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Revolutionizing Women's health: the quest for materials for next-generation, non-hormonal intrauterine devices

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With over 200 million users worldwide, copper intrauterine devices (Cu-IUDs) are the world's most popular, non-hormonal, long-acting, and reversible contraception method. Cu-IUDs cause uncomfortable side effects such as longer and heavier menstruation and cramping, all of which persist for the duration of use and often lead to early removal. With the rise in concern about potential physical and psychological side effects from hormonal contraceptive use, an improvement in non-hormonal contraceptive options is needed to alleviate discomforting side effects and inhibit costs. This perspective article provides an overview of the current state of non-hormonal IUDs and experimental factors to consider when developing new materials that have potential as alternative contraceptives, including copper alloys, zinc, iron, and passive metals. It also explores the sustainability and socioeconomic impact of advancing non-hormonal contraceptive options and considers international policy, cultural factors, and costs that must be considered when developing these options. Overall, the article highlights the interdisciplinary nature of this field, the complexities involved in creating effective non-hormonal contraceptives, and the need for innovation and equity in contraceptive care.

Intrauterine devices

Approximately 1 billion individuals with internal reproductive organs utilize some form of contraception[1]. The right and ability to control one's reproductive health helps individuals plan their lives. The growing use of contraceptive methods has also contributed to reducing infant and maternal mortality rates[2], and higher education and economic prospects for users[3,4].

Intrauterine devices (IUDs) are the most popular form of long-acting and reversible contraceptive methods[1]. IUDs are used by 17% of women, making them the third most common form of birth control worldwide, just behind the male condom (21%) and female sterilization (24%)[5]. Although IUDs have taken many shapes throughout history[5], current IUDs are T-shaped to secure the device within the uterus and prevent it from moving out of place (Fig. 1a). There are two types of IUDs: hormonal and non-hormonal.

The hormonal IUD consists of a capsule containing progestin levonorgestrel (LNG), a synthetic steroid hormone. The LNG is released into the uterus and suppresses the endometrium's growth throughout the ovulation cycle, promotes the formation of a more viscous cervical mucus, and degrades the motility of sperm cells[6]. The hormonal IUD is an effective contraceptive, however, users frequently endure multiple physical and psychological side effects from its usage, including increased risks of dysmenorrhea, irregular bleeding, acne, breast tenderness, anxiety, and depression[7,8]. In a cross-sectional Swedish study ($n = 212$, users aged 16–50 years), 40% of users expressed concerns about using *hormonal*

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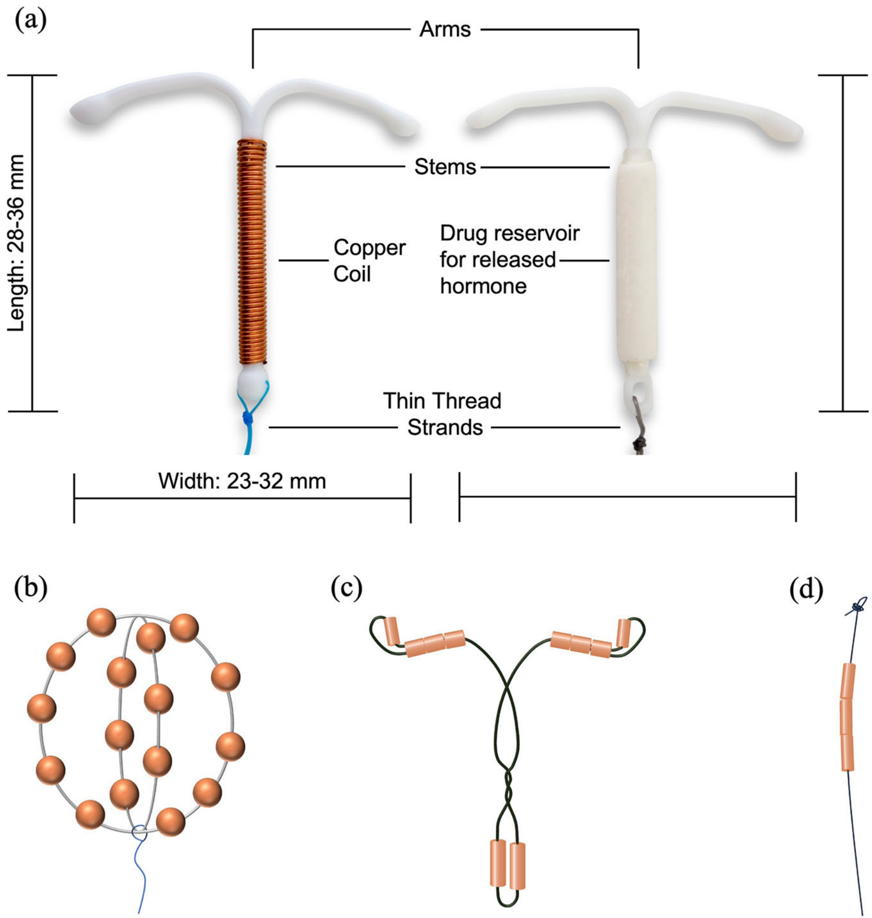

