# What is the Impact of Iron Homeostasis Disruption on Ovulatory Function in Women of Reproductive Age?

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## BACKGROUND / SIGNIFICANCE

**Iron metabolism** is a fundamental biochemical process that is tightly regulated by the hepcidin–ferroportin axis, which controls intestinal iron absorption and tissue iron availability, to maintain metabolic and cellular homeostasis.[1] Beyond its role in hemoglobin and oxygen transport, iron is essential for mitochondrial energy production, DNA synthesis, and steroidogenesis, pathways which are essential for normal reproductive function. [2,3] However, iron deficiency remains one of the most prevalent micronutrient disorders worldwide, disproportionately affecting women of reproductive age.[1,4] These iron-dependent pathways also regulate follicular development, ovulation, and implantation, suggesting that disturbances in iron homeostasis may may influence ovarian function through altered cellular iron delivery and oxidative stress and adversely affect fertility. [5,6]

**Current animal studies show:**

- Mice fed a low-iron diet developed arrested estrous cycles and impaired follicular growth, both of which normalized following iron repletion. [7]
- Loss of the estrogen receptor in mouse ovaries led to iron accumulation and disrupted folliculogenesis, highlighting the hormonal regulation of ovarian iron metabolism.[8]
- Excessive iron cause irregular cycles, oxidative damage, and fewer corpora lutea in rodents, indicating impaired ovulation.[8]
- High iron exposure also suppressed granulosa cell proliferation via activation of the p38 MAPK–p53–p21 pathway suggesting iron induced cellular stress.[9,10]

These findings display a relationship in which both iron deficiency and overload can disrupt ovarian physiology. Animal data provides strong mechanistic evidence, the extent to which these processes occur in humans remains uncertain. Clarifying these pathways could identify iron status as a modifiable target for improving ovulatory function and fertility**. This review evaluates current evidence linking iron deficiency and iron overload with ovulatory function and fertility in women of reproductive age, emphasizing proposed biological mechanisms and the translational relevance of animal models.**

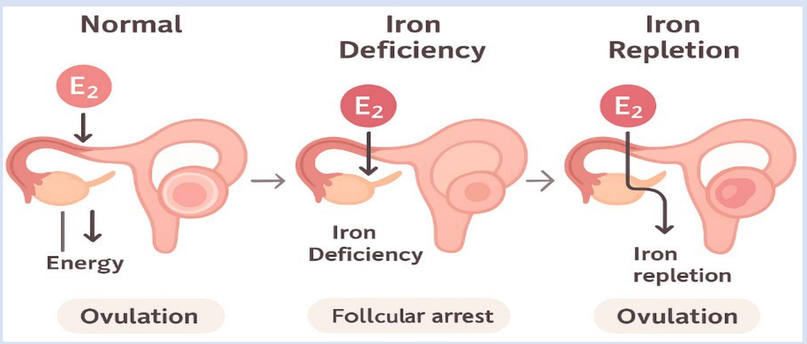
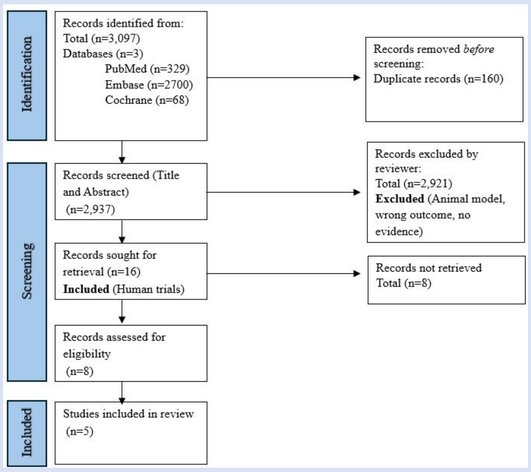



**Figure 1:** The figure above was generated using ChatGPT and describes the suggested mechanism behind fertility loss in rodents with low iron supplement as described by past studies to be implemented and connected to the human model.

