure S2).

4 | DISCUSSION

To our knowledge, this study is the first to assess the association between iron deficiency and pregnancy outcomes in patients seeking treatment for infertility. In this study population, the rapid restitution

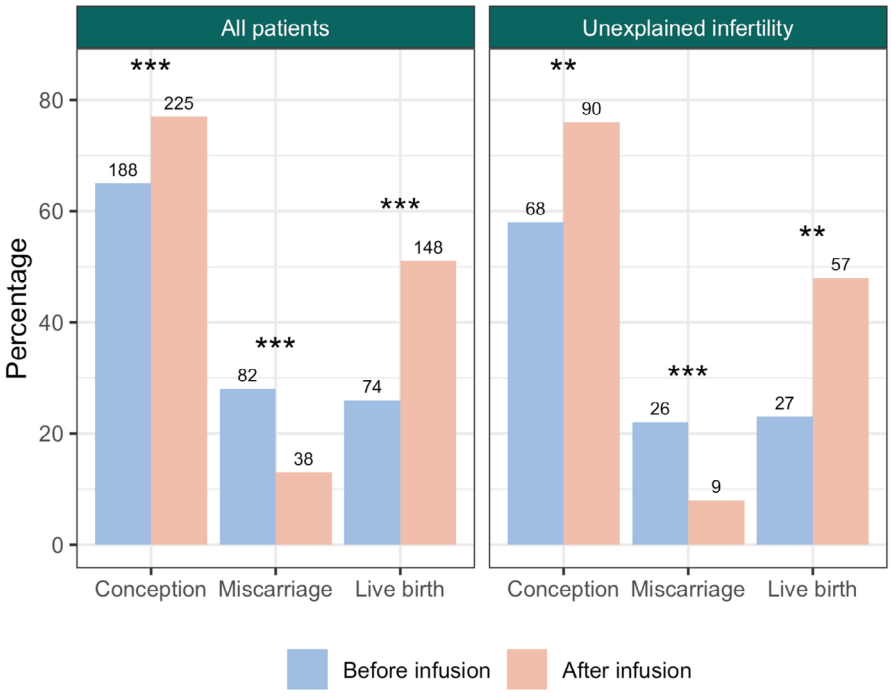

FIGURE 1 Proportion and number (n above each bar) of conceptions, live births, and miscarriages before ($n=290$) and after ($n=291$) i.v. iron infusion in women with diagnosed iron deficiency and history of infertility and for women with unexplained infertility (UI; $n=118$). For pregnancies, miscarriages, and live births, only the last one before and the first one after i.v. iron infusion were considered. The asterisks refer to statistical p-values of risk ratio tests: *<0.05, **<0.01, ***<0.001. Information on the variables was not available for all patients.