Fig. 1 | Schematics of IUDs. a Images of the non-hormonal Cu-IUD (left) and hormonal IUD (right). Obtained from iStock.com/lalocraclo. Illustrations of flexible Cu-based IUDs **b** intrauterine ball (IUB)[26], **c** Veracept[24], and **d** Gynefix[68].

contraceptives, with the greatest fears stemming from potential side effects[9]. Another European study (n = 1391, users aged 18–45 years) found that 58% of previous users of hormonal contraception methods discontinued usage due to past adverse physical and psychological effects[10]. Some individuals reported that medical conditions (i.e., LNG allergy, history of blood clots, vulnerability to infection)[11,12] or personal beliefs/concerns[13] preclude them from using hormonal contraceptives. Thus, *non-hormonal* contraceptive options, like the Cu-IUD, should be available.

The Cu-IUD is a coiled Cu wire wrapped around the length of a polyethylene (PE) plastic backbone (Fig. 1). Introduced by Tatum and Zipper in 1969, the Cu-IUD was one of the first forms of effective and passive long-term birth control[14]. Cu was chosen as it is a large component of the silver alloy used in the historical silver ring IUD, and possibly due to its anti-microbial properties[15]. The exact contraceptive mechanism of the Cu-IUD remains unknown due to the difficulties in ethically and practically extrapolating findings from animal and human studies. The proposed mechanism of action involves the combination of a local sterile inflammatory reaction in response to the insertion of a foreign object within the uterine cavity: the presence of cupric ions (Cu^{2+}) produced due to Cu corrosion (oxidation) is toxic to embryos and impedes spermatozoa viability[16]. The Cu-IUD also acts as an emergency contraceptive (EC), where it reduces the risk of pregnancy by over 99% and can be used up to 5 days after unprotected intercourse[17]. Cu-IUDs are a safe, reversible, highly effective (>99.2%), and long-lasting (>5 years) non-hormonal strategy for preventing pregnancy[18].

Motivation for new non-hormonal options

The current Cu-IUD was developed in 1984 and has remained the same since commercialization in 1988[19]. Despite high efficacy, Cu-IUDs cause uncomfortable side effects for 67% of users, including longer and heavier menstruation, increased spotting, and increased dysmenorrhea (n = 2043, users aged 18–40 years)[20]. Although the severity of side effects decreases over the first year of use[18], they can persist and are the main reason for premature device removal[21]. Despite the persistent side effects, no long-term reversible non-hormonal alternatives to Cu-based IUDs exist. There is a need to develop an alternative, nonhormonal contraception with similar efficacy and minimal side effects.

Searching for alternative non-hormonal IUDs

In recent decades, understanding of the problems with Cu-IUDs has improved. There are two leading hypotheses about the causes of adverse side effects: (1) the physical rigidity of Cu-IUDs that leads to irritation[22], and (2) the presence of Cu^{2+} that cause an inflammatory response in the uterine lining[23]. This understanding has laid the foundation for the research activities outlined in this section.

Altering the physical shape of Cu-IUDs

Ultrasound studies suggest that the uterine width in nulliparous individuals is frequently narrower than the width of extant IUDs[22]. To alleviate discomfort, recent innovation has focused on altering the physical shape of the device[24–26]. New designs include a flexible T-shaped frame with low-dose Cu (VeraCept)[24], spherical and flexible Cu-IUDs (named "IUBs" for "intrauterine ball")[26], and frameless devices that anchor to the top of the uterine cavity (GyneFix) (Fig. 1)[25]. A drop in side effects was reported for the flexible VeraCept Cu-IUD, likely due to its smaller Cu surface area, generating a smaller quantity of Cu^{2+} ions present[24], which resulted in reduced inflammatory reaction within the uterine cavity.

