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Research article

Iron deficiency anemia during pregnancy and maternal and neonatal health outcomes: A prospective study, Spain, 2021–2022

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1. Introduction

Iron deficiency (ID) is the most common micronutrient deficiency in the world and the leading cause of anemia in women of reproductive age. A significant percentage of persons start pregnancy with low or depleted iron stores, iron requirements will progressively increase, and it is common that even in pregnant individuals with no iron deficiency at baseline, dietary iron will be insufficient to meet maternal and foetal needs [1]. Iron deficiency is a process in which iron stores can become depleted and disappear, resulting in iron deficiency anemia. Anemia will be a late, not an early, consequence of iron deficiency [2].

Ferritin is an iron storage protein in serum and plasma and is the recommended biomarker for assessing iron deficiency in pregnancy [3]. There is no consensus in the scientific community on the threshold serum ferritin (SF) value that should be used to define iron deficiency in pregnancy. A recent systematic review showed variation in the SF threshold used to diagnose iron deficiency, both in research studies and in national and international guidelines [1]. The English clinical practice guideline, updated in 2019, argues that, as pregnancy is associated with a physiological increase in acute phase proteins and until there is better high-quality evidence, it is acceptable to adopt a SF threshold of<30 μg/L for the ID diagnosis pregnant individuals [3].

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Data on the prevalence of iron deficiency in pregnancy are scarce and vary widely depending on the definition and characteristics of the population studied. First trimester iron deficiency has been reported with SF values < 30 μg/L in 14.2 % of pregnant individuals in Denmark [4] and 14 % in North America [5]; SF < 15 μg/L in 2.8 % of Danish pregnant individuals [4] and 6.1 % of Belgian [6]; and SF < 12 μg/L in 19,6 % of Australian[7], 7.3 % of American [8], and 16.2 % of Spanish pregnant individuals [9].

There is general agreement to recommend pharmacological iron supplementation in pregnant individuals with iron-deficiency anemia (IDA) [10]. However, in the absence of anemia, the benefit of iron supplementation is less clear. In a recent systematic review of guidelines for the management of IDA, universal iron supplementation was recommended in only six of the sixteen guidelines included [11].

Data on the clinical outcomes of iron deficiency in pregnancy are few and unclear. Iron deficiency has been associated with increased preterm birth, small-for-gestational-age neonates, peripartum haemorrhage or maternal mortality [12,13], but most studies do not discriminate between ID and IDA. In the Spanish context, one study did find an association between higher non-anemia iron deficient pregnant individuals (NAID) with lower birth weight [14], and a Danish study also reported that NAID had a higher risk of stillbirth [4]. The correlation between maternal iron deficiency and foetal iron deficiency could support a possible adverse impact on foetal neurodevelopment manifesting in neurological dysfunction in childhood [15,16]. However, evidence from randomised controlled trials comparing the cognitive function or behaviour of the children of pregnant individuals who received iron (iron and folic acid) supplements with those of placebo-supplemented pregnant individuals has conflicting results [17,18].

There is currently a lack of studies examining the adverse outcomes of iron deficiency without anemia on clinical outcomes in pregnancy [4,19]. To make clinical decisions about the optimal management of non-anaemic iron-deficient pregnant individuals, it is necessary to know whether iron deficiency without anemia increases the risk of adverse health outcomes for the mother and her child and whether supplementing this deficit with pharmacological oral iron modifies the risk [3]. Therefore, our objective was to determine the prevalence of non-anaemic iron deficient (NAID) in the first and second trimester of pregnancy, to describe the evolution of iron status in pregnant individuals without anemia and to analyse the association of NAID with adverse obstetric and perinatal outcomes.

2. Methods

2.1. Design

Prospective cohort study on the effect of iron deficiency without anemia on the clinical prenatal and postnatal control of pregnancy with the midwives of the public health system of La Rioja (Spain).

2.2. Sampling

The sample size was calculated based on a population probability of the prevalence of iron deficiency of 16 % [9], a precision of 5 %, a confidence level of 95 %, and a percentage of loss of 30 %. With these assumptions, the estimated minimum sample size was 633 pregnant individuals. Consecutively, all pregnant individuals attending the first antenatal care visit (before 13 weeks of pregnancy) were invited to participate. The data were collected between March 2021 to March 2022.

2.3. Inclusion and exclusion criteria

All pregnant individuals who attended the midwife's office to initiate pregnancy monitoring before 13 weeks gestation for one year and who signed the informed consent to enrol in this study were eligible.

Pregnant individuals with a diagnosis of high-risk pregnancy (chronic or severe illness, pre-existing haemoglobinopathies and history of adverse obstetric outcomes), multiple pregnancy, smokers, those already taking iron supplementation at the start of pregnancy and those with cognitive or linguistic limitations that prevented them from consenting to the study were excluded.

