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Assessment of copper corrosion from frameless copper IUDs after long-term in utero residence ☆,☆☆

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Abstract

Objective: To assess the site-specific corrosive behavior of the frameless intrauterine device (IUD) following long-term exposure to the uterine environment.
Study design: A qualitative and morphological study using X-ray diffraction (XRD) and scanning electron microscopy (SEM).
Results: Three GyneFix® IUDs that were in site up to 150 months were examined. In utero corroded copper sleeves were divided into 10 different groups based on their shape (U or O), orientation (inside or outside) and in utero residence time. XRD indicated the presence of solely cuprite (Cu_2O) as corrosion product on both the inside and the outside of the copper sleeves, regardless of their shape. These results were confirmed by backscattered electron micrographs recorded on the inside, the outside and the cross-section of the IUD sleeve. SEM results suggest that shape and orientation slightly affect the corrosion rate.
Conclusion: The apparent copper loss from both sides of GyneFix copper tubes proves that both sides are a potential copper source and therefore justifies the design of GyneFix IUD. This could be beneficial for women as the IUD could be reduced in size and therefore better tolerated. The impact on bleeding could also be minimized.
Implication statement: Release of copper ions from both sides of the copper tubes of the frameless GyneFix® IUD allows the IUD to be reduced in size, contributing to better toleration. The impact on menstrual bleeding is also minimized by a smaller size of the foreign body.

Keywords: Frameless IUD; Corrosion; XRD; Synchrotron radiation; Copper; In utero

1. Introduction

Intrauterine devices (IUD) are a very popular method for long-acting reversible contraception. With nearly 160 million users, the IUD is the second most popular contraceptive method after sterilization and the most widely used form of reversible birth control. Beside the levonorgestrel-releasing intrauterine system, the copper-bearing IUDs are approved in the European Union and currently marketed [1–4]. The primary contraceptive effect of intrauterine contraception is the prevention of fertilization and implantation by interfering with sperm motility and survival. The reaction of the intrauterine foreign body (copper) with the endometrium activates the release of leukocytes and prostaglandins that act not only in the uterus but also in the oviduct and cervix to impede sperm and egg development [5].

GyneFix® (Contrel Research, Ghent, Belgium) belongs to a new generation of frameless copper IUDs. The frameless IUD was developed to provide a solution for the side effects observed with conventional IUDs, such as bleeding, pain and

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☆☆ Conflict of interest: Pieter-Jan Sabbe, Mark G. Dowsett, Victoria Flexer, Paul Thompson, David Walker, Pam A. Thomas, Annemie Adriaens: nil. Dirk Wildemeersch has been involved in the optimization of new, innovative, drug delivery systems for use in the uterus. He is currently advisor in devising new concepts in controlled release for contraception, gynecological treatment and prevention of infectious diseases.

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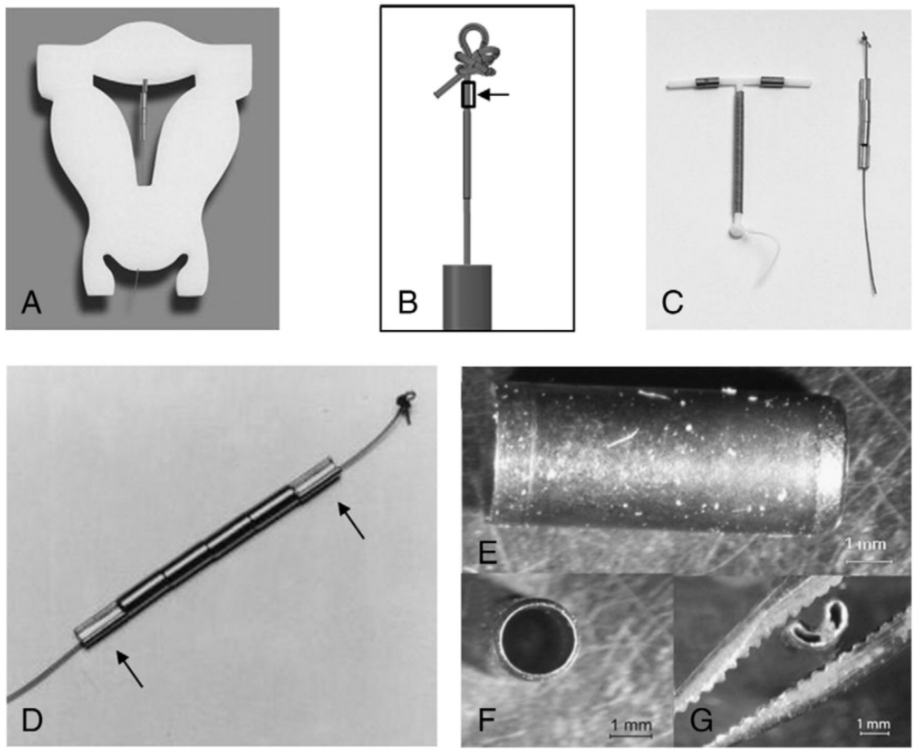