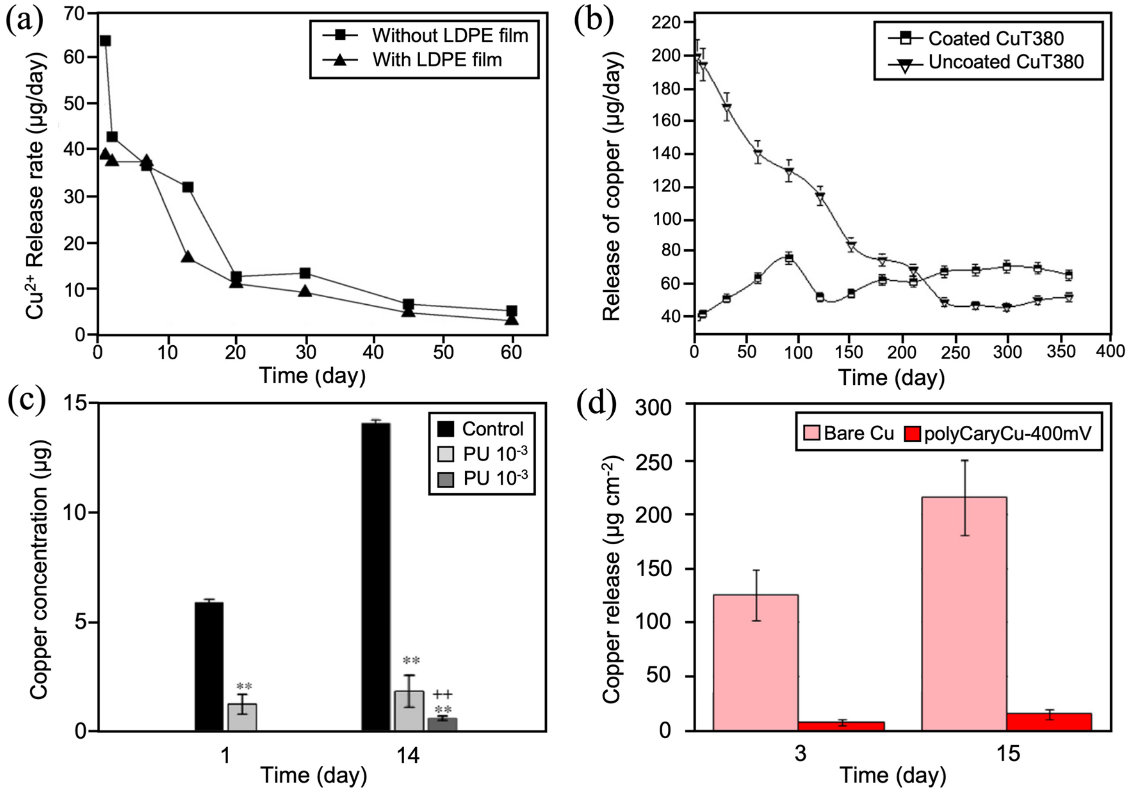

Fig. 2 | Copper release rates from various studies. a Release rate of Cu^{2+} as a function of time for samples with and without LDPE films. Reprinted from Effects of LDPE film on the properties of Cu/LDPE composites for intrauterine contraceptive device, 62 (26), Z. Yang, C. Xie, S. Cai, X. Xia, 3 pgs., Copyright (2008), with permission from Elsevier. **b** Comparison of Cu^{2+} released from PLGA-coated Cu and uncoated Cu (mean±S.D., $n = 6$). Reprinted from Controlled release of copper from an intrauterine device using a biodegradable polymer, 92 (6), R. Ramakrishnan, A. S. Aprem, 4 pgs, Copyright (2015), with permission from Elsevier. **c** Dissolution of Cu wire with and without a purine coating. Reprinted from Reduction of the "burst release" of copper ions from copper-based intrauterine devices by organic inhibitors, 85 (1), F. Alvarez, P. L. Schilardi, M. Fernandez Lorenzo de Mele, 8 pgs, Copyright (2012), with permission from Elsevier. **d** Cu^{2+} release from samples with and without a polymerized carvacrol coating after immersion in simulated uterine fluid (37 °C). $^{**}p \leq 0.01$. Reprinted from Eradication of burst release of copper ions from copper-bearing IUDs by a phytocompound-based electropolymeric coating, 252, M. Bertuola, C. A. Grillo, M. Fernandez Lorenzo de Mele, 4 pgs, Copyright (2019), with permission from Elsevier.

Inhibiting the "Burst Effect" of Cu-based IUDs

Another proposed cause for the side effects of Cu-IUDs is the high concentrations of Cu^{2+} that cause an inflammatory response in the uterine lining[23]. When first inserted, the Cu-IUD corrodes at a faster rate due to the equilibration with the uterine environment[27]. This "burst effect" of cupric ions can result in dissolution rates up to 296 μg/day and has been suggested to be responsible for excessive bleeding and pain within the first two months of use[28]. As the metal-solution interface reaches a steady state, the Cu^{2+} concentration decreases over the device's life span, with an average dissolution rate of 43.8 μg/day for 21–41 months of use[23].

