Investigating the Effect of Iron Supplementation on Fertility Outcomes in Women With a History of Infertility

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Abstract- Iron deficiency is a common condition in women of reproductive age and has been associated with infertility and suboptimal pregnancy outcomes. Iron supplementation may improve fertility outcomes, but its effects on embryo quality and other reproductive parameters remain unclear. This study aimed to evaluate the effect of iron supplementation on pregnancy outcomes, embryo number, and embryo quality in women undergoing in vitro fertilization (IVF). This randomized, double-blind, controlled clinical trial included 112 women aged 20-39 undergoing IVF. Participants were divided into two groups: one receiving iron supplements and the other serving as a control group. The study assessed pregnancy outcomes, the number of embryos, and embryo quality. Data were analyzed using statistical tests, including two-way ANOVA and logistic regression, with a significance threshold of $P<0.05$. Women who received iron supplementation had significantly higher pregnancy rates (50%) compared to the control group (28.5%, $P=0.020$). The number of embryos was also significantly higher in the iron group (5.00±3.297) than in the control group (3.39±0.888, $P=0.001$). However, embryo quality did not differ significantly between the two groups ($P=0.055$). BMI was positively associated with the number of embryos ($P=0.002$). Still, other factors, including age, endometrial thickness, and years of infertility, showed no significant effects on pregnancy outcomes or embryo quality. Iron supplementation improves pregnancy outcomes and the number of embryos in women undergoing IVF, but does not significantly impact embryo quality. These findings highlight the potential of incorporating iron supplementation into IVF protocols; however, further research is needed to determine the optimal dosing and long-term effects.

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Introduction

Iron is essential for the function of all cells through its role in oxygenation, electron transport, and enzyme activity. Cells with high metabolic rates require more iron and are at greater risk for dysfunction when iron is deficient. (1) Iron deficiency is a common disease worldwide, with an estimated 25% of the world's population suffering from anemia (2). While the effects of iron deficiency on physical health are well known, there is growing evidence that the condition can also affect women's reproductive health.

One of the areas affected by iron deficiency is fertility. Several studies have shown that low iron levels may contribute to infertility, especially in women who are trying to conceive, and women with iron deficiency anemia are more likely than women without anemia. Are subject to infertility (3). Women with low levels of serum ferritin (a measure of iron stores in the body) are at risk of infertility and miscarriage (4). These findings suggest that maintaining adequate iron levels may play an important role in promoting fertility and healthy

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pregnancy outcomes.

Iron deficiency may also affect the success of fertility treatments. Women undergoing in vitro fertilization (IVF) with low iron levels have lower pregnancy rates compared to women with normal iron levels (5). Additionally, women who received iron supplementation during IVF had better outcomes compared to those who did not (6).

The inability to conceive leads to significant emotional and economic consequences for those affected by it. Anxiety and depression are more common in infertile couples than in fertile couples. Assisted reproductive technologies are available for the treatment of infertility, but they have a high cost (7).

It is important to note that iron deficiency can have other effects beyond fertility on women's reproductive health. For example, iron deficiency anemia during pregnancy is associated with an increased risk of preterm delivery, low birth weight, and infant mortality (8). Additionally, iron deficiency may increase the risk of menstrual irregularities, heavy menstrual bleeding, and other menstrual disorders (9).

Identifying modifiable risk factors for infertility can lead to cheap and effective interventions to prevent this problem. Although the relationship between dietary factors and infertility has not been widely investigated, it is likely to be very important. A small clinical trial investigated the effectiveness of iron supplements in infertile women, who had a higher pregnancy rate. In addition, in mothers who are suffering from celiac disease and usually have a deficiency of iron and micronutrients, reproductive disorders such as delayed menarche, early menopause, and infertility due to unknown causes have been seen, which suggests that some components of this disease affect ovulation (10).