2.4. Measurements and procedures

Variables collected: maternal age (years), nationality (Spanish or others), race (Caucasian, black, Latina, Asian or Arab), parity (primipara or multipara) and body mass index (BMI) as underweight<18.5, healthy weight = 18.5–24.9, overweight = 25.0–25.9 and obesity ≥30). Venous blood samples were assessed for serum ferritin and haemoglobin (Hb) concentrations, first at 8–12 weeks' gestation (WG), and second at 24–28 WG. At 39 weeks or right before delivery if delivery happened before 39 weeks and in the first 48 h postpartum only Hb was measured. Information on maternal Hb and SF was extracted from the hospital laboratory databases. Definitions of anemia used were: first and third-trimester anemia = Hb < 11 g/dl, second-trimester anemia = Hb < 10.5 g/dl and postpartum anemia = Hb < 10 g/dl, the SF value for diagnosis of ID was SF < 30 μg/L. Pharmacological oral iron supplementation (40 mg elemental iron/daily) was recommended to all pregnant individuals with ID, some of them accepted (supplementation), but others did not (non-supplementation). Outcome clinical measures were: fatigue was measured with the translated and validated Spanish questionnaire [20] and self-perceived general health with a 0–10 visual analogue scale (VAS) where 0 indicates the worst possible health and 10 indicates optimal health [21], both measures were taken between week 24–28 of pregnancy and in the 2 weeks before delivery (the final blood test is typically conducted in the 39th week of pregnancy. In cases where labor begins earlier than expected, the test is carried out on an emergency basis), gestational age (weeks of gestation at birth) and dichotomous measures [anemia, Apgar Score <7 at 1 min and at 5 min, Caesarean section, stillbirth (Death of a baby between 24 week of gestation and birth), peripartum

blood (bleeding that causes maternal haemodynamic disturbance and requires medical intervention of a pharmacological or surgical nature), Low birth weight (Birthweight <2500 g), blood transfusion and formula Feeding at discharge].

Data were collected from medical records in which midwives prospectively recorded these elements as they occurred.

To discriminate the effect of early iron deficiency alone on health outcomes, we classified the iron status of pregnant individuals without anemia into three groups based on the Hb and SF values of the first blood test: NAIS (1) = non-anaemic iron sufficient pregnant individuals (Hb ≥ 11 g/dl and SF ≥ 30 μg/L); NAID-s (1) = non-anaemic iron deficient pregnant individuals (Hb ≥ 11 g/dl and SF < 30 μg/L) with supplementation, and NAID-ns (1) = non-anaemic iron deficient pregnant individuals (Hb ≥ 11 g/dl and ferritin<30 ng/ml) non-supplementation. These three groups form part of sub-cohort 1, which included 1027 pregnant individuals. Later in the pregnancy, with the results of the second analysis (between 24 and 28 weeks), we repeated the process and again established the three groups of maternal iron status (maternal iron status): NAIS (2) if Hb ≥ 10.5 g/dl and SF ≥ 30 μg/L, NAID-s (2) if Hb ≥ 10.5 g/dl and SF ≥ 30 μg/L with supplementation and NAID-ns (2) if Hb ≥ 10.5 g/dl and SF < 30 μg/L non-supplementation, this sub-cohort 2 included 911 pregnant individuals, all of whom had no anemia in both the first and second blood tests (Fig. 1).

2.5. Data analysis

The variables were summarized using means and standard deviations (SD), median and interquartile range (IQR), or frequencies and percentages, depending on the type of variable and the type of distribution. We estimated the prevalence of ID as the number of pregnant individuals diagnosed divided by the number of pregnant individuals screened at weeks 8–12 and at weeks 24–28, these results were presented as percentage with 95 % confidence intervals (CI).

Analyses between the groups were done with the non-parametric Kruskal– Wallis test and, when the association was significant, pairwise comparison with Bonferroni correction and chi-squared test and, when the conditions for chi-square test are not met, post hoc Z-test with Bonferroni correction. We build logistic regression models, the odds ratio (OR) and adjusted odds ratio (aOR) after adjusting for age, body mass index, nationality and parity and a 95 % confidence interval (CI) were calculated, for maternal and neonatal outcomes that showed significant statistical differences between the groups. p-value <0.05 was considered statistically significant. Statistical analyses were performed with the SPSS statistical package (version 28.0, IBM Corp, NY, USA).

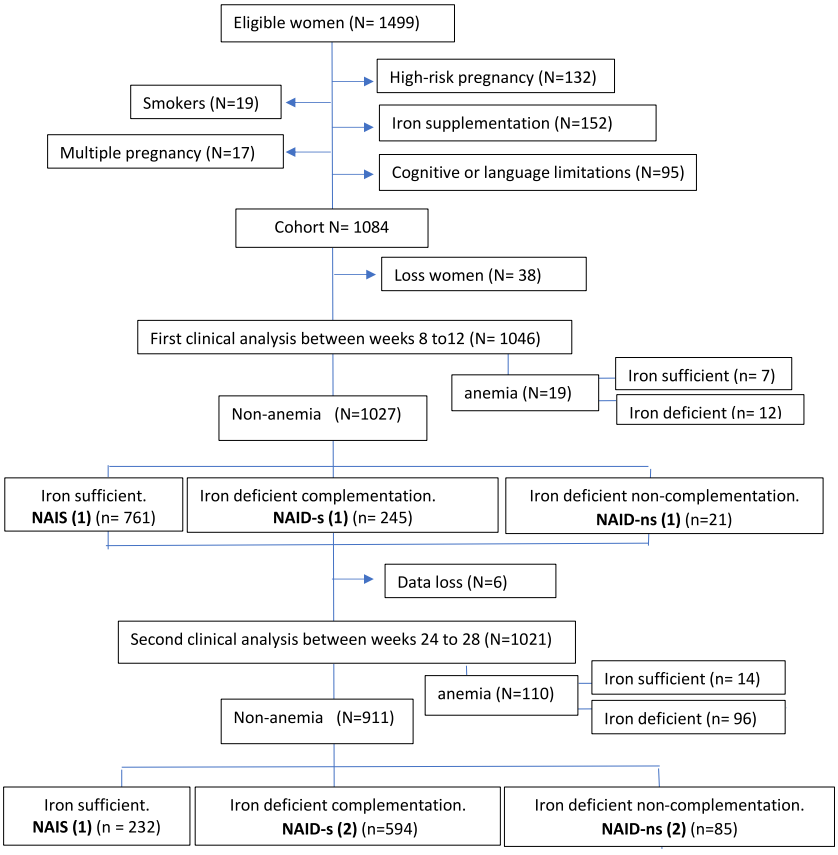

Fig. 1. Flow chart.