Fig. 1. (A) GyneFix® 200 IUD inserted in a foam uterus. (B) The IUD has a knot on top that serves to anchor the IUD in the fundus. Below the anchor is a small metal tube (arrow) threaded on the suture that serves as a marker to visualize the anchor at insertion and follow-up. (C) The total foreign body surface area (copper+plastic frame) of the TCu380A IUD is approximately 3 times greater than that of the small GyneFix® IUD. (D) GyneFix® 330 IUD that has two copper tubes more that the smaller version. The top and bottom tubes are crimped onto the suture thread (arrow) to avoid sliding off of the tubes from the suture. (E) Depending on their position on the suture, the tubes are present in two different shapes. The middle tubes are cylindrical, while the end tubes are pinched cylinders. The former are named O-shaped tubes (F) while the latter are referred to as U-shaped tubes (G).

expulsion that are attributed to disproportion between the IUD and the uterine cavity [4]. Whereas traditional IUDs exist out of a copper wire wound around a plastic T-shaped stem, GyneFix 200 consists of a polypropylene suture threaded with only 4 copper sleeves (Fig. 1A and B). The larger GyneFix 330 IUD has 6 copper sleeves. The top and bottom tubes are crimped onto the suture thread to prevent the other sleeves from sliding off (Fig. 1D).

The rate of dissolution of the copper is proportional to the size of the exposed copper surface area; hence, the risk of pregnancy decreases with the increasing copper surface area in a device [6]. Although it is not exactly known how much copper is necessary for contraception, studies suggest that a good contraceptive efficacy is obtained with IUDs having a minimal surface area of 200 mm^2. Moreover, when the surface area exceeds 380 mm^2, no additional reduction in failure rate is perceived, a phenomenon that can be attributed to the limited amount of dissolving agent present necessary for in utero copper dissolution [7,8].

As a consequence of the design of GyneFix IUD, the effective copper surface area is the same as the nominal copper surface area, which is a fundamental difference compared to conventional IUDs. Theoretically, all surface areas, in total 330 mm^2 for the larger version and 200 mm^2 for the smaller version, are exposed to the uterine environment [7]. However, it is unknown whether the reduced space inside a copper GyneFix sleeve affects the accessibility for the uterine fluid to enter the cavity and act as a dissolving agent, especially in the sleeves pinched onto the suture at the beginning and the end of the device.

If in utero corrosion of GyneFix is not site dependent, this would explain the high efficacy of this small frameless IUD. This is important, as the bigger the size of the IUD, the more the amount of menstrual blood loss that can occur. Erratic and increased menstrual blood loss is the main reason why women request removal of a copper IUD. Maximizing the release of copper while minimizing the size of the intrauterine foreign body is therefore an important objective to enhance the acceptability of the IUD. Clinical studies confirm the high acceptance of the small GyneFix 200 by women [2]. Fig. 1C illustrates the size difference between the small frameless IUD and the TCu380A IUD.

We compared the corrosion products present on the inner and outer surface of 3 different GyneFix samples corroded in utero up to 150 months. In utero studies usually show some limitations concerning the individual variability of the uterine environment with corollary data scatter. Nevertheless, the value of these experiments must not be underestimated since certain physical (viscosity, surface tension, etc.) and physiological (composition