Many metal ions, including Cu^{2+}, can generate reactive oxygen species (ROS), damaging cellular components and lead to inflammation[29,30]. In the mouse endometrium, it has been previously described that the implantation of a Cu-IUD induces inflammatory cytokines like tumor necrosis factor α (TNF-α) and interleukin-1β (IL-1β)[31]. In human endometrial glandular cells, TNF-α expression, and thus inflammatory response by extension, displayed a dose-dependent effect to increasing concentrations of cupric ions in vitro[31]. Additionally, a study by Sharma et al. reported elevated levels of inflammatory cytokines (TNF-α, IL-6, IL-1α, and IL-1β) at the cervicovaginal area 4-weeks after implantation of a Cu-IUD[32]. It is evident that an inflammatory response in internal reproductive organs is typical in the presence of Cu-IUDs, and is a probable cause for the adverse side effects users endure. However, it is noted that more than one mechanism may be at play and may be more pronounced depending on the individual.

To inhibit the burst effect at the beginning of Cu-IUD use, thin films and alloying strategies have been proposed as outlined in the following sections.

The use of polymer films. Polymer coatings and composites have been proposed to reduce the burst effect within the first month of implantation. Low-density polyethylene (LDPE) and Cu micro composite materials were first proposed to control the release of Cu^{2+} ions from the device[33]. The metal ion release rate of the composites coated with an additional LDPE film was lower for a short period (1-2 days) (Fig. 2a). To extend the inhibition effect, efforts focused on using other polymer coatings, including poly(DL-lattice-co-glycolide) (PLGA) to decrease the initial burst effect of cupric ions[34]. Utilizing a film wrapping technique, the Cu was successfully coated with the PLGA and tested using immersion studies in simulated uterine fluid (SUF), an electrolyte that emulates the chemical composition of the uterus[35], for various time intervals (see Fig. 2b). The added polymer layer decreased initial Cu concentrations when Cu corrosion rates were the highest. It has been noted that the solvents used in creating such PLGA films are not eco-friendly, and alternatives to PLGA coatings include films made of purine and thiourea. A dip-coating method showed that purine and thiourea coatings on Cu successfully reduced Cu's corrosion rate for the first 14 days of immersion (Fig. 2c). Another polymeric coating was electrodeposited onto Cu surfaces[36]. The phytocompound, carvacrol, showed decreased Cu^{2+} concentration when samples were immersed in SUF for 14 days (Fig. 2d).

While promising, the effect of coating Cu-IUDs with polymers has resulted in reduced corrosion over timeframes significantly shorter than the burst effect period linked to undesirable side effects. This is likely due to dissolution of the polymer coatings under physiological conditions, where longer experimental validation studies are required

