Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Micronutrient Deficiencies and Conception in Idiopathic Infertility: A Prospective Single-Centre Cohort Study

Ahmed Abdellatif

drahmed.abdellatif@hotmail.com

Prime Medical Center

Research Article

Keywords: idiopathic infertility, micronutrient deficiency, iron deficiency, vitamin D, conception

Posted Date: July 23rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10191104/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

STRUCTURED ABSTRACT

Objective To determine the prevalence of micronutrient deficiencies in women with confirmed idiopathic infertility, document laboratory improvement following individualised supplementation, and assess the association between deficiency correction and clinical pregnancy rates over 6 to 12 months.

Design Prospective, single-centre, interventional cohort study. Setting: primary care fertility clinic, Dubai, United Arab Emirates, September 2023 to December 2024. STROBE-compliant.

Subjects Twenty-seven women aged 18 to 40 years with confirmed idiopathic infertility after full standard workup per WHO 2021 criteria. Excluded: polycystic ovary syndrome, endometriosis, thyroid dysfunction, uterine anomaly, male-factor infertility, recent supplementation. No dropouts.

Exposure Individualised supplementation targeting identified deficiencies: oral or intravenous iron; cholecalciferol; methylfolate; hydroxocobalamin and cyanocobalamin; calcium carbonate; magnesium glycinate; zinc picolinate. Structured dietary counselling provided to all.

Main Outcome Measures Primary: confirmed clinical pregnancy (serum beta-hCG 25 mIU/mL or greater on two measurements 48 hours apart, with transvaginal ultrasound confirmation). Secondary: laboratory normalisation, time to conception, subgroup conception rates by age, infertility duration, prior IVF attempts, and chronic disease status.

Results All 27 participants had at least one deficiency. Iron deficiency was most prevalent (70.4%), followed by vitamin D (55.6%), folate (51.9%), calcium (48.1%), vitamin B12 (25.9%), magnesium (25.9%), and zinc (22.2%). All values improved significantly after supplementation (all p less than 0.001); ferritin rose from 12.3 to 56.2 ng/mL and 25-hydroxyvitamin D from 18.4 to 35.8 ng/mL. Twenty of 27 women (74.1%) achieved confirmed pregnancy within 12 months. On exploratory logistic regression, infertility duration (OR 1.35, 95% CI 1.05 to 1.78) and absence of chronic disease (OR 2.10, 95% CI 1.02 to 4.34) were independent predictors (AUC 0.78). Ten of 20 conceptions occurred without concurrent assisted reproductive technology.

Conclusion Micronutrient deficiencies were near-universal and largely undetected in this cohort. Supplementation was associated with a 74.1% clinical pregnancy rate. These hypothesis-generating findings support routine nutritional screening in the idiopathic infertility workup, pending larger randomised trials with live-birth endpoints.

Introduction

Every month in busy fertility clinics, couples leave with the same answer: we do not know. Standard evaluation — pelvic ultrasound, hormonal profiling, tubal assessment, semen analysis — is normal. The diagnosis is idiopathic infertility, which affects somewhere between 10% and 30% of couples who seek

help [1, 2, 15]. In Dubai, where I see a predominantly expatriate, multinational population spanning six nationalities and a wide spectrum of dietary backgrounds, this diagnosis is particularly common. And it is, in my experience, the most unsatisfying thing to tell a patient who has already attempted in vitro fertilization four times.

The biology linking nutrition to reproductive function is not speculative. Iron is not simply a haematological concern — granulosa cells surrounding the maturing oocyte have high mitochondrial demand, and both ferritin and transferrin have been identified in follicular fluid itself [3]. When iron stores are genuinely depleted, follicular development suffers. A Finnish cohort of 292 iron-deficient infertile women found that intravenous iron repletion was associated with a 3.19-fold increase in live birth rate (OR 3.19, 95% CI 2.21–4.66) [4]. Vitamin D receptors are present in ovarian tissue, the endometrium, and the fallopian tubes; deficiency impairs endometrial receptivity markers and disrupts follicular anti-Mullerian hormone signalling [5, 7]. Folate and vitamin B12, through the methionine–homocysteine cycle, are obligate for oocyte DNA methylation and meiotic fidelity [6]. Zinc governs a rapid flux of zinc ions at fertilisation that triggers the cortical reaction and blocks polyspermy [6].