2.6. Ethical approval

La Rioja Clinical Research Ethics Committee (CEICLAR) approved the study (Reference P.I 261). All pregnant individuals were informed of the purpose of the study and gave written informed consent. Data confidentiality has been maintained.

4. Results

4.1. Sample characteristics and prevalence of non-anaemic iron deficient pregnant individuals, Spain (2021–2022)

A total of 1499 pregnant women were eligible for this study, of whom 415 were excluded by applying the following exclusion criteria. We started follow-up with a cohort of 1084 pregnant individuals with low-risk, non-smoking pregnancies, with a mean age of 33.37 years. The majority were Spanish (76.8 %), Caucasian (84.9 %), of healthy weight (60.6 %) and nulliparous (63.35). (Table 1). We lost 38 pregnant individuals for whom we have no maternal or neonatal health outcomes.

The prevalence of NAID was 25.4 % between 8 and 12 weeks gestation and increases to 66 % at 24–28 weeks. The estimated prevalence of ID and NAID, with different cut-off points, are shown in Table 2.

4.2. Changes in iron status

Regarding the evolution of iron status in pregnant individuals without anemia in the first analysis (n = 1027) we observed that, in the group with sufficient iron reserves, 63.6 % of cases progressed towards iron deficiency in the second analysis and 18.1 % towards anemia (8.6 % in the second analysis and 9.5 % before delivery). Among pregnant individuals with iron deficiency in the first analysis who took iron, 8.7 % recovered sufficient levels and 33.2 % progressed to anemia (17.8 % in the second analysis and 15.4 % before delivery). Finally, in the group with iron deficiency in the first analysis who did not take iron supplements, none recovered sufficient iron levels in the second analysis and 28.5 % had anemia (9.5 % in the second analysis and 19 % before delivery) (Table 3).

There were no cases of severe anemia. In the sub-cohort (1), pregnant individuals without first trimester anemia, 110 cases of

Table 1
Baseline Characteristics of women with singleton and low-risk pregnancies, Spain (2021–2022).

Maternal age (years) (mean, SD)	33.37 (5.36)
	N (%)
Country of birth (N = 1084)	
- Spanish	833 (76.8)
- Other countries	251 (23.1)
Race/Ethnicity (N = 1082)	
- Caucasian	919 (84.9)
- Latina	78 (7.2)
- Asian	8 (07)
- Black	10 (0.9)
- Arab	67 (6.2)
Parity (N = 1084)	
- Primipara	398 (36.7)
- Multipara	686 (63.3)
Body mass index (N = 1042)	
- underweight (<18.5)	35 (3.2)
- Healthy weight (18.5–24.9)	657 (60.6)
- Overweight (25–29.9)	237 (21.9)
- Obesity (>30)	115 (10.6)
First measurement (N = 1046)	
- Non-anemia iron sufficient (NAIS)	761 (72.8)
- Non-anemia iron deficient (NAID)	266 (25.5)
- Iron deficient anemia (IDA)	11 (1.1)
- Anemia (others)	7 (0.7)
Second measurement (N = 1040)	
- Non-anemia iron sufficient (NAIS)	234 (22.5)
- Non-anemia iron deficient (NAID)	687 (66.0)
- Iron deficient anemia (IDA)	104 (10.0)
- Anemia (others)	15 (1.5)
Anemia (N = 1027)	
- yes	119 (11.4)
- no	908 (86.9)
Iron supplementation (N = 1045)	
- yes	872 (83.4)
- no	173 (16.6)

Abbreviations: SD = standard deviation; N = frequency; (%) = percentage.

Table 2
Prevalence of iron deficiency (according to different cut-off points), Spain (2021–2022).

SF values: Cut-off points	First analytic (8–12 weeks) N = 1046		Second analytic (24–28 week) N = 1040	
Definition used in this study	ID (1) prevalence (95 % IC)	NAID (1) prevalence (95 % IC)	ID (2) prevalence (95 % IC)	NAID (2) prevalence (95 % IC)
SF < 30 μg/L	26.6 % (23.85%–29.30 %)	25.4 % (22.7 %–28,1 %)	76.6 % (73.4%–78.7 %)	66 % (63.1%–69.0 %)
Other definitions	prevalence (95 % IC)	prevalence (95 % IC)	prevalence (95 % IC)	prevalence (95 % IC)
SF < 20 μg/L	15.8 % (13.5 %–18.0 %)	13.1 % (11.0 %–15.2 %)	61.0 % (60.0 %–64.0 %)	58.4 % (55.3 %–61.4 %)
SF < 15 μg/L	6.8 % (5.2 %–8.4 %)	5.9 % (4.5 %–7.4 %)	49.7 % (46.6 %–52.8 %)	43.8 % (40.8 %–46.9 %)
SF < 12 μg/L	5.5 % (4.1 %–7.0 %)	3.8 % (2.6 %–5.0 %)	33.6 % (30.6 %–36.5 %)	30.0 % (27.2 %–32.8 %)

Abbreviations: ID = iron deficiency, with anemia (IDA) or without anemia (NAID); NAID = non anemia iron deficiency.