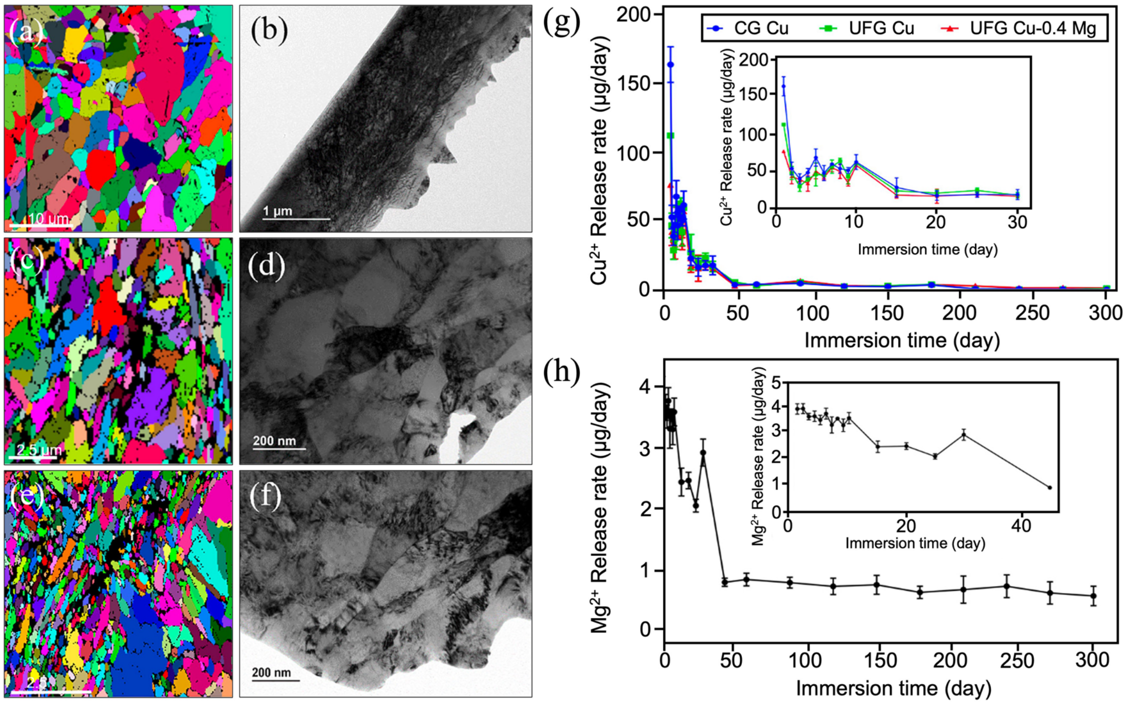

Fig. 3 | Effect of microstructure and composition on release rate. The microstructures of the Cu materials characterized using electron back-scattered diffraction and transmission electron microscopy: coarse grained (CG) Cu (**a**, **b**), ultra-fine grained (UFG) Cu (**c**, **d**), and UFG Cu-Mg (**e**, **f**). Long-term Cu^{2+} release rate **g** of CG Cu, UFG Cu and UFG Cu-0.4Mg and Mg^{2+} release rate of UFG Cu-0.4Mg **h** immersed in simulated uterine fluid at 37 °C up to 300 days. Reprinted from Effective easing of the side effects of copper intrauterine devices using ultra-fine-grained Cu-0.4Mg alloy, Q. Fan, G et al., 128, 7 pgs, Copyright (2021), with permission from Elsevier.

and the efficacy of a coated device with a lower Cu^{2+} concentration are investigated.

Development of Cu-based alloys. An alternative strategy for minimizing the burst effect involves modifying the metal by composition and/or microstructure. Such developments take advantage of understanding the corrosion mechanisms of different metals. The development of ultra-fine-grained (UFG) Cu reduced the high release of Cu^{2+} due to the high density of grain boundaries that led to uniform corrosion and distribution of protective corrosion products upon immersion[37,38]. Another study proposed using aluminum to form a protective passive film on a copper-zinc-aluminum (Cu–Zn–Al) alloy to inhibit the cathodic reduction of oxygen, thus decreasing the alloy's corrosion rate in SUF[39]. Both studies utilized a passive (protective) corrosion film to decrease metal ion diffusion into the environment[40].

Other methods to curb the Cu corrosion rate include preferential dissolution of more active metals. For instance, an ultra-fine-grained (UFG) copper-magnesium (Cu–Mg) alloy (0.4 wt% Mg) was investigated as a potential IUD material to attempt to decrease the corrosion rate of Cu and avoid unwanted side-effects (Fig. 3)[41]. The galvanically coupled Mg in the alloy metal matrix acted as a sacrificial anode and oxidized, while neighbouring Cu was cathodic and was protected from oxidizing. Mg was justified as it is biocompatible and anti-inflammatory[42]. Furthermore, the hydrogen evolution from Mg corrosion resulted in a porous corrosion layer, which was considered beneficial for long-term Cu^{2+} release[41]. In rats, the Cu-Mg alloy demonstrated better histocompatibility with less damage to uterine tissues caused by moderate inflammatory reactions compared to pure Cu implants[41]. Moreover, fertility rates for rats with Cu–Mg alloy material were 0%, indicating that adding Mg did not compromise the contraceptive effectiveness of the Cu material[41]. Nonetheless, such a device results in a low Cu^{2+} concentration and verification of the long-term contraceptive efficiency of the material is still required.

Another Cu alloy alternative proposed to inhibit the burst effect are copper-zinc (Cu–Zn) alloys[43]. The initial release rate of Cu^{2+} ions in the Cu-Zn alloy group was significantly lower than the pure Cu (Fig. 4a). As a result, human endometrial epithelial and stromal cells showed less in vitro cytotoxicity[43]. Moreover, during in vivo implant experiments, the Cu-Zn alloy exhibited improved short and long-term biocompatibility in uterine tissue (Fig. 4b). Like pure Cu, the contraceptive efficacy of the Cu-Zn device remained high. Thus, it could be a suitable candidate material for IUDs[43].

Despite these innovations, it is unclear whether the reduced corrosion rate reduces side effects. Since side effect severity tends to decrease within the first year of use, the Cu release rate should improve users' experience, but further investigation is required. The alteration of the concentration of Cu^{2+} in the uterus during initial insertion through material modifications may influence the device's efficacy both as a long-term and emergency contraceptive. Quantitative studies on the amount of metal ions required for effective birth control without inducing inflammatory responses are required to inform the next generation of IUDs.

Innovation in materials science: exploring other metals and coating strategies for new non-hormonal IUDs

Due to the inflammatory response caused by Cu^{2+}, alternative metals as potential IUD replacements are outlined in this section. Pure zinc (Zn) is a viable option as a non-hormonal IUD alternative. Shankie-Williams et al. compared the efficacies of Cu and Zn IUDs in vivo and identified that both metals were equally effective in inhibiting embryo implantations in rats[44]. Their analysis of uterine tissues revealed metaplasia for both metals; however, the severity of the Zn-induced effect was milder than the Cu-induced effect, suggesting that an Zn-IUD may be a more comfortable alternative[44]. It is noted that this study only explored three months of use; thus, the fast corrosion rate of Zn may limit this metal's realistic use as a long-acting contraceptive[44].