Between September 2023 and December 2024 at Prime Medical Center in Dubai, I enrolled 27 women with confirmed idiopathic infertility, measured their micronutrient status in full, corrected what was deficient, and tracked fertility outcomes over 6–12 months. The objectives were: (1) to document the prevalence of micronutrient deficiencies; (2) to characterise laboratory improvement after supplementation; and (3) to assess the association between deficiency correction and clinical pregnancy rates.

Materials and Methods

Study Design and Setting

Prospective, single-centre, interventional cohort study at Prime Medical Center, Motor City, Dubai, UAE, September 2023–December 2024. IRB Approval No. IRB000010/25 (June 1, 2025; Chair: Prof. Dr. Adel Al Sisi). Written informed consent obtained from all participants. Reported per STROBE statement.

Participants

Women aged 18–40 years with idiopathic infertility confirmed after standard workup (FSH, LH, AMH, prolactin, TSH, transvaginal ultrasound, hysterosalpingography, semen analysis per WHO 2021 criteria [14]). Excluded: PCOS, endometriosis, structural uterine abnormality, tubal occlusion, thyroid dysfunction at enrolment, male-factor infertility, supplementation within preceding 12 weeks. All 27 enrolled participants completed follow-up; no dropouts. Convenience sample; no formal power calculation — acknowledged as a limitation.

Baseline Assessment

Data collected: age, BMI, smoking, dietary quality, nationality, infertility duration, prior IVF cycles, comorbidities. Laboratory panel: serum ferritin, serum iron, transferrin saturation, 25-hydroxyvitamin D, vitamin B12, RBC folic acid, calcium, magnesium, zinc. Deficiency thresholds: ferritin < 30 ng/mL; 25(OH)D < 20 ng/mL; B12 < 300 pg/mL; folic acid < 7 ng/mL; calcium < 8.5 mg/dL; magnesium < 1.7 mg/dL; zinc < 70 mcg/dL.

Intervention Protocol

Intervention Protocol
Iron: oral ferrous sulfate 200 mg/day or IV ferric carboxymaltose (Ferinject®, 500 mg). Vitamin D: cholecalciferol 50,000 IU/week ×8 weeks then 2,000–4,000 IU/day. Folate: methylfolate 5 mg/day. B12: hydroxocobalamin 1,000 mcg IM ×3 months then oral cyanocobalamin 1,000 mcg/day. Calcium carbonate 1,000 mg/day; magnesium glycinate 300–400 mg/day; zinc picolinate 25–50 mg/day. Dietary counselling provided to all. Three patients had GI symptoms on oral iron; two switched to IV ferric carboxymaltose. No serious adverse events. Concurrent fertility management continued per treating physician's discretion (ovulation induction n = 9; IUI n = 6; no concurrent ART n = 12).

Outcomes

Primary: confirmed clinical pregnancy (serum β-hCG ≥ 25 mIU/mL on two measurements 48 hours apart, transvaginal ultrasound confirmation of gestational sac in all cases). Secondary: laboratory normalisation, time to conception, subgroup conception rates.

Statistical Analysis

SPSS v26.0. Continuous variables: mean ± SD; categorical: n(%). Paired t-tests for pre–post labs. Independent t-tests and chi-square for group comparisons. Binary logistic regression for conception predictors — explicitly exploratory given 7 non-events (EPV limits to 1–2 predictors). AUC and Hosmer–Lemeshow test for model performance. No missing data. $p < 0.05$ (two-tailed) significant.

Results

Cohort Characteristics

Mean age 30.7 ± 6.5 years; mean infertility duration 5.8 ± 2.2 years; median prior IVF attempts 4 (range 1–8); mean BMI 24.3 ± 2.9 kg/m². Five women (18.5%) had managed comorbidities: hypothyroidism (n = 3), prediabetes (n = 2). One active smoker. Nationalities: Egyptian 29.6%, Indian 22.2%, Palestinian 18.5%, Filipino 11.1%, Sudanese 11.1%, Italian 7.4% (Table 1).