Table 3
Changes in iron status in non-anemic women in the group of first sub-cohort groups (N = 1027) and of second sub-cohort groups (N = 911), Spain (2021–2022).

Iron status groups	2nd analytic (24–28 gestational weeks)								3rd analytic (0–2 week before birth)				
1st analytic (8–12 gestational weeks) FS: [median (IQR)]	NAIS (2)n (%)	NAID-s (2)n (%)	NAID-ns (2)n (%)	Second-trimester Anemia					Third trimester Anemia				
				Totaln (%)	grades[a]			Lowest Hb value	Totaln (%)	grades[b]			Lowest Hb value
					Mi (n)	Mo (n)	S (n)			Mi (n)	Mo (n)	S (n)	
NAIS (1) [61 (43–93)] μg/L	211 (27.8 %)	416 (54.8 %)	67 (8.8 %)	65 (8.6 %)	57	8	0	8.0 g/dl	71 (9.5 %)	57	14	0	7.2 g/dl
NAID-s (1) [19 (15–25)] μg/L	21 (8.7 %)	177 (73.5 %)	0 (0.0 %)	43 (17.8 %)	39	4	0	8.9 g/dl	37 (15.4 %)	24	13	0	8.0 g/dl
NAID-ns (1) [17 (13–24,5)] μg/L	0 (0.0 %)	1 (4.8 %)	18 (85.7 %)	2 (9.5 %)	2	0	0	9.8 g/dl	4 (19.0 %)	1	3	0	8.8 g/dl
2nd **analytic (24–28 gestational weeks)**FS: [median (IQR)]									Third trimester Anemia				
									Totaln (%)	grades[b]			Lowest Hb value
										Mi (n)	Mo (n)	S (n)	
NAIS (2) [41 (34–55,8) μg/L]									6 (2.6 %)	5	1	0	8.8 g/dl
NAID-s (2) [12.5 (9–18) μg/L]									55 (9.4 %)	49	6	0	9.3 g/dl
NAID-ns (2) [17 (12–23) μg/L]									9 (10.7 %)	7	2	0	8.8 g/dl

NAIS = non-anemic iron sufficient women; NAID-s = non-anemic iron deficient women with supplementation; NAID-ns = non-anemic iron deficient women non-supplementation.
[a] Second-trimester Anemia is classified as Mi = mild (Hb ≤ 10.4 and ≥ 9.5), Mo = moderate (Hb ≤ 9.4 and ≥ 7.0) and S = severe (>7.0).
[b] Third trimester Anemia: is classified as: Mi = mild (Hb ≤ 10.9 and ≥ 10), Mo = moderate (Hb ≤ 9.9 and ≥ 7) and severe (>7.0).

anemia were diagnosed in the second trimester, 98 (89 %) mild and 12 (11 %) moderate. The lowest Hb level, in the late second trimester, was 8 mg/dl in the NAIS group (1). And in the third trimester there were 112 cases of anemia, 82 (73 %) mild and 30 (27 %) moderate. The lowest Hb value was 7.2 g/dl, and this value was found in one pregnant individual in the NAIS group (1). In the sub-cohort (2), pregnant individuals who had not had anemia in either the first or second trimester, 70 cases of anemia were diagnosed in the third trimester, 61 (87.1 %) mild and 9 (12.9 %) moderate with a minimum Hb value of 8.8 (Table 3).

4.3. Association between iron deficiency without anemia and obstetric and neonatal outcomes

In non-anaemic pregnant individuals, first trimester iron status [NAIS (1), NAID-s (1), and NAIS-ns (1)] is not related to fatigue or self-perceived health in the second half of pregnancy or at the end of pregnancy. Neither was there any association with the observed clinical outcomes: birthweight, gestational age, gestational diabetes. Pre-eclampsia/eclampsia, Caesarean section, Apgar Score<7 at 1 and 5 min, low birth weight, stillbirth, blood transfusion, peripartum bleeding, and formula feeding. Differences were observed in the blood test results, the two NAID groups (NAID-s and NAID-ns) presented higher percentages of diagnosed anemia than the NAIS group, both in the second trimester (17.7 % and 9.5 % vs 8.5 %) and before delivery (15.3 % and 19 % vs 9.6 %), although, at these two points, only the differences between the NAID-s (1) vs NAIS (1) groups reached statistical significance (17.7 % vs 8.5, $p < 0.05$; 15.3 % vs 9.6 %). There was no difference in postpartum anemia (Table 4).

When the diagnosis of NAIS or NAID is made between 24 and 28 weeks, it is also not associated with greater fatigue or poorer health perception at the end of pregnancy, nor with most obstetric clinical outcomes, except for two: low birth weight and stillbirth. There was a lower percentage of low birth weight infants in the NAID-s (2) and NAID-ns (2) groups than in the NAIS(2) group (4 %, 5.9 % and

Table 4
The obstetric and perinatal outcomes in iron sufficient non anemic women, iron-deficient non-anemic women with supplementation and iron-deficient non-anemic women without supplementation. Spain (2021–2022).