Consequently, iron deficiency is a complex condition that can have significant effects on women's reproductive health. Maintaining an adequate level of iron through a healthy diet and taking supplements as needed may help improve fertility outcomes and prevent pregnancy complications. Considering the very negative effects that infertility can have on people in a society, this study aims to investigate the effect of iron supplementation on fertility outcomes in women with a history of infertility.

Materials and Methods

This interventional study is a randomized controlled trial (RCT). The target population includes women of reproductive age (after menarche and before the onset of menopause symptoms) and married between the ages of 20 and 39 years old who are candidates for IVF/ICSI in Sayad Shirazi Hospital in Gorgan during 2023. The participants should have had frequent and unprotected intercourse for at least 12 months. The samples were selected from among the above-qualified women using the available sampling method.

Inclusion criteria

1. Married women with infertility complaints aged 20 to 39 years
2. Confirmed infertility by definition (at least 12 months of frequent unprotected intercourse trying to conceive)
3. IVF/ICSI candidate
4. 1<AMH<4.5
5. Referral for the first or second embryo transfer
6. Consent to participate in the study

Exclusion criteria

1. Women with a history of hematopoiesis with iron deficiency or iron deficiency anemia (hemoglobin less than 12, ferritin less than 15, and TIBC more than 380 (11))
2. Confirmed endometriosis
3. At least three failures in the nest of the previous option (RIF)
4. Uterine adenomyosis or myomatosis
5. If the couple's infertility was related to Tese

The participants in this study were divided into two groups: 1) the control group (subjects who did not receive iron supplements); and 2) the group that received iron supplements along with other recommended supplements. The method of distribution of iron was blinded, and the researcher (female assistant project manager) did not know about the type of treatment received. The iron supplement was placed in the medicine basket provided by the Nahal Center and distributed among the participants.

At the beginning of the study and before the start of the intervention, baseline assessments were performed to measure participants' iron status (with ferritin and TIBC tests), fertility outcomes, and other health-related factors that may affect fertility, such as age, body mass index, and smoking status. done Follow-up evaluations were done two weeks after the third transfer by hospital experts. Iron status was assessed using serum ferritin, serum iron, and hemoglobin concentration. Women who had at least one embryo with grade A quality and endometrial thickness greater than 8 cm were candidates for transfer. At the end of the data collection, fertility

results using criteria such as endometrial thickness, quality, and number of embryos (before transfer) and positive beta test results (followed two weeks after each transfer and up to three transfer stages) were evaluated and recorded by the study researcher. Became. The relationship between the measured indicators was measured with statistical methods.

Statistical analysis

The data obtained from the study were analyzed using the required statistical methods, including paired T-tests, independent T-tests, chi-square tests, ANOVA, and two-way ANOVA in SPSS statistical software version 26, and the difference in fertility results between the iron supplement group and the Control was evaluated. Subgroup analyses were performed to examine potential differences in the relationship between iron deficiency and fertility based on factors such as age, BMI, and smoking status. *P* less than 0.05 was considered statistically significant.

Results

Before intervention

In this study, we evaluated 192 cases, comprising 112 participants in the case group and 56 participants in the control group. The average age of the participants in this study was 31.69±5.26 years. The average BMI of the participants was 27.23±4.24. The average duration of infertility was 5.27±3.18 years, and the average endometrial thickness before implantation was 9.13±1.35 cm. According to the independent T-test, there was a significant difference between the groups, specifically in terms of age and BMI (*P*=0.020 and *P*=0.007, respectively). The case group had a higher BMI and age than the control group. However, the remaining variables, including years of infertility and previous endometrial thickness, showed no significant difference between the two groups from embryo implantation (*P*=0.676 and *P*=0.157, respectively) (Table 1).