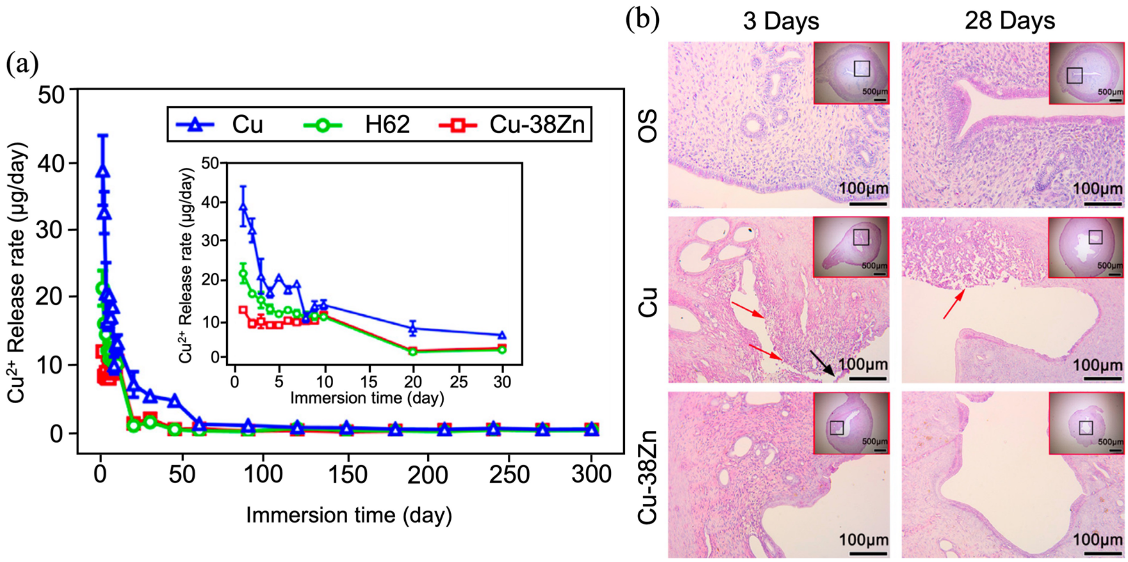

Fig. 4 | Copper release rates and its impact on rat endometrium. a Cu^{2+} release rate, determined by inductively coupled plasma atomic emission spectrometry, of pure Cu, H62 (62.5 wt% Cu and Zn balance), Cu-38 Zn alloys (38.5 wt% Zn, Cu balance) immersed in simulated uterine fluid (no Albumin) at 37 °C for 300 days. **b** Histopathology of endometrium in Sprague-Dawley rat after inserting pure Cu, H62 and Cu-38 Zn for 3 and 28 days. The black arrow shows where the uterine cavity exudates. The observed bare endometrial lamina propria is indicated by red arrows. Reprinted from Feasibility evaluation of a Cu-38 Zn alloy for intrauterine devices: In vitro and in vivo studies, K. Wang et al., 138, 14 pgs, Copyright (2022), with permission from Elsevier.

Iron (Fe) is a strong candidate to serve as an alternative to Cu because among the many metal ions that are successful at impeding spermatozoa motility and viability, Fe is more effective than Cu while being nontoxic, soluble, sustainable, and not eliciting inflammatory responses[45–47]. It has been widely documented that Fe levels correlate with male infertility, as an imbalance in endogenous Fe levels induces oxidative damage that diminishes sperm quality[48]. Similarly, brief exposure of isolated rat spermatozoa to Fe in vitro elevated biomarkers for oxidative DNA damage[49]. This demonstrates that exposure to exogenous Fe is also unfavourable for sperm survival, suggesting a high potential for using ferrous metals for contraception. Furthermore, stainless steel rings (SSR) were popular in China as a contraceptive method, suggesting that ferrous metals may be safe IUD materials[50]. Unfortunately, SSRs were less effective than Cu-IUDs in preventing pregnancy (90% efficiency rate) due to stainless steel's corrosion resistance. Thus, they were discontinued in 1994. Nevertheless, no differences in side effects were observed between SSR users and non-users, indicating that ferrous metals may alleviate discomfort that is common in Cu-IUD users[50]. However, like Zn, a downside of Fe is a higher corrosion rate than Cu which may present challenges in utilizing pure Fe as a long-term contraceptive option.

Other new IUD materials may involve Fe and Zn alloys designed to lower corrosion rates. Passive (i.e., low corrosion rate) metals, such as titanium (Ti) and aluminum (Al), could also be explored as potential IUD materials, as Ti has been used as bone and dental implants[51]. Further investigation of their contraceptive abilities would be necessary to initiate such exploration, as their corrosion rates are very low due to the protective oxide layer spontaneously formed.