		Maternal iron status in First clinical analysis (8-12 weeks)						
	N	NAIS (1)		NAID-s (1)		NAID-ns (1)		
		n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	p#
Fatigue (24-28 GW)	1027	761	18 (16-21)	245	19 (16-22)	21	19 (17.5-24.0)	0.2
Fatigue (36-38 GW)	1010	748	23 (21-26)	241	24 (21-26)	21	24 (21.5-29)	0.2
self-perceived health (24-28 GW)	995	749	7 (6-8)	225	7 (6-8)	21	7 (6-8)	0.6
self-perceived health (36-38 GW)	1011	749	6 (6-8)	241	7 (6-8)	21	6 (6-7)	0.1
Birthweight (grams)	1026	760	3290 (2980-3580)	245	3365 (3040-3630)	21	3350 (3028-3480)	0.3
Gestational age at birth (GW)	1027	761	39.6 (38.5-40.5)	245	39.6 (39.0-40.5)	21	40 (38.7-41.0)	0.4
Hb (24-28 GW)	1021	759	11.5 (10.9-12.1) [a]	241	11.2 (10.7-11.9) [b]	21	12.0 (11.1-12.3) [a, b]	<0.01* (NAIS vs NAID-s)
Hb (0-2 week before birth)	1009	747	12.2 (11.6-12.8)	241	12.1 (11.4-13.0)	21	12.4 (11.2-12.7)	0.8
Hb (24-48 hours postpartum)	1027	761	10.9 (10.0-11.7)	245	11.1 (10.1-12.0)	21	11.3 (10.2-11.9)	0.4
		N (%)		N (%)		N (%)		p##
Second-trimester anemia								
- yes	110	65 (8.6) [a]		43 (17.8) [b]		2 (9.5) [a, b]		< 0.05* (NAIS vs NAID-s)
- no	911	694 (91.4) [a]		198 (82.2) [b]		19 (90.5) [a, b]		
Third-trimester anemia								
- yes	112	71 (9.5) [a]		37 (15.4) [b]		4 (19.0) [a, b]		< 0.05* (NAIS vs NAID-s)
- no	897	676 (90.5) [a]		204 (84.6) [b]		17(81.0) [a, b]		
Postpartum anemia								
- yes	243	181 (23.8)		57 (23.3)		5 (23.8)		0.1
- no	784	580 (76.2)		188 (76.7)		16 (76.2)		
Gestational diabetes								
- yes	52	38 (5.0)		12 (4.9)		2 (9.5)		0.6
- no	972	721 (95)		232 (95.1)		19 (90.5)		
Pre-eclampsia/eclampsia								
- yes	19	15 (2.0)		3 (1.2)		1 (4.8)		>0.05
- no	1038	744 (98.0)		241 (98.8)		20 (95.2)		
Caesarean section								
- yes	202	154 (20.2)		43 (17.6)		5 (23.8)		0.6
- no	825	607 (79.8)		202 (82.4)		16 (76.2)		
Apgar score <7 at 1 min								
- yes	53	41 (5.4)		12 (4.9)		0 (0.0)		0.5
- no	972	718 (94.6)		233 (95.1)		21 (100)		
Apgar score <7 at 5 min								
- yes	17	13 (1.7)		4 (1.6)		0 (0.0)		>0.05
- no	1008	746 (98.3)		241 (98.4)		21 (100.0)		
Low birth weight (<2,500 g)								
- yes	64	48 (6.3)		15 (6.1)		1 (4.8)		0.1
- no	962	712 (93.7)		230 (93.9)		20 (95.2)		
Stillbirth								
- yes	12	8 (1.1)		4 (1.6)		0 (0.0)		>0.05
- no	1012	751 (98.9)		240 (98.4)		21 (100.0)		
Blood transfusion								
- yes	24	15 (2.0)		9 (3.7)		0 (0.0)		0.2
- no	1003	746 (98.0)		236 (96.3)		21 (100.0)		
Peripartum bleeding								
- yes	85	59 (7.8)		24 (9.8)		2 (9.5)		0.6
- no	941	701(92.2)		221(90.2)		19 (90.5)		
Formula Feeding at discharge								
- yes	112	91(12.1)		20 (8.3)		1 (4.8)		0.2
- no	902	660 (87.9)		222 (91.7)		20 (95.2)		
	N	**Maternal iron status in second half of pregnancy second clinical analysis between week 26-28**						
		NAIS (2)		**NAID-s (2)**		**NAID-ns (2)**		
		n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	p#
Fatigue (36-38 GW)	896	225	23 (20-26)	587	23 (21-26)	84	24 (22-27)	0.1
self-perceived health (36-38 GW)	897	225	7 (6-8)	588	6 (6-8)	84	6 (6-7)	0.3
Birthweight (grams)	910	232	3210 (2860-3450) [a]	593	3350 (3020-3660) [b]	85	3290 (3036-3527) [a, b]	< 0.01** (NAIS vs NAID-s)

(*continued on next page*)

Table 4 (*continued*)