Table 1. Frequency of age, BMI, infertility years, and endometrial thickness

			Mean	Standard deviation	Minimum	Maximum	*P**
Age	Group	Control	32	5	19	40	.020
		Case	32	5	19	39	
		total	31.86	5.14	19	40	
BMI	Group	Control	26.76	3.16	17.93	32.86	.007
		Case	27.42	5.04	15.91	39.21	
		total	27.09	4.19	15.91	39.21	
Infertility years	Group	Control	4.9	3.1	.6	16.0	.676
		Case	5.6	3.2	.6	15.0	
		total	5.27	3.16	.6	16	
Endometrial thickness	Group	Control	8.78	1.43	7.20	12.00	.157
		Case	9.36	1.18	7.49	11.50	
		total	9.07	1.33	7.20	12	

* Independent T-test

In this study, 79 subjects (70.53%) were Fars, 31 subjects (27.67%) were Turkmen, and 2 subjects (1.7%) were Baluch. None of the participants mentioned any drug addiction. Seventy-four subjects (66.07%) had no underlying disease, 5 subjects (4.46%) had diabetes, 8 subjects (7.14%) had polycystic ovaries, and 15 subjects (13.39%) had hypothyroidism. Eight subjects (7.14%) were taking metformin, and 12 subjects (10.71%) were taking levothyroxine (the other two individuals with hypothyroidism who were not taking levothyroxine were prescribed it by the attending physician, and the other was self-administered). Twelve subjects (10.71%) had a history of one previous delivery, and one person (0.89%) had a history of two previous deliveries. Sixty-six subjects (58.92%) had primary infertility, and the remaining 46 subjects (41.07%) had secondary infertility. According to the Chi-Square test, there was no significant relationship between the variables of infertility type, race, number of previous births (Para), underlying diseases, and drug history of the participants. (*P*=0.701, *P*=0.342, *P*=0.329, *P*=0.147 and *P*=0.082, respectively) (Table 2).

After intervention

After conducting this study, a total of 44 subjects (39.28%) of the participants had become pregnant; 28 subjects were in the case group, and 16 subjects were in the control group. Additionally, a statistically significant relationship was found between these two groups using the Chi-Square test (P=0.020). However, in the control group, there were 22 embryos of type A only, which number was 10 in the case group, and 28 embryos of type A and B in the control group, compared to the case group, there were 37, and 6 embryos of type A, B, C were in the

control group and 7 subjects were in the case group, in total, both groups had almost the same type of embryo according to the Chi-Square test. No significant difference was observed between the groups (P=0.055). On the other hand, the number of embryos in the case group was greater than in the control group, with an average of 5.00±3.297 embryos in the case group compared to 3.39±0.888 in the control group (Table 3 and Table 4).

Table 2. Frequency of infertility type, ethnicity, Para, past medical history, and drug history

Variables		Group		Total	*P**
		Control	Case		
Infertility type	Primary	34	32	66	.701
	Secondary	22	24	46	
Ethnicity	Fars	41	38	79	.342
	Turkman	15	16	31	
	Balouch	0	2	2	
Para	0	46	46	92	.329
	1	8	10	18	
	2	2	0	2	
Past medical history	Without PMH	39	35	74	.147
	Diabetes	3	2	5	
	PCOs	6	2	8	
	Hypothyroid	4	11	15	
	Myomectomy	2	0	2	
	Laparoscopy	2	2	4	
	Minor Thalassemia	1	3	4	
	Bartholin cyst	0	2	2	
Drug history	Without any drug history	44	47	92	.082
	Metformin	7	1	8	
	Levothyroxine	5	7	12	

* Chi-Square test

Table 3. The number of embryos formed in the study category

	Group	Count	Mean	Standard deviation	Error deviation	*P**
Embryo's count	Control	56	3.39	.888	.119	.001
	Case	56	5.00	3.297	.441	

*Independent T-test

Table 4. Embryo quality and pregnancy outcomes in two study groups

Variables		Group		Total	*P**
		Control	Case		
Embryo's quality	A	22	10	32	.055
	A, B	28	37	65	
	A, B, C	6	7	13	
Pregnancy	Negative	40	28	68	.020
	Positive	16	28	44	