Utilizing a barrier coating on alternative metals to inhibit the burst effect of Cu, could afford control over corrosion rate and alleviate such drawbacks. The ever-growing number of biocompatible polymers available creates endless opportunities for the specific roles that polymers can play in addressing the rapid corrosion of metal IUDs. Here, we propose three strategies for future IUD development to improve corrosion inhibition for metal IUDs. (1) Assessment of the influence of polymer porosity and coating density on the release rate of metal ions; (2) Creation of semi-permanent and potentially biodegradable polymer coatings covalently bound to the metal to prevent polymer dissolution; (3) The combination of surface passivation and antibacterial characteristics offered by biocompatible polyelectrolytes.

Critical factors in developing new metallic IUDs

One criticism of the use of Cu-IUDs is that the threshold of Cu^{2+} needed to induce a contraceptive response while avoiding an inflammatory response has not been well-defined. In the search for alternative IUD materials, the experimental methodologies used to estimate corrosion rate and biotoxicity should be reproducible and hold analytical merit.

In vitro experimental considerations

Long-term, in vitro studies are required as the first step to ensure the metal's reliability in preventing pregnancy and estimate the device's lifetime. The literature lacks information on Cu-IUDs' corrosion using native uterine fluid due to the small fluid volume within the endometrial cavity[16]. Many experimental parameters should be considered while quantifying in vitro corrosion rates (metal ion concentration) of metal-based IUD materials. The corrosive environment must be tailored to simulate a uterine cavity as closely as possible. Corrosion studies of metal IUDs that utilize electrochemical techniques use cells that contain >100 mL of electrolyte[23,27,52]. However, the uterine cavity holds less than a millilitre of liquid[53]. It is recommended that a thin electrochemical cell with a similar shape and size to that of a uterus cavity be used.

It is typical to employ a polished disk-shaped working electrode while electrochemically studying the corrosion behaviour of potential IUD materials. Yet current devices are thin wire coils flush to a frame, potentially causing crevice corrosion. The bending of a metal wire may induce deformation and stress, leading to stress corrosion cracking. This also applies to the innovative device shapes and designs discussed previously (Fig. 1). Thus, the effect of the working electrode shape during electrochemical measurements should be further investigated.

The solution implemented should simulate the uterus fluid in terms of composition (including oxygen concentration), pH, viscosity, and temperature (i.e., physiological temperature of 37 °C)[54]. Many studies use the simulated uterine fluid (SUF) developed by Zhang et al. in 1996, which does not contain proteins (Table 1)[35]. Proteins have been identified in human uterine fluid, including albumin and transferrin[55]. The relationship between metal corrosion and proteins is complex[56], where metal ion binding to proteins can accelerate corrosion. Without studying the effect of proteins on metal corrosion, metal release rates may be underestimated during in vitro studies[57]. Yet, studies focused on

Table 1 | Chemical composition of different simulated uterine fluid (SUF) used in the literature[35,57]

Reference	Concentration (g/L)							
	$NaHCO_3$	$NaH_2PO_4 \cdot 2H_2O$	Glucose	Urea	Albumin	$CaCl_2$	KCl	NaCl
Zhang et al.[35]	0.25	0.072	0.50	–	–	0.167	0.224	4.97
Mora et al.[57]	0.25	0.072	0.50	0.48	–	0.167	0.224	4.97
Mora et al.[57]	0.25	0.072	0.50	0	35	0.167	0.224	4.97
Mora et al.[57]	0.25	0.072	0.50	0.48	35	0.167	0.224	4.97

quantifying metal release for metal IUD applications did not investigate the effect of proteins on corrosion. Studies should also consider changing the solution throughout a corrosion study to reflect physicochemical fluctuations across the menstrual cycle[58].

The analytical techniques used to study metal release rate widely vary, such as inductively coupled plasma (ICP), optical emission spectroscopy (OES), ICP-mass spectrometry (MS), flame atomic absorption spectroscopy (FAAS), atomic absorption spectroscopy (AAS), spectrophotometric measurements, or electrochemical techniques[16]. As studies do not use the same analytical technique, comparing the corrosion rates extracted from different methods would shed light on which methods are systematically reliable. This may advance the metal IUD community by enabling the confident quantification of metal ion concentrations needed for contraception without adverse side effects.