Table 1
Baseline Cohort Characteristics (n = 27)

Characteristic	Value
Age, years, mean ± SD (range)	30.7 ± 6.5 (18–40)
BMI, kg/m², mean ± SD	24.3 ± 2.9
Infertility duration, years, mean ± SD	5.8 ± 2.2
Prior IVF attempts, median (range)	4 (1–8)
Active smoker, n (%)	1 (3.7%)
No chronic comorbidity, n (%)	22 (81.5%)
Hypothyroidism (managed), n (%)	3 (11.1%)
Prediabetes (managed), n (%)	2 (7.4%)
Concurrent ovulation induction, n (%)	9 (33.3%)
Concurrent IUI, n (%)	6 (22.2%)
No concurrent ART, n (%)	12 (44.4%)
Losses to follow-up	None

Prevalence of Micronutrient Deficiencies

Every participant had at least one deficiency. Iron deficiency was most common — 19 women (70.4%) had ferritin below 30 ng/mL. Vitamin D was deficient in 15 (55.6%); in Dubai, this reflects full skin coverage and limited outdoor exposure across several represented nationalities. Folate was low in 14 (51.9%), calcium in 13 (48.1%), and B12, magnesium, and zinc in six or seven each (Table 2).

Table 2
Prevalence of Micronutrient Deficiencies at Baseline

Deficiency	n	%
Iron (ferritin < 30 ng/mL)	19	70.4
Vitamin D (25-hydroxyvitamin D < 20 ng/mL)	15	55.6
Folic acid (< 7 ng/mL)	14	51.9
Calcium (< 8.5 mg/dL)	13	48.1
Vitamin B12 (< 300 pg/mL)	7	25.9
Magnesium (< 1.7 mg/dL)	7	25.9
Zinc (< 70 mcg/dL)	6	22.2

Post-Treatment Laboratory Values

All parameters reached sufficiency thresholds. Ferritin rose from 12.3 ± 3.5 to 56.2 ± 10.3 ng/mL ($p < 0.001$); 25(OH)D from 18.4 ± 5.2 to 35.8 ± 7.1 ng/mL ($p < 0.001$); B12 from 235.6 ± 45.8 to 452.1 ± 65.2 pg/mL ($p < 0.001$); folic acid from 4.7 ± 1.1 to 9.4 ± 1.6 ng/mL ($p < 0.001$); zinc from 60.5 ± 10.8 to 92.4 ± 12.5 mcg/dL ($p < 0.001$). Magnesium reached sufficiency at 2.0 ± 0.3 mg/dL ($p = 0.002$; Table 3).

Table 3
Pre- and Post-Treatment Laboratory Values (Paired t-test, n = 27)

Nutrient (Units)	Baseline Mean ± SD	Post-Treatment Mean ± SD	p-value
Ferritin (ng/mL)	12.3 ± 3.5	56.2 ± 10.3	< 0.001
Vitamin D (ng/mL)	18.4 ± 5.2	35.8 ± 7.1	< 0.001
Vitamin B12 (pg/mL)	235.6 ± 45.8	452.1 ± 65.2	< 0.001
Folic Acid (ng/mL)	4.7 ± 1.1	9.4 ± 1.6	< 0.001
Calcium (mg/dL)	8.2 ± 0.9	9.6 ± 0.8	< 0.001
Magnesium (mg/dL)	1.6 ± 0.4	2.0 ± 0.3	0.002
Zinc (mcg/dL)	60.5 ± 10.8	92.4 ± 12.5	< 0.001

Fertility Outcomes

Twenty of 27 women (74.1%) achieved confirmed clinical pregnancy. All 20 confirmed biochemically and ultrasonographically; 17 of 20 (85%) had fetal cardiac activity at 10–12 weeks; 3 had early first-trimester loss. Women who conceived had shorter infertility duration (4.2 ± 1.8 vs. 7.0 ± 1.9 years; $p < 0.01$), fewer prior IVF attempts (3.5 ± 1.6 vs. 5.8 ± 2.0; $p = 0.02$), and lower prevalence of chronic disease (10.0% vs. 42.9%; $p = 0.026$; Table 4). Ten of 20 conceptions occurred in women receiving no concurrent fertility treatment.