* Chi-Square test

Based on the results of the two-way ANOVA test presented in the table, the quality of embryos and pregnancy outcomes were assessed in relation to various variables, including age, BMI, infertility years, and endometrial thickness (ET), across case and control groups. The corrected model for all variables was significant, indicating that the overall model effectively explains variations in the dependent variables. Age significantly influenced both embryo quality (P=0.006) and pregnancy outcomes (P=0.002), but there was no significant interaction between age and group (P=0.390 for embryo quality and P=0.002 for pregnancy outcomes). Similarly, BMI had a significant effect on both embryo quality (P<0.001) and pregnancy outcomes (P<0.001), with group interactions also showing significant contributions. Infertility years were not significantly associated with embryo quality (P=0.125), but were significant for pregnancy outcomes (P=0.022). The interaction with group remained non-significant for both. Endometrial thickness did not have a significant effect on embryo quality (P=0.077) but did have a significant impact on pregnancy outcomes (P=0.005),

with no significant interactions observed. These findings highlight the complex relationships between these variables and their influence on reproductive outcomes. (Table 5).

Table 5. Age, BMI, years of infertility, and endometrial thickness, and their effect on embryo quality and pregnancy

Dependent variable	Variable	*P* For the group (case/control) effect	*P* For variable effect	*P* For interaction (Group× variable)	Corrected model *P**
Embryo's quality	Age	.031	.006	.390	.009
Pregnancy	Age	.015	.002	.002	<0.001
Embryo's quality	BMI	.001	<0.001	<0.001	<0.001
Pregnancy	BMI	<0.001	<0.001	<0.001	<0.001
Embryo's quality	Infertility years	.125	.271	.001	.002
Pregnancy	Infertility years	.022	.109	.253	.041
Embryo's quality	ET	.718	.077	.194	.040
Pregnancy	ET	.035	.005	.677	.005

Two-way ANOVA test

The logistic regression analysis revealed that PMH and group status significantly influenced pregnancy outcomes, with both factors reducing the odds of achieving pregnancy. However, for embryo quality categorized into three groups (A, A & B, A & B & C), the predictors did not show statistically significant effects on transitions between the categories. The overall model for pregnancy was significant (P=0.005), while the model for embryo quality was borderline significant (P=0.070). These findings suggest that while PMH and group status are critical for predicting pregnancy, their impact on embryo quality requires further investigation with larger datasets (Table 6).

Table 6. Logistic Regression Results for Pregnancy and Embryo Quality

Outcome	Predictor	B	Wald	*P*	Odds ratio (Exp(B)) and 95% CI
Pregnancy (non-pregnant vs Pregnant)	PMH	-0.210	4.569	0.033	0.811 (0.669–0.983)
Pregnancy (0 vs 1)	Group	-0.820	4.038	0.044	0.440 (0.198–0.980)
Embryo Quality (A → A&B)	PMH	0.246	1.095	0.295	1.295 (0.807–2.026)
Embryo Quality (A → A&B)	Group	-0.682	2.275	0.131	0.506 (0.358–1.361)
Embryo Quality (A&B → A&B&C)	PMH	0.159	1.171	0.285	1.171 (0.876–2.098)
Embryo Quality (A&B → A&B&C)	Group	-0.002	1.000	0.171	0.997 (0.297–3.352)

The univariate analysis of variance (ANOVA) demonstrated that group classification (case/control) consistently and significantly influenced the number of embryos across all models (P<0.01). Age and infertility status were not significant predictors (P>0.05), while BMI had a significant positive effect on the number of embryos in its respective model (P=0.002). Endometrial thickness (ET) and other clinical factors, including parity and infertility type, did not show significant associations with the number of embryos (P>0.05), except for past medical history (PMH), which was significant in the comprehensive model (P=0.016). The comprehensive model, incorporating multiple predictors, was statistically significant (P=0.001) with an adjusted R^2 of 0.143, indicating that group classification and PMH were key contributors to the variability in the number of embryos. These results highlight the importance of group classification and BMI in influencing embryo outcomes, while other factors had limited or model-specific effects.

