OPINION

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DOES COPPER INTRAUTERINE DEVICE PROMOTE ENDOMETRIOSIS?

Introduction

Since 2004, the French High Authority for Health has recommended copper intrauterine devices (IUDs) for nulliparous women [1]. However, this recommendation is questionable considering two well-established risk factors for endometriosis. First, heavy menstrual bleeding is a known contributor to endometriosis development [2,3], and copper IUDs are well-documented to increase menstrual blood loss by 50–100% compared to pre-insertion levels [4–7]. Second, nulliparity itself has increasingly been recognized as a vulnerability risk factor for endometriosis [2,3].

Beyond its mechanical action, the copper IUD involves the continuous release of copper ions, a heavy metal, directly into the uterine environment [8]. While copper is an essential trace element at physiological levels, it becomes toxic in excess. The toxicity of heavy metals, including copper, has been extensively documented, with growing evidence implicating them in endocrine disruption and inflammation [9,10]. However, its local concentration in IUDs is rarely disclosed to users, even though dose plays a critical role in pharmacological safety.

In the current context of growing disenchantment with female medical contraception [11], the use of copper IUDs raises renewed concern, which we explore through a narrative literature review. This narrative review aims to investigate a set of rarely examined hypotheses and to highlight potential blind spots in gynecological research related to the copper IUD. While many of the ideas presented remain speculative, they are discussed here to encourage further research on the topic.

Method

This work draws on both foundational studies and a non-systematic literature search (2020–2025), conducted via PubMed, Google Scholar, and Google, to identify recent developments and relevant updates. The following keywords were used to identify relevant studies: copper, copper in farming, copper intrauterine device and endometriosis, copper endocrine disruption, endocrine disruptor, metalloestrogen, cuproptosis, endometriosis and endocrine disruptors, heavy metals in gynecological diseases, heavy metals and ovarian function.

Results and discussion

Copper's environmental impact

Copper has been used for nearly ten thousand years in many fields, including craftsmanship, agriculture, industry, and hygiene. In farming, it has been approved as a pesticide, particularly in the form of Bordeaux mixture, to treat diseases like downy mildew. However, it is also classified as a non-biodegradable heavy metal [12]. Due to its persistence, copper accumulates in air, soil, and water, where it contributes to biodiversity loss and degradation of soil quality. In response to these risks, the European Food Safety Authority has issued warnings regarding its environmental impact. Consequently, the European Union has implemented restrictions on copper use in agriculture and promotes the search for sustainable alternatives [13]. While copper's toxicity to environmental organisms is well documented, much less is known about its long-term biological effects when used internally, such as in copper IUDs. This observation raises the question of whether its accumulation and reactivity within the human body, particularly in sensitive systems such as the female reproductive tract, deserve further investigation.

Copper as a metalloestrogen: implications for endocrine disruption

Metalloestrogens are metal ions that can bind to steroid hormone receptors and mimic or disrupt their signaling, particularly affecting progesterone receptors [14,15]. Copper, officially classified as a metalloestrogen in 2006, is among several metals in this category, including cadmium, lead, and mercury [16]. Although this concept has existed for over two decades [17-19], it remains underrecognized in clinical practice.

Through their interaction with estrogen receptors, metalloestrogens act as endocrine disruptors, mimicking or interfering with hormonal signaling pathways [20]. This endocrine disruption is now recognized as a central mechanism in the pathophysiology of estrogen-dependent conditions such as endometriosis, breast and endometrial cancer [21,22]. The concept of endocrine disruption, formalized in the early 1990s, refers to substances that interfere with hormonal signaling at very low doses, affecting reproduction, development, and homeostasis [20–22]. Endocrine disruptors include many synthetic chemicals

such as pesticides and plastics. Copper, through its estrogenic activity, may contribute to such disruptions, particularly in hormone-sensitive tissues.

According to the U.S. Environmental Protection Agency, endocrine disruptors can impair normal endocrine functions and may lead to reproductive disorders (i.e. impaired egg or sperm production) and developmental anomalies (i.e. disrupted fetal growth) in both humans and wildlife [23]. Unlike other toxic agents, endocrine disruptors are known for their delayed effects that can even extend across generations [24]. Given the hormonal sensitivity of reproductive tissues, certain organs may be particularly vulnerable to these disruptions. The endometrium, for instance, is a key target tissue for endocrine disruptors due to its hormone sensitivity, which is a contributing factor to its cyclical development [25]. Vulnerability is particularly high during fetal development and the neonatal period, when endocrine systems are especially sensitive [26].