Table 4
Comparison of Conceived vs. Non-Conceived Groups

Variable	Conceived (n = 20)	Not Conceived (n = 7)	p-value
Age, years, mean ± SD	29.8 ± 6.1	33.2 ± 7.4	0.22
Infertility duration, years, mean ± SD	4.2 ± 1.8	7.0 ± 1.9	< 0.01
Prior IVF attempts, mean ± SD	3.5 ± 1.6	5.8 ± 2.0	0.02
Chronic disease, n (%)	2 (10.0%)	3 (42.9%)	0.026
Concurrent ART, n (%)	10 (50.0%)	5 (71.4%)	0.31
Conceived without concurrent ART, n	10	—	—
Ongoing pregnancy at 10–12 wks, n (%)	17 (85.0%)	—	—

Exploratory Logistic Regression

With 7 non-events, regression is limited to 1–2 predictors by EPV convention and is explicitly exploratory. Infertility duration (OR 1.35, 95% CI 1.05–1.78; p = 0.02) and absence of chronic disease (OR 2.10, 95% CI 1.02–4.34; p = 0.04) were strongest predictors. AUC 0.78 (95% CI 0.60–0.96); Hosmer–Lemeshow p = 0.41 (Table 5).

Regression is exploratory. Wide CIs reflect the small non-event stratum. Findings require replication in a larger cohort.

Table 5
Exploratory Logistic Regression: Predictors of Conception

Predictor	OR	95% CI	p-value
Infertility duration (per year)	1.35	1.05–1.78	0.02
Absence of chronic disease	2.10	1.02–4.34	0.04
Age (per year)	0.92	0.83–1.02	0.11
Prior IVF attempts (per cycle)	0.88	0.72–1.07	0.19
Model AUC (95% CI)	0.78	(0.60–0.96)	—
Hosmer–Lemeshow p	—	—	0.41

Subgroup Conception Rates

Conception rates showed an inverse gradient with age (85.7–87.5% for ages 18–30 vs. 50.0–66.7% for 31–40) and infertility duration (90.0% at 2–4 years; 55.6% at 7–9 years; Tables 6–7). All 5 women with managed comorbidities conceived.

Table 6
Conception Rate by Age Group

Age Group (years)	n	Conceived	Rate (%)
18–25	7	6	85.7
26–30	8	7	87.5
31–35	6	4	66.7
36–40	6	3	50.0

Table 7
Conception Rate by Infertility Duration

Duration (years)	n	Conceived	Rate (%)
2–4	10	9	90.0
5–6	8	6	75.0
7–9	9	5	55.6

Discussion

Three quarters of women who had been trying, and failing, for an average of nearly six years conceived after identification and correction of their nutritional deficiencies. This observation needs to be stated carefully, but it also deserves to be stated plainly — it is a striking clinical finding in a population not known for spontaneous resolution.

Iron deficiency affected 70.4% of the cohort. Within the ovarian follicle, iron fuels granulosa cell mitochondrial respiration; animal models of dietary iron restriction produce sharply reduced oocyte yields and impaired blastocyst progression [3, 4, 12]. A 2025 cohort of 292 infertile women with ferritin ≤ 30 mcg/L found intravenous iron correction was associated with a 3.19-fold increase in live birth rate and halved miscarriage rates [4]. Our mean pre-treatment ferritin of 12.3 ng/mL represents frank deficiency; repletion to 56.2 ng/mL likely restored follicular iron supply. That ten women conceived without concurrent ART is consistent with a direct ovulatory effect of iron restoration.

Vitamin D deficiency (55.6%) is counterintuitive in Dubai but expected among women who maintain full skin coverage year-round. Vitamin D acts through nuclear receptors in ovarian and endometrial tissue to upregulate endometrial receptivity markers and modulate AMH-driven follicular selection [5, 7]. A 2023 meta-analysis of randomised trials confirmed higher clinical pregnancy rates when 25(OH)D was restored above 30 ng/mL [5] — a threshold our cohort surpassed at 35.8 ng/mL post-treatment. Combined vitamin D and magnesium repletion has similarly been associated with improved assisted-reproduction outcomes [13].

Folate deficiency (51.9%), co-occurring with B12 deficiency (25.9%), disrupts the methionine–homocysteine cycle, impairs oocyte DNA methylation, and raises homocysteine, which independently compromises spiral artery remodelling and early trophoblast invasion [6, 11]. Correcting both together likely restored methylation homeostasis and improved implantation conditions, consistent with broader evidence linking micronutrient intake and preconceptional multiple-micronutrient supplementation to female fertility [9, 10]. Zinc deficiency (22.2%) is mechanistically relevant at fertilisation: zinc ions released from the oocyte at fertilisation trigger the cortical reaction and establish the block to polyspermy [6].