		Maternal iron status in First clinical analysis (8-12 weeks)						
	N	NAIS (1)		NAID-s (1)		NAID-ns (1)		
		n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	P#
Gestational age at birth (GW)	911	232	39.5 (38.5-40.5)	594	39.6 (38.6-40.5)	85	39.8 (38.4-40.6)	0.2
Hb (0-2 week before birth)	896	225	12.4 (11.8-13.0) [a]	587	12.2 (11.6-12.8) [b]	84	12.2 (11.6-12.7) [b]	< 0.01** (NAIS vs NAID-s) 0.02* (NAIS vs NAID-ns)
Hb (24-48 hours postpartum)	911	232	11.1 (10.2-11.9)	594	11.0 (10.1-11.8)	85	11.0 (9.9-11.8)	0.5
		N (%)		N (%)		N (%)		p##
Third-trimester anemia								
- yes	70	6 (2.6) [a]		55 (9.4) [b]		9 (10.7) [b]		<0.05* (NAIS vs NAID-s)
- no	826	219 (97.3) [a]		532 (90.6) [b]		75 (89.3) [b]		<0.05* (NAIS vs NAID-ns)
Postpartum anemia								
- yes	192	44 (19.0)		126 (21.2)		22 (25.9)		0.4
- no	719	188 (81.0)		468 (78.8)		63 (74.1)		
Gestational diabetes								
- yes	47	18 (7.8)		24 (4.1)		5 (5.9)		0.1
- no	862	214 (92.2)		568 (95.9)		80 (94.1)		
Pre-eclampsia/eclampsia								
- yes	15	7 (3.0)		6 (1.0)		2 (2.4)		>0.05
- no	894	225 (97)		586 (99.0)		83 (97.6)		
Caesarean section								
- yes	183	55 (23.7)		110 (18.5)		18 (21.2)		0.2
- no	728	177 (76.3)		484 (81.5)		67 (78.8)		
Apgar score <7 at 1 min								
- yes	50	20 (8.7)		29 (4.9)		1 (1.2)		>0.05
- no	859	210 (91.3)		565 (95.1)		84 (98.8)		
Apgar score <7 at 5 min								
- yes	16	5 (2.2)		10 (1.7)		1 (1.2)		>0.05
- no	893	225 (97.8)		584 (98.3)		84 (98.8)		
Low birth weight (<2500 g)								
- yes	59	30 (12.9) [a]		24 (4.0) [b]		5 (5.9) [a, b]		<0.05* (NAIS vs NAID-s)
- no	851	202 (87.1) [a]		569 (96.0) [b]		80 (94.1) [a, b]		
Stillbirth								
- yes	10	6 (2.6) [a]		3 (0.5) [b]		1 (1.2) [a, b]		<0.05* (NAIS vs NAID-s)
- no	899	226 (97.4) [a]		589 (99.5) [b]		84 (98.8) [a, b]		
Blood transfusion								
- yes	17	4 (1.7)		12 (2.0)		1 (1.2)		>0.05
- no	894	228 (98.3)		582 (98.0)		84 (98.8)		
Peripartum bleeding								
- yes	72	13 (5.6)		52 (8.8)		7 (8.3)		0.3
- no	838	219 (94.4)		542 (91.2)		77 (91.7)		
Formula Feeding at discharge								
- yes	102	28 (12.4)		70 (11.8)		4 (4.8)		0.1
- no	799	198 (87.8)		521 (88.2)		80 (95.2)		

P# = p-value Kruskal-Wallis rank test or pairwise comparison with Bonferroni correction; p## = p-value Pearson's chi-squared test or value Z-test with Bonferroni correction· Within a group, values with different superscript letters [a,b] were significantly different (P < 0.05, with Bonferroni correction).

NAIS = non-anemic iron sufficient women; NAID-s = non-anemic iron deficient women with supplementation; NAID-ns = non-anemic iron deficient women non-supplementation.

12,9 % respectability), although only the difference between the NAID-s (2) versus NAIS(2) groups reached statistical significance (4.2 % vs 12.9 %, p < 0.05). Similarly, there was a lower percentage of foetal death in the NAID-s (2) and NAID-ns (2) groups than in the NAIS(2) group with a significant difference between the NAID-s (2) versus NAIS(2) groups (0.5 % vs 2.6 %, p < 0.05). However the percentage of pregnant individuals with anemia diagnosed before delivery was significantly higher in both NAID-s (2) and NAID-ns (2) groups than in the NAIS(2) group (9.6 % vs 2,6 %, p < 0.05 and 11.5 % vs 2.6 %, p < 0.05) (Table 4).

Table 5 shows the crude and adjusted odds ratio (OR) of the analytical and clinical results that had shown statistically significant differences between the 3 groups into which we classified pregnant individuals without anemia with data from the first and second blood tests. pregnant individuals who were iron-deficient at the first blood test, even if they took iron supplements, were more likely to be anaemic in the second and third trimester [OR 2.16 (IC95 % 1.40–3.33) and 1.7 (IC95 % 1.1–2.65), respectively] than pregnant individuals with sufficient iron. When iron deficiency was diagnosed in the second blood test, the odds of anemia before delivery were almost 5 times higher [OR = 4.74 (IC95 % 1.60–14.06)] than in iron-sufficient pregnant individuals. However, the odds of having a baby weighing less than 2500 g [OR = 0.38 (IC95 % 0.21–0.70)] or stillbirth [OR = 0.18 (IC95 % 0.04–0.77)] were lower in iron-deficient pregnant individuals who supplemented than in those who were not iron-deficient in the second trimester.

Table 5
Risk of anemia, low birth weight and stillbirth in the iron-deficient groups compared by the iron status group. Spain, 2021–2022.