## METHODS




**Search String** → (("Iron Deficiency"[Mesh] OR "iron deficiency" OR "low ferritin" OR "low serum iron" OR "iron depletion" OR "iron status" OR "anemia" OR "iron deficiency anemia" OR "IDA") AND ("Ovulation"[Mesh] OR "Ovulation Disorders"[Mesh] OR "anovulation" OR "ovulatory dysfunction" OR "ovulatory disorder" OR "menstrual cycle" OR "cycle regularity" OR "luteal phase defect" OR "folliculogenesis" OR "oocyte maturation" OR "reproductive function" OR "infertility" OR "subfertility") AND ("Women"[Mesh] OR "female" OR "women of reproductive age" OR "reproductive-aged women" OR "premenopausal women" OR "reproductive age"))

**Figure 2:** PRISMA Flow Diagram

Human studies published between 2000 and 2025 evaluating iron status and ovulatory function or fertility in women of reproductive age were identified using **PubMed, Embase,** and the **Cochrane Library**. Exclusion criteria included Animal or in vitro studies, non-reproductive populations, review articles, case reports, conference abstracts, duplicate studies, and studies not evaluating reproductive outcomes related to iron status.

## RESULTS

| Author / Year | Population / Model | Key Findings |
|---|---|---|
| **Tulenheimo-Silfvast (2025)** | 292 infertile women with ferritin ≤30 µg/L; before and after IV iron . | After iron repletion conception rates increased 65→77%, miscarriage rates decreased 28→13%, live birth rates increased 26→51% |
| **Liu et al. (2024)** | Mendelian randomization using European GWAS (11,442 infertility cases; 107,564 controls). | No clear causal link between ferritin and infertility, but a trend toward higher serum iron increasing infertility risk → suggests both low and high iron may affect ovulation. |
| **Holzer et al. (2023)** | 36 women with unexplained infertility vs. 36 fertile controls. | Low ferritin (< 30 µg/L) was strongly associated with unexplained infertility. |
| **Jiménez-Cardozo (2023)** | 582 U.S. women in fertility clinics; iron intake vs. ovarian reserve. | High iron supplements (≥65 mg/day) were associated with 32% lower anthral follicle count and ↑ FSH → Suggests excess iron may reduce ovarian reserve. |
| **Chavarro et al. (2006)** | 18,555 U.S. premenopausal women; 8 year follow up. | Iron supplement use decreased ovulatory infertility by 40% and higher non-heme iron intake lowered infertility risk. |

**Table 1:** The table above displays the results from the human studies on the effects of low iron in female reproductive cycle irregularity and fertility.

## DISCUSSION

Iron is a critical component to the survival of most organisms, however, when expressed at inappropriately low or high levels it can be detrimental.[11] while animal models provide compelling mechanistic evidence, translating these findings to humans remains challenging because ovarian iron regulation is influenced by additional genetic, hormonal, and environmental factors. **This review demonstrates evidence of a potential relationship between iron status and female reproductive health, where both iron deficiency and iron overload can impair fertility.**

- Multiple studies suggest that iron deficiency is linked with reduced conception and higher miscarriage rates.[12,13]
  - One study reported significantly lower serum ferritin concentrations in women with unexplained infertility, whereas another observed improved conception rates, reduced miscarriage, and increased live births following intravenous iron therapy.[12,13] ***These findings suggest that iron deficiency may contribute to ovulatory dysfunction and implantation failure, and that its correction can restore fertility potential.***
- One study observed that women taking ***high dose iron supplements*** had reduced antral follicle counts and elevated FSH levels, indicating possible ovarian aging or oxidative stress.[14]
- Another study further showed that moderate iron intake from supplements was associated with a 40% lower risk of ovulatory infertility, thus reinforcing the benefit of adequate, but not excessive, iron intake.[15]

***Overall, maintaining iron homeostasis within an optimal physiological range may support ovulation, implantation, and healthy pregnancy outcomes. However, prospective clinical trials are needed before routine fertility screening or treatment recommendations can be made.***

## FUTURE DIRECTIONS

**Iron balance emerges as a key component linking metabolism and reproduction. Defining how iron availability shapes ovarian and endometrial function will be essential for advancing fertility care. Future investigations, especially large randomized trials, should determine whether restoring iron homeostasis can transform infertility management from a reactive process to a preventive, nutrition based intervention.**

## REFERENCES