Discussion

The relationship between nutritional status and unexplained infertility is still a controversial topic among studies and is constantly being addressed. One of the important deficiencies that is usually observed in infertile women and women who are trying to conceive is iron deficiency. Adequate iron supply plays a vital role in maintaining health and affects numerous physiological and cellular processes (12). Due to the wide-ranging effects of iron deficiency on various body systems, there is concern that insufficient iron levels may lead to

infertility or repeated miscarriages.

Iron homeostasis is usually assessed through serum ferritin levels. The World Health Organization defines iron deficiency as a ferritin level of less than 15 µg/L; however, some have suggested that this limit should be increased to less than 30 µg/L to improve the sensitivity of this parameter in detecting iron deficiency in both diseased and non-diseased populations. Women are known to be more iron-deficient than men due to blood loss during menstruation. In a normal menstrual cycle, an average of 16 milligrams of iron is lost. Logically, women with abnormal uterine bleeding (menorrhagia) are more likely to have iron deficiency and thus anemia (13-16).

According to various studies, maintaining an adequate level of iron through a healthy diet and taking supplements if necessary may help improve fertility outcomes and prevent pregnancy complications, considering the very negative effects that infertility can have on people in society. The study was designed to investigate the effect of iron supplementation and pregnancy outcomes in women with a history of infertility.

The findings of this study demonstrate that iron supplementation plays a significant role in improving fertility outcomes in women undergoing IVF. Our results revealed that participants who received iron supplements had a significantly higher pregnancy rate (50%) compared to those in the control group (28.5%, P=0.020). This aligns with previous studies highlighting the importance of maintaining adequate iron levels for optimizing reproductive outcomes (12,13). However, it is critical to note that iron supplementation did not significantly impact embryo quality (P=0.055), suggesting that while iron may influence ovulation and implantation success, its effect on embryonic development requires further investigation.

Interestingly, BMI was identified as a significant predictor of the number of embryos (P=0.002), with participants having a higher BMI producing more embryos. While previous studies, such as those by Bartolacci *et al*., and Duijn *et al*., have suggested mixed findings on the effect of BMI on embryo development, our results corroborate the hypothesis that maternal BMI influences early preimplantation growth (17,18). However, this observation should be interpreted cautiously, as BMI differences at baseline between the groups may have contributed to this outcome.

The lack of significant relationships between other clinical factors, including age, endometrial thickness, and infertility years, with pregnancy outcomes further emphasizes the complexity of infertility and the multifactorial nature of its management. Previous studies have yielded mixed results regarding the influence of these variables, which warrant further research to clarify their exact roles (19,20).

Lastly, the potential risks of iron overload, as highlighted by Zhang *et al*., must not be overlooked. Excessive iron supplementation has been associated with adverse reproductive outcomes, including ovarian damage and reduced endometrial receptivity. Therefore, optimizing iron dosage is essential for achieving desired outcomes while minimizing potential risks (21).

This study highlights the positive impact of iron supplementation on pregnancy outcomes in women undergoing IVF, with a significant improvement in pregnancy rates and the number of embryos produced. However, no significant effect was observed on embryo quality. BMI emerged as a significant factor in embryo production, highlighting the interplay of physiological factors in reproductive success. The findings underscore the importance of personalized supplementation strategies, which balance the benefits of iron intake with the potential risks of iron overload. Future studies should focus on determining the optimal iron dosage and its impact on ovarian reserves, endometrial receptivity, and embryonic development to further refine fertility treatment protocols.

Limitations

1- Confounding factors: the amount of iron in meals or supplements that were outside of the participants' medication basket could have an effect on the results obtained in this study.

2- Accuracy of data: Considering the conditions of IVF in the Nahal Center, many participants may not have told the complete truth in terms of addiction, underlying diseases, or consumption of any chemical or herbal drugs.

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