Outcomes	group of first sub-cohort (First analytic between 8 and 12 GW)				
	Reference group: NAIS (1)	Odds Ratio (95 %CI)	p	Adjusted Odds Ratio (95 % CI)	p
Second-trimester anemia	NAID-s (1)	2.31 (1.53–3.52)	<0.01**	2.16 (1.40–3.33)	<0.01**
	NAID-ns (1)	1.12 (0.26–4.93)	0.8	0.97 (0.22–4.37)	1
Third-trimester anemia	NAID-s (1)	1.73 (1.13–2.65)	0.01*	1.70 (1.10–2.65)	0.02*
	NAID-ns (1)	2.24 (0.734–6.84)	0.2	1.88 (0.59–6.07)	0.3
	Reference group: NAID-ns (1)	Odd Ratio (IC95 %)	p	Adjusted Odd Ratio (IC95 %)	p
Second-trimester anemia	NAID-s (1)	2.03 (0.46–9.19)	0.3	2.22 (0.49–10.15)	0.3
Third-trimester anemia	NAID-s (1)	0.77 (0.25–2.42)	0.7	0.87 (0.28–2.97)	0.9
	group of second sub-cohort (second analytic between 24 and 28 GW)				
	Reference group: NAIS (2)	Odds Ratio (95 %CI)	p	Adjusted Odds Ratio (95 %CI)	p
Third-trimester anemia	NAID-s (2)	3.77 (1.60–8.89)	<0.01*	3.68 (1.53–8.84)	<0.01*
	NAID-ns (2)	4.34 (1.51–12.72)	<0.01*	4.74 (1.60–14.06)	0.01*
Low birth weight (<2500 g)	NAID-s (2)	0.28 (0.16–0.50)	<0.01**	0.38 (0.21–0.70)	<0.01*
	NAID-ns (2)	0.42 (0.16–1.12)	0.08	0.57 (0.21–1.55)	0.3
Stillbirth	NAID-s (2)	0.19 (0.05–0.77)	0.02*	0.18 (0.04–0.77)	0.02*
	NAID-ns (2)	0.45 (0.05–3.78)	0.5	0.44 (0.05–3.85)	0.5
	Reference group: NAID-ns (2)	Odds Ratio (95 %CI)	p	Adjusted Odds Ratio (95 %CI)	p
Third-trimester anemia	NAID-s (2)	0.85 (0.40–1.79)	0.7	0.76 (0.36–1.63)	0.5
Low birth weight (<2500 g)	NAID-s (2)	0.675 (0.25–1.82)	0.4	0.67 (0.25–1.83)	0.4
Stillbirth	NAID-s (2)	0.42 (0.04–4.11)	0.5	0.41 (0.04–4.02)	0.4

Adjusted Odds Ratio by age, body mass Index, nationality and parity. Abbreviations: NAIS = non-anemic iron sufficient women; NAID-s = non-anemic iron deficient women with supplementation; NAID-ns = non-anemic iron deficient women non-supplementation.

5. Discussion

In this cohort the prevalence of iron deficiency without anemia in the first trimester was 25.5 % and increased to 66 % in the second trimester. Diagnosis of NAID in the first trimester is associated with a higher probability of anemia in the second and third trimester of pregnancy, and diagnosis of NAID in the second trimester with a lower probability of low birthweight and stillbirth. No significant differences were found in analytical or clinical outcomes between the two groups of iron-deficient pregnant individuals, i.e. between those accepting or refusing iron supplementation.

In this study, the prevalence of NAID for the first trimester threshold SF < 30 μg/L,25.5 % is almost double that reported in Denmark [4] or USA [5], 14.2 % and 14 % respectively, but much lower than the 46.7 % estimated in Latvia for the same threshold [22]. Another Spanish study reports a prevalence of 16 % with a cut-off value SF < 12 μg/L [9], which is almost three times higher than the 5.5 % which according to our data would be the prevalence of NAID if we had used the same threshold. These wide differences in prevalence data are justified by the multifactorial aetiology of the deficit, which has been related to age, physiological and pathological conditions, alcohol and tobacco consumption, environmental, socioeconomic, and dietary factors of the pregnant woman [22,23] which makes it very difficult to compare the populations studied.

During pregnancy, serum ferritin is the recommended biomarker for assessing iron deficiency. Alternatively, biomarkers like transferrin saturation, soluble transferrin receptor (sTfR), reticulocyte hemoglobin, or hepcidin lack sufficient evidence to confirm their effectiveness in pregnancy [3,24]. However, there is a potential that utilizing biomarkers which are less affected by inflammation and the physiological transformations in pregnancy compared to serum ferritin could more accurately reflect maternal iron levels and reveal different prevalence rates [25].

We found no statistically significant differences in most clinical outcome measures between the three groups of non-anaemic mothers (sufficient iron stores, insufficient with supplementation or insufficient without supplementation). The association that iron deficiency diagnosed in the second trimester would have on the risk of low birthweight and stillbirth deserves to be considered with great caution as the estimated risk is imprecise due to the small number of events which condition the width of the CI. A Danish study showed significant associations between first trimester non-anaemic iron deficiency with supplementation and stillbirth but not between iron deficiency anemia and stillbirth. Our data do not support this relationship and we have not found any other studies linking non-anaemic iron deficiency with stillbirth [7] while there are consistent data linking maternal anemia with stillbirth [26]. In this study we have found that ID in the second half of pregnancy seems to act as a protective factor rather than a risk factor, which is equally surprising. We have not found any other studies that have explored this result, but other studies have established an association between elevated levels of SF and increased risk of preterm birth and low birth weight [27,28], which in turn are risk factors for stillbirth [27]. We know that the causal pathways of stillbirth are complex and involve multiple factors [29], including social determinants such as poverty or maternal socioeconomic and cultural status, which have not been evaluated in this study along with other factors involved, such as smoking, maternal chronic diseases or lack of prenatal care, which we did control by excluding these cases in the studied sample. In addition, an excessively high maternal haemoglobin level, more likely among pregnant individuals without iron deficiency, has been associated with undesirable events such as stillbirth [26,28]. Regarding the effect of iron deficiency in relation to low birth weight, the results in the literature consulted are scarce and contradictory. One study shows an association between first trimester iron deficiency and birth weight >90th percentile [7] another finds no association between iron deficiency and

birth weight [4], and a third associates iron deficiency without anemia with lower birth weight [14]. There is strong evidence of an association of maternal anemia with low birth weight and preterm birth, but it is not possible to determine to what extent this association may be attributable to iron deficiency [19,26,30].