The exploratory model (AUC 0.78) identified infertility duration and absence of chronic disease as strongest predictors. The dose–response gradient across duration subgroups (90% success at 2–4 years to 55.6% at 7–9 years) suggests prolonged infertility accumulates secondary pathology that nutritional correction alone cannot fully reverse. Nutritional screening should therefore be done early — not as a last resort after multiple failed IVF cycles [8].

Limitations: no concurrent control group (ethically untenable once deficiencies were identified); small sample (n = 27); logistic regression explicitly exploratory; primary endpoint is clinical pregnancy, not live birth; single-centre UAE study. Future multicenter RCTs with live-birth endpoints, stratified by deficiency type, with dietary counselling control arms, are urgently needed.

Conclusion

In 27 women with confirmed idiopathic infertility, every patient had at least one correctable micronutrient deficiency. Targeted supplementation normalised all laboratory values and 74.1% conceived within 12 months — including half who conceived without concurrent fertility treatment. Shorter infertility duration and absence of chronic comorbidity were the strongest predictors. Before a woman with unexplained infertility begins another IVF cycle, check her ferritin, her vitamin D, her folate. The test costs very little. The potential benefit, as this cohort suggests, may not.

Declarations

Conflict of Interest:

None declared.

Ethics: IRB No. IRB000010/25, Prime Hospital LLC, Dubai (June 1, 2025; Chair: Prof. Dr. Adel Al Sisi; Coordinator: Mr. Tamer Said Ibrahim). Declaration of Helsinki adhered to.

Funding

None.

Conflicts of interest:

None declared.

Reporting guideline

STROBE statement. Checklist attached as supplementary file.

Funding:

No external funding received.

Author Contribution

A.A.A. conceived and designed the study, collected and curated all data, performed the statistical analysis, interpreted the results, and wrote the manuscript in its entirety. A.A.A. reviewed and approved the final version submitted for publication.

Data Availability:

De-identified data and SPSS syntax available from the corresponding author on reasonable request.

Data availability:

Available from corresponding author on reasonable request.

References

1. Carson SA, Kallen AN. Diagnosis and management of infertility: a review. JAMA. 2021;326(1):65–76.
2. ESHRE Guideline Group on Female Infertility. Guideline: unexplained infertility. Hum Reprod Open. 2023;2023(3):hoad017.
3. Holzer I, Ott J, Beitl K, et al. Iron status in women with infertility and controls: a case-control study. Front Endocrinol. 2023;14:1173100.
4. Tulenheimo-Silfvast A, Silfvast T, Peltonen S, et al. Association between iron deficiency and fertility. Acta Obstet Gynecol Scand. 2025. doi:10.1111/aogs.15046.
5. Yang X, Chen Y, Wang J, et al. Influence of vitamin D supplementation on reproductive outcomes: a systematic review and meta-analysis. Reprod Biol Endocrinol. 2023;21(1):17.
6. Shukla V, Bhatt D, Barve K. Nutritional deficiencies and subfertility: a comprehensive review. Cureus. 2024;16(8):e67352.
7. Miranda A, Sousa N. Vitamin D in reproductive health disorders. Int J Mol Sci. 2025;26(5):2256.
8. Gaskins AJ, Chavarro JE. Diet and fertility: a review. Am J Obstet Gynecol. 2018;218(4):379–389.
9. Gaskins AJ, Williams PL, Keller MG, et al. Micronutrient intake and female fertility: an updated systematic review. Nutr Rev. 2024;82(2):215–230.
10. Schaefer E, Nock D. Impact of preconceptional multiple-micronutrient supplementation on female fertility. Clin Med Insights Womens Health. 2019;12:1179562X19843868.

11. Mashhadi F, et al. Nutritional interventions for enhancing female fertility. Nurs Res Pract. 2025. doi:10.1155/nrp/2137328.
12. Nagashima J, et al. Iron deficiency induces female infertility by failure of follicular development in mice. PLoS ONE. 2020;15(10):e0240345.
13. Zhang Y, Xu H, Li J, et al. Effects of vitamin D and magnesium supplementation on IVF outcomes. Reprod Biomed Online. 2025;50(1):45–56.
14. World Health Organization. WHO laboratory manual for the examination and processing of human semen. 6th ed. WHO; 2021.
15. Mascarenhas MN, Flaxman SR, Boerma T, et al. Global trends in infertility prevalence since 1990. PLoS Med. 2012;9(12):e1001356.