While copper is essential to human physiology in trace amounts, its toxicity at supra-physiological concentrations is well established across multiple biological systems [27-29]. It serves as a cofactor for numerous enzymes, including those involved in reproductive hormone synthesis. However, when copper accumulates in tissues or circulates at elevated levels, it can become highly reactive and harmful. This is particularly true for copper nanoparticles. which are increasingly used in medical applications such as aseptic therapies yet have raised significant toxicological concerns due to their capacity to induce oxidative stress in mammalian cells [30]. The redox activity of copper is central to its cytotoxicity, as it can overwhelm cellular antioxidant defenses, leading to oxidative damage and DNA instability [31]. In the reproductive system, this manifests notably through the disruption of cytochrome P450 enzymes involved in steroidogenesis, with excess copper altering their expression via oxidative or transcriptional mechanisms [32]. Experimental studies have also shown that copper exposure reduces granulosa cell viability and induces apoptosis, thereby compromising follicular development and ovarian function [33].

These adverse effects have been observed in various organisms, particularly aquatic species [34-38], but also in humans. For example, genotoxic effects have been documented in copper smelter workers, illustrating the risks of chronic exposure [39]. Given that copper nanoparticles can cross tissue barriers [40], it seems unlikely that the endometrium and adjacent structures provide complete protection from their diffusion and accumulation. Although further research is needed to establish direct links between copper exposure and endometriosis, these findings support the need to re-examine the biological safety of prolonged and localized copper exposure in IUDs.

Cuproptosis, angiogenesis due to copper

Cuproptosis is a recently identified form of copper-dependent cell death, triggered by intracellular copper overload [41]. While this mechanism plays a physiological role in tissue homeostasis, its dysregulation has been implicated in various pathological conditions. At the cellular level, excess copper disrupts mitochondrial function, leading to apoptosis and broader disturbances in cell viability [42]. Although the study of cuproptosis is still in its early stages, emerging hypotheses suggest it may play a role in gynecological diseases, though direct evidence remains scarce [43]. Additionally, copper has also been shown to promote cell proliferation and angiogenesis processes commonly associated with tumor development [44,45]. However, to date, there is no conclusive evidence that copper IUD directly induce carcinogenesis.

While copper's cytotoxic action is deliberately harnessed in intrauterine contraception by targeting spermatozoa, its effects on surrounding tissues, particularly the endometrium exposed to sustained local copper overload, warrant closer examination. These biological mechanisms provide essential context for re-evaluating the use of copper in IUDs.

The use of copper in IUDs

Copper IUDs are widely promoted as non-hormonal contraceptive methods, reinforcing the common assumption that they act exclusively through a local mechanical effect, namely, the prevention of fertilization, without broader physiological implications. This perception of neutrality regarding endocrine function has contributed significantly to their popularity. In contrast, hormonal contraceptives often elicit greater public concern, largely due to their explicit interaction with the endocrine system and their direct influence on female reproductive health. Interestingly, such apprehensions are rarely expressed in relation to non-sex hormone replacement therapies (i.e. thyroid or adrenal insufficiency), or even to agents like vitamin D, which functions as a steroid hormone. Yet copper, while classified as a trace element essential to human physiology, possesses reactive properties that enable it to interact continuously with bodily tissues. Its biological effects vary according to dose, duration, and route of exposure. The discrepancy between the perception of copper IUDs and their potential systemic effects suggests that public attitudes toward hormonal contraception may be influenced less by pharmacological properties than by cultural narratives surrounding reproduction and sexuality [11].

Technologically, copper IUDs have evolved through three generations, each designed to enhance efficacy and longevity. A key advancement has been the increase in the active copper surface area, from 200 mm^2 in earlier models to 375 or 380 mm^2 in current devices. Today, third-generation IUDs with a surface area of 375 or 380 mm^2 are the most prescribed [46]. The most used copper IUD contains 180 mg of copper [47], which is two to three times the total amount of copper normally present in the human body. Despite the substantial amount of copper present in the device and its prolonged intrauterine use, the scientific literature on copper blood levels in IUD users remains extremely limited. To date, only one small-scale study has reported that mean blood copper levels in users of the T380A IUD were significantly higher than in non-users and even exceeded the upper limit of the normal physiological range [48]. A more recent review found the available data inconclusive [49]. Although current evidence remains limited, the potential for systemic copper accumulation in IUD users, combined with the chronic and localized nature of intrauterine exposure, calls for a more nuanced understanding of copper's bioactivity and a reevaluation of its presumed inertness.