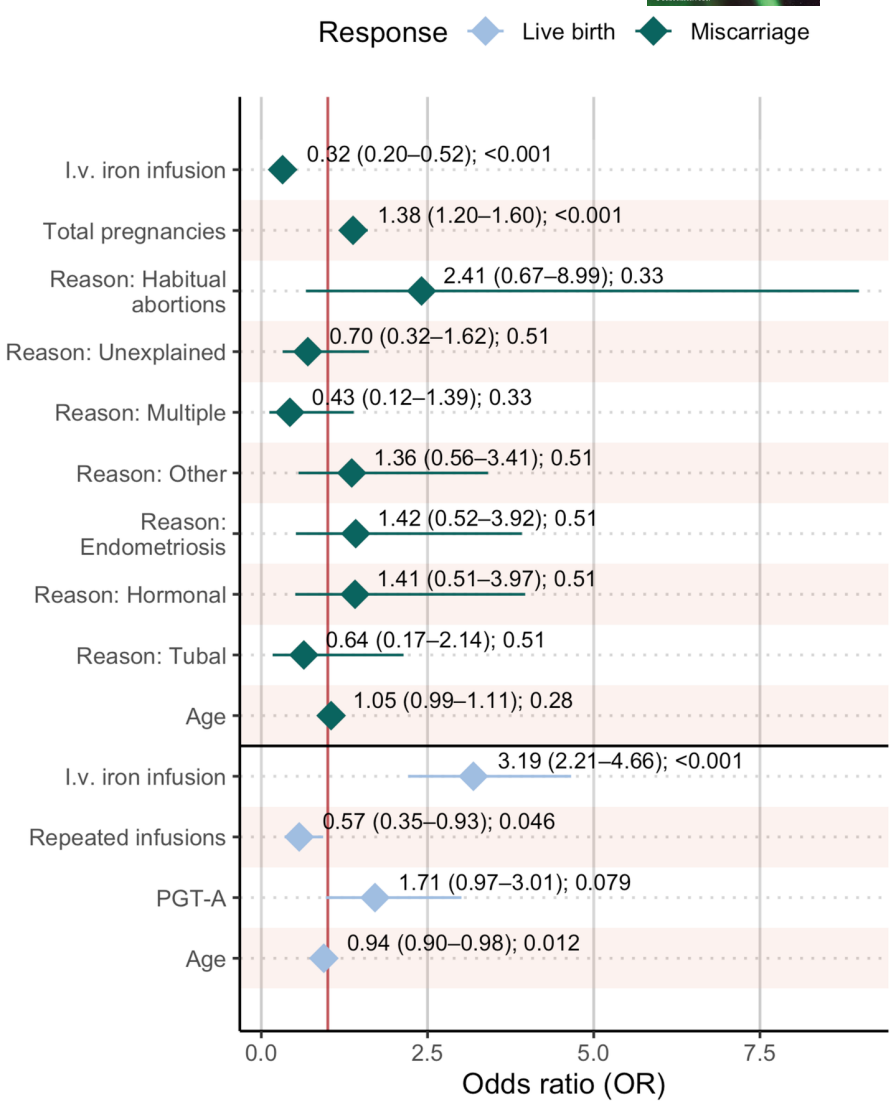

FIGURE 2 Statistical details for the models analyzing the probability of a live birth and miscarriage within the same patient, for recent pregnancies before and after i.v. iron infusion. Only patients who became pregnant before and/or after iron infusion were included in the analysis ($n = 264$). The (pseudo) coefficients of determination (R^2) for the models explaining the incidence of live birth and miscarriage are 0.11 and 0.17, respectively. The values beside each point represent the odds ratio (OR) estimate, 95% confidence interval, and p-value, respectively. For infertility reasons-(Reason), the reference category was infertility due to males.

of iron deposits with intravenous iron was preferable due to their long infertility history, high fertile age, and, therefore, lack of time to wait. Treatment of iron deficiency was positively associated with conception rates and, importantly, with 3.2 times higher LBR and 68% lower miscarriage rate. The results suggest that iron status is important for women when planning for pregnancy.

Studies in a Danish population have indicated that approximately 40% of menstruating, non-pregnant women have s-ferritin levels ≤30 μg/L, and thus an unfavorable iron status with respect to an upcoming pregnancy.[7] In addition, preliminary data from the Dextra Fertility Clinic indicate that as much as 40% of patients seeking treatment for infertility suffer from iron deficiency, as defined by ferritin levels ≤30 μg/L (NS, unpublished results). Initial studies have suggested that iron deficiency is associated with infertility and higher miscarriage rates. However, only a few studies have assessed the role of iron supplementation and pregnancy outcomes in women suffering from infertility, and such results have been partly contradictory.[5,10,14,15]

Our study indicates that the proportion of patients giving live birth doubled after iron infusion (26% before vs. 51% after). Remarkably, when adjusted for potential confounding factors, treatment of iron deficiency was found to be associated with 3.2 times higher LBR. The increase in LBR likely results from the higher conception rate, as well as from the decreased miscarriage rate. A significantly higher proportion of patients conceived after (77%) compared with before iron infusion (65%), suggesting that treatment of iron deficiency is associated with improved conception results in infertility patients. The percentage increase in conception rates was even higher in patients with unexplained infertility (58% before vs. 76% after iron infusion), considering that this group had a mean duration of infertility of 40.8 months and a mean age of 36.3 years, and therefore considered as a low prognosis group. The hypothesis that higher ferritin levels are associated with improved conception rates is also supported by a recent study on polycystic ovary syndrome or unexplained infertility.[25]

In addition to higher conception rates, the risk of a miscarriage was 68% lower after treatment of iron deficiency and the proportion of patients with miscarriages decreased significantly (28% before vs. 13% after iron infusion). This is in line with a recent study by Georgsen et al. reporting that s-ferritin level was inversely related to the number of previous miscarriages in women with recurrent pregnancy loss.[10] No association was found between s-ferritin levels and

an ability to conceive in the mentioned study. This may be explained by the relatively small sample size and low prevalence of iron deficiency in the study group, where 35.7% of patients with recurrent pregnancy loss versus 13.7% of patients from the comparison group had s-ferritin <30 μg/L. In our study population, all patients had an s-ferritin level of ≤30 μg/L prior to infusion. In addition, there was no follow-up of iron supplementation in the Danish study during the 2-year follow-up, which can cause confounding and could dilute the results. It should be noted that the s-Hb levels of the patients in our study were within the normal range, suggesting that non-anemic iron deficiency may have adverse effects on pregnancy outcomes.