The literature confirms the increased risk of anemia in pregnant individuals with iron deficiency in early pregnancy [9]. In this study no woman reaches a severe level of anemia either in the second half of pregnancy or before delivery, the adverse effects of anemia are more closely associated with lower haemoglobin levels [31,32]. Furthermore, in some studies the relationship between maternal anemia and poor obstetric and neonatal outcomes is established with first trimester anemia, but not with anemia occurring in the second and third trimester [19,33,34], both findings, mostly mild anemias in all three groups and their occurrence earlier in pregnancy could explain why we found no differences in most of the clinical outcomes observed.

We also found no differences in any clinical outcome between pregnant individuals with iron deficiency who did or did not take iron supplementation. In the Danish study, after prescription of oral iron in iron-deficient non-anaemic pregnant individuals for 4 weeks, iron deficiency persisted in most cases (67.7 %) [4], and this persistence of iron deficiency after supplementation is also observed in our study and in other Spanish studies [9,14]. Studies on the effect of iron supplementation on iron deficiency without anemia are contradictory and do not clarify the recommendation for its use [19,35]. Iron supplementation has been shown to improve haemoglobin values but its effect on clinical outcomes is debated, because there is limited prospective evidence demonstrating the impact of iron supplementation in adverse obstetric outcomes [11,28]. The liver hormone hepcidin regulates iron absorption, plasma iron concentrations and the distribution of iron between organs and tissues. In pregnancy, maternal hepcidin decreases and it decreases even more when there is iron deficiency, which favours a greater increase in maternal iron uptake at intestinal level, but foetal hepcidin also decreases, so that foetal iron uptake also increases, thus ensuring greater absorption and utilisation of ingested iron in both the mother and the foetus when they need it most [28]. Therefore, if in pregnant inidviduals with ID, the iron ingested through the diet is adsorbed and utilised more efficiently, dietary advice is particularly relevant in pregnant individuals without anemia and should not be overlooked [23].

5.1. Implications for clinical practice and future research

In high-income countries where the national health system guarantees prenatal screening and access to health resources and pharmacological drugs and supplements, the results of this study support that, in healthy pregnant individuals with low-risk pregnancies, adding universal SF screening to Hb screening for first and second trimester iron status does not seem to lead to better maternal and neonatal health outcomes, except in the case of a diagnosis of maternal anemia. On the other hand, pharmacological oral iron supplementation in iron deficiency without anemia also does not achieve clinically different health outcomes than non-supplementation, which would further debate the appropriateness of recommending or not recommending iron supplementation. Until we have better evidence, we seem reasonable to continue recommending the iron supplementation but at the same time, and provided that adequate monitoring of analytical indices and maternal and fetal health status is ensured, we can support the non-anaemic woman's decision to reinforce iron intake through pharmacological preparations or diet. Future research should explore the impact of dietary counselling in healthy iron-deficient women without anemia on maternal and neonatal health outcomes". Finally, it is necessary to extend research to other pregnant individuals with unfavorable health conditions or high-risk pregnancies, because it is likely that the effect of iron deficiency without anemia and iron supplementation will show different results than those found in this study.

5.2. Strengthens and limitations of the study

The main strength of this study was the retrospective follow-up of a cohort of healthy, non-anaemic pregnant individuals from early pregnancy to delivery, with a limited number of losses and up-to-date data collection at each point in the process. Its main limitation is that the sample size was insufficient for the analysis of rare outcomes. The small group of iron-deficient pregnant individuals who refused iron supplementation prevented some of the differences observed, relative to the other groups, from reaching statistical significance. In addition, the confidence intervals of the OR that reach statistical significance are too large and imprecise. A larger sample size would have given more complete and accurate information, consequently, it is necessary to reevaluate of the effect of iron deficiency on the risk of low birthweight and stillbirth with further research in adequately powered studies warranted. A larger sample size would have given more complete and accurate information. In addition, the study excluded pregnant individuals due to language limitations, resulting in an overrepresentation of Spanish and Caucasian pregnant individuals. On the other hand, we did not measure adherence to pharmacological iron intake, so the daily amount of elemental iron ingested may have varied from one woman to another, and it is not known whether pregnant individuals who were not prescribed pharmacological iron increased their intake through diet or multivitamins.

6. Conclusion

In healthy pregnant individuals without anemia, iron deficiency does not increase the risk of maternal or neonatal adverse events and when diagnosed in the second half of pregnancy there could be association between iron deficiency and lower incidence of low birth weight and stillbirth, but these results are imprecise and needs to be reevaluated in subsequent studies. Iron supplementation in iron-deficient pregnant individuals without anemia does not result in significant changes in maternal and neonatal clinical outcomes.

CRediT authorship contribution statement

Regina Ruiz de Viñaspre-Hernández: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Raúl Juárez-Vela:** Supervision, Project administration, Methodology, Investigation, Conceptualization. **José Antonio Garcia-Erce:** Supervision, Methodology. **Kapil Nanwani-Nanwani:** Visualization, Software, Resources. **Silvia González-Fernández:** Project administration, Methodology. **Vicente Gea-Caballero:** Validation, Resources, Investigation. **Ignacio Larrayoz-Roldán:** Writing – review & editing, Writing – original draft, Visualization. **Alberto Tovar-Reinoso:** Resources, Project administration. **Pablo del Pozo-Herce:** Resources. **Pilar Sanchez-Conde:** Software. **Clara Isabel Tejada-Garrido:** Investigation. **Manuel Quintana-Diaz:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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