While estrogen receptors have been identified in the gastrointestinal tract [50], given that copper can bind to these receptors, the endometrium may not be optimally equipped to eliminate copper in the same way. Indeed, findings indicate that copper may persist in the uterus long after IUD removal [51]. This localized retention raises further questions about the systemic implications of copper exposure, particularly given that standard assessments may overlook biologically active forms. Studies reporting stable serum copper levels in IUD users generally assess total copper, not the potentially toxic free form [49,52]. It remains unclear to what extent copper ions released locally can enter the systemic circulation or accumulate in distant tissues. The long-term impact of localized and chronic copper exposure from IUDs, particularly in hormonally sensitive organs such as the endometrium, remains underexplored and warrants further investigation.

Endometriosis

Endometriosis is currently defined as a systemic, estrogen-dependent, inflammatory disease, characterized by the symptomatic or asymptomatic presence of active endometrium-like tissue located outside the uterine cavity. According to the World Health Organization, it affects approximately 190 million women and girls of reproductive age worldwide.

Although endometriosis has likely existed for centuries, it remained underdiagnosed and poorly understood until the 20th century, largely due to social invisibility and gendered assumptions about pelvic pain and infertility. Early descriptions of lesions date back to the 18 and 20th century with Rokitansky and Cullen [53,54]. Interestingly, its medical recognition coincided with expanding industrialization. This historical coincidence prompts reflection: could the first clinical observations of endometriosis have coincided with a growing environmental burden, including early, unrecognized endocrine disruptors? While speculative, this question is increasingly relevant, as endocrine disruptors are now among the suspected contributors to endometriosis's pathogenesis [55].

These concerns are further illustrated by the clinical case that inspired this article: a 23-year-old woman, with no history of gynecological or obstetric conditions, nor previous hormonal treatment, who developed a unilateral endometrioma within a year of copper IUD insertion. She reported no prior symptoms suggestive of endometriosis, and transvaginal ultrasound imaging performed at the time of IUD insertion was normal. While this observation cannot establish causality and may reflect a previously undiagnosed condition, it highlights the need for further investigation into possible iatrogenic contributors to endometriosis, particularly considering copper's emerging biological effects.

One of the earliest and most influential explanatory models of endometriosis is John A. Sampson's implantation theory, which remains referenced today. According to this hypothesis, retrograde menstruation leads to ectopic endometrial-like tissue which raised a fundamental question that remains relevant today: is the refluxed tissue viable or simply debris? [56]. His theory was foundational but insufficient to explain systemic manifestations of endometriosis. The recognition of endometriosis as a systemic disorder is relatively recent and remains debated. Yet, growing evidence supports this broader view. Several studies have shown that individuals with endometriosis exhibit not only gynecological symptoms, but also a range of metabolic, neurological, and immunological comorbidities [57,58]. As one research emphasized: *"Endometriosis is now considered a systemic disease rather than a condition predominantly affecting the pelvis. It affects metabolism in the liver and adipose tissue, leads to systemic inflammation, and alters gene expression in the brain, contributing to pain sensitization and mood disorders"* [59]. Interestingly, Sampson also hypothesized the possibility of venous dissemination, whereby endometrial tissue could enter the bloodstream and implant in distant organs [60]. Current models highlight multifactorial origins involving stem cells, immune dysregulation, and genetic predispositions, supported by advances in immunology [61-63]. The disease is now widely described as a chronic inflammatory condition involving both innate and adaptive immune responses.

In addition to immune dysfunction, angiogenesis has also been identified as a contributing mechanism in the pathophysiology of endometriosis. *"Angiogenesis describes the process of blood vessel formation, which is an essential requirement for human growth and development. When the complex interplay between pro- and antiangiogenic mediators falls out of balance, angiogenesis can quickly become harmful"* [64]. To date, ferroptosis, a form of regulated cell death triggered by intracellular iron accumulation, may be implicated in angiogenesis [65]. A recent study has highlighted ferroptosis as a process that may facilitate endometriosis lesions progression [66]. According to Li and colleagues, stromal cells undergoing ferroptosis can secrete pro-angiogenic cytokines through paracrine signaling, which may enhance benign cell proliferation and accelerate the progression of endometriosis [67].

Recent findings suggest copper, like iron, may promote angiogenesis and influence gene expression relevant to endometriosis, yet mechanisms remain incompletely understood. In a recent study, Onuma and colleagues reported a correlation between the progression of ovarian peritoneal cancer lesions and copper-induced angiogenesis [68]. Another study suggests that copper exposure may alter the gene expression patterns involved in decidualization, including genes associated with endometriosis, infertility, and other gynecological conditions [69]. Given that heavy metals tend to accumulate in biological tissues, their long-term presence could exacerbate the chronic nature of the disease. Despite these advances, the precise pathophysiological mechanisms underlying endometriosis remain incompletely understood, and several competing hypotheses continue to coexist [70].