In the multivariate model adjusted for possible confounding factors, repeated iron infusions were found to be associated with a lower LBR. A plausible explanation is that patients who received several infusions had a higher loss of iron, and the used standard dose of 500 mg of ferric carboxymaltose was too low. Of the other factors, there was a tendency toward higher LBR with PGT-A, which has previously been reported to be associated with a greater probability of live birth among women who are 35 years of age and older and undergoing IVF.[26] As expected, in the multivariate models higher age was negatively associated with LBR, but not with miscarriages. Interestingly, the use of donor oocytes or donor sperm was not associated with either LBR or miscarriages in our study, although the use of donor cells increased after iron infusion. It should also be noted that the iron status of the oocyte donors was not known, which may cause additional confounding if iron affects fertility via an oocyte-related mechanism. On the other hand, the lack of difference detected when donor oocytes were used, could also mean that iron is important in endometrial receptivity. Possible mechanisms by which iron affects pregnancy rates and outcomes could include improvement of endometrial receptivity.[27] Iron may also directly affect oocyte quality.[28,29] Both ferritin and transferrin are found in the developing follicles, although their physiological function is still unclear.[30,31]

Although oral iron is the first-line treatment for iron deficiency, there are considerable side effects and filling of the iron stores may take a long time. Therefore, in this study, we opted to use iron infusion, which is a fast and safe way of filling the iron stores,[19,20] and it creates a sharp reference point, diminishing possible confounding factors occurring during the 3–6-month period of filling iron deposits with oral iron. For the patients at our clinic, age was a crucial factor and thus, no time was to be wasted before starting the infertility treatments.

The main strength of the study was the relatively large study population with all patients treated at one clinic with standardized treatment protocols. The retrospective nature of our study obviously created certain limitations. As the analyses were based on data from electronic patient charts documenting routine treatment, there were gaps in the data. Although the results indicated a positive association between the iron infusion with conception results and pregnancy outcomes, the study design did not show causal relationships, as unmeasured confounders can still play a role. The study population was also heterogeneous in terms of demographic and clinical characteristics, including the reason and duration of infertility. The heterogenicity of ART treatments used could also be a strength, indicating the importance of iron regardless of the chosen treatment method. In the subsample analysis in patients who underwent IVF followed by ET or FET both in the pre- and post-iron treatment period, the iron infusion remained a significant predictor of live births, indicating that the positive association between iron infusion and LBR was not due to the higher number of patients treated with ART after iron infusion. However, in this subgroup, the effect on miscarriages was no longer significant likely due to the limited sample size. Another limitation applies to the possible study population selection bias due to the nature of the study design. It should be noted that an outcome in the pre-iron treatment period can affect the individual's decision to seek fertility care again. If the outcome in pre-iron treatment period is live birth, this may lead to the situation that a person may not hope for more children and is thus excluded from the post-iron treatment analysis population. In addition, patients' ferritin levels were not measured before a possible pregnancy in the pre-iron treatment period, and thus, the association between iron levels and conception results and pregnancy outcomes in this phase could not be directly assessed.

5 | CONCLUSION

Our study provides the largest dataset hitherto reported on the association between treatment of iron deficiency, conception results (higher number of pregnancies), and pregnancy outcomes (higher LBR and lower miscarriage rates) in patients seeking treatment for infertility in real-world clinical practice. The results suggest an association between iron deficiency and infertility and address the need to screen iron status at an early phase for patients seeking help for infertility problems.

AUTHOR CONTRIBUTIONS

The concept for the study was developed by Annika Tulenheimo-Silfvast. Annika Tulenheimo-Silfvast and Niklas Simberg both participated in planning of the study, data collection, interpreting and discussing the results, and preparing the manuscript. Lasse Ruokolainen-Pursiainen performed statistical analyses of the data and participated in interpreting the data and discussing the results. All authors read, revised, and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

A.T.S. is a Senior Consultant at Dextra Fertility Clinic. NS was the Head of Dextra Fertility Clinic at the time of data collection. L.R.P made the statistical analyses when employed at MedEngine Oy.

DATA AVAILABILITY STATEMENT

The aggregate-level data underlying this article will be shared on reasonable request to the corresponding author.

ETHICS STATEMENT

We collected data from patient charts to evaluate clinical practice. According to Finnish regulations, retrospective non-interventional registry studies do not require an ethics committee review. The Finnish Social and Health Data Permit Authority (Findata) granted the permit for the individual-level data (THL/7013/14.02.00/2020). Findata pseudonymized the individual-level data, which we stored, handled, and analyzed in their secure data processing environment. The date of data permit approval was June 23, 2021.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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