In vivo-like experimental considerations

IUDs have varying effects on the reproductive systems of different species, making it difficult to discern their impact on humans. Cu^{2+} ions released from Cu-IUDs induce uterine inflammation, affecting sperm and embryo viability. Studies show lower embryo formation rates in IUD users. The primary action of IUDs is not to destroy embryos in the uterus, but rather to affect gamete viability, reducing fertilization rates and embryo survival before they reach the uterus[59]. Therefore, it is important to test novel metallic IUD materials on human spermatozoa, emerging human synthetic embryos (or “blastoids”), and uterine organoids[60]. These tests would evaluate the in vitro implantation potential of human blastoids and assess any cytotoxicity of human endometrial and stromal cells. This approach would result in a more in vivo-like uterine organoid exposure test to evaluate new metallic IUD materials.

Furthermore, the next generation of devices are proposed to last at least 3–5 years to avoid frequent replacement. The surface of the metal IUD will most likely be covered in biofilms. Although Cu is known to be antimicrobial, Actinomyces israelii biofilms form on Cu-IUDs and survive due to their porous structure[61]. Determining biofilms’ role in long-term corrosion in vivo studies will be necessary for future work characterizing corrosion rates of new metallic IUD materials.

Understanding barriers and sustainability needs for global use of new non-hormonal IUDs

Socioeconomically disadvantaged individuals, immigrants, ethno-racial minorities, and members of low and middle-income countries (LMICs) have lower rates of contraceptive use, particularly the usage of long-acting, reversible, and very effective methods of contraception, like Cu-IUDs[62–64]. This has been attributed to multiple factors, including, but not limited to, the high upfront costs of IUDs, limited access to reproductive health care, stigma toward IUD usage and consequent users fear of side effects, and Government policies restricting access to IUD usage[62,64].

Several conditions must be met to ensure sustained IUD use. First, new non-hormonal IUDs must be lower cost and have fewer maintenance requirements. This would ensure that socioeconomically disadvantaged individuals, particularly in LMIC countries, can access and use them. Given the rising cost of Cu, there is a need for IUDs that use another material to ensure affordability[65]. Zn-IUDs have been proposed as an alternative; however, the supply of Zn may not meet the demand by mid-century[65], precluding it from being an economic alternative. A Fe-based IUD would be more affordable than Cu-IUDs[50], making it widely available to a global population needing access to reliable, effective, and low-cost contraceptive devices. Overall, a cost analysis of scalability and affordability is important to consider for any newly designed non-hormonal IUDs to ensure its global accessibility. Second, there has to be an acknowledgement that barriers to IUDs are multifaceted and the salience of particular barriers to IUD usage may differ across distinct settings[62,63]. Greater efforts must be made to identify barriers to IUD usage in specific settings and to remove them[62–64]. Third, greater efforts must be made to train professionals who can insert the IUD and increase the availability of reproductive health clinics that can provide same-day insertion[66]. Finally, public education about a newly developed device will be required. Once new non-hormonal and long-term methods with fewer side effects are available, dissemination of culturally appropriate information about the newly developed IUDs will be required to help spread knowledge about the improved innovation[62–64].

Outlook and final remarks

Worldwide, nearly half of all pregnancies are unplanned and unintended[67]. The development of a cost-effective non-hormonal contraceptive requiring minimal maintenance and fewer side effects will be particularly beneficial to those in marginalized populations who have higher rates of contraceptive non-use due to their economic disadvantage and barriers to accessing family planning services. The Cu-IUD is also an emergency contraceptive. The development of alternative metal and coated metal IUDs with similar properties can also help individuals in places with bans on abortion that may force some people into having unwanted and unintended births. A practical, comfortable, non-hormonal contraceptive could have an immense societal impact on the psychological and physical health of people with internal reproductive organs.

This perspective highlights the need to advance metallic IUD research by developing standardized in vitro and *in vivo* testing methods, as the concentration of heavy metal ions, including Cu^{2+}, needed for contraceptive action remains unknown. Developing new metallic IUDs is an exciting challenge with many opportunities for materials science and biomedical engineering researchers. Further, given the socioeconomic and technical barriers in the development of new contraceptive technology, there is a need for interdisciplinarity work with experts in natural and biological sciences (corrosion, medicine, biochemistry, chemistry, metallurgy, materials engineering) and social sciences (sociology, gender and women’s studies, and psychology) to eliminate challenges that may decrease discontinuation of use. As this field is in its infancy, new non-hormonal IUD research is uniquely poised to bridge multiple disparate disciplines to develop effective and tolerable contraceptive options.

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Author contributions

S.M.G. prepared the manuscript outline and wrote most of the draft. J.J.M.B. prepared the schematics and figures and wrote a part of the introduction. D.H.B. and Z.C.L.L. wrote section 4.2 and contributed to the writing of section 3.2. J.B.G. contributed text to the polymer discussion in section 3.3. K.O. and B.B. wrote the discussion about hormonal IUDs. K.C. and L.C. wrote section 5. B.A.R. contributed text to the introduction. All authors reviewed and edited the manuscript.

Competing interests

The authors declare no competing interests.

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