Copper and the endometrium: a pathognomonic marker of gender inequality in healthcare

The history of female contraception illustrates how structural gender bias in medical research can result in long-term harm. The underrepresentation of women in pharmacological studies, along with the neglect of sex-specific health risks, has led to delayed recognition of adverse effects and to disproportionate toxic outcomes in women [71]. Awareness of these biases grew in the 1990s, particularly following evidence that

women's symptoms of ischemic heart disease were frequently misdiagnosed or overlooked [72,73]. A striking example is diethylstilbestrol (DES), a synthetic estrogen prescribed between the 1940s and 1970s to prevent miscarriages and pregnancy complications. Decades later, DES was officially recognized as an endocrine disruptor, linked to rare cancers, genital malformations, infertility, and pregnancy complications in the offspring of exposed women [74-76]. Similar effects have been reported with other endocrine-disrupting chemicals such as bisphenol A, especially regarding increased breast cancer risk following fetal exposure [77,78]. These cases highlight both the latency of scientific accountability in women's health and the cumulative risks of insufficiently regulated chemical exposure. The copper IUD may represent a contemporary parallel. Often described as a non-hormonal contraceptive, it may still interfere with hormonal signaling and contribute to estrogen-dependent conditions such as endometriosis.

This scientific gap is not neutral. It raises important questions about how research priorities are defined and whose health is considered a priority. Copper's toxic effects on sperm are well known and form part of the device's contraceptive action. However, its harmful impact on ovarian function remains largely overlooked. Although copper's oxidative and cytotoxic effects on reproductive tissues are documented, such as apoptosis in granulosa cells [33,79] and disruption of cytochrome P450 enzymes involved in hormone synthesis [32], these mechanisms are rarely studied in the context of IUD use.

In addition, the copper IUD has been linked to ethically problematic practices. In several countries of the Global South, it has been used without informed consent as part of population control programs [80]. This adds a geopolitical and gendered dimension to the issue, reinforcing the lack of transparency and oversight in its application. The limited scientific exploration of copper IUD adverse effects on the endometrium raises questions about whether the response would differ if similar exposure occurred in male reproductive systems, highlighting a possible asymmetry in research focus.

Conclusion: what could have led to heavy metals being placed in women's wombs?

This article aims primarily to raise awareness about the under-investigated biological effects of prolonged exposure to copper IUDs. Despite increasing evidence of copper's toxicity at supra-physiological levels, its potential to accumulate in the endometrium [81], and its designation as both a metalloestrogen and a trigger of cuproptosis [43], the biological effects of prolonged intrauterine exposure remain poorly understood and largely under-investigated.

Originally introduced as a tool of reproductive autonomy in industrialized countries, the copper IUD has also been deployed as an instrument of population control in low-income settings, often without informed consent. This dual history highlights the contradiction between reproductive autonomy and systemic oversight, especially in contexts where fertility regulation is not accompanied by educational or socio-political empowerment. These contradictions are compounded by a broader societal failure to grasp the full impact of industrialization and endocrine-disrupting chemicals on human health and reproductive systems.

Deep-seated gender inequalities in medical research and healthcare delivery [82,83] have further delayed recognition of harm. Endometriosis, for instance, has long been underdiagnosed, and symptoms reported by copper IUD users, such as heavy bleeding and pelvic pain, are frequently minimized or dismissed as benign. Yet two plausible biological mechanisms now point to the copper IUD as a potential contributor to iatrogenic endometriosis: its tendency to increase menstrual blood flow and its capacity to disrupt hormonal signaling [84]. Moreover, emerging data suggest that copper overload may play a role in other gynecological conditions, including premature ovarian insufficiency [85] and broader reproductive dysfunctions [86].

Therapeutic alternatives exist, notably newer hormonal IUDs. Patients should be fully informed of the risks and benefits of each option. Further independent studies are urgently needed to investigate the relationship between copper IUDs and gynecological disease, particularly endometriosis. That such research has remained marginal more than fifty years after copper IUDs entered the market, and more than thirty years after the identification of endocrine-disrupting chemicals, is a stark reminder of persistent gender bias in science [87]. While our findings do not establish causality between copper IUD use and subsequent development of endometriosis, they underscore the urgent need for a prospective European study following nulliparous individuals without prior gynecological history who are prescribed copper IUDs, compared to controls. Closing the knowledge gap on copper IUDs is not only a matter of scientific integrity, but also a matter of long-standing underestimation of gender-specific risks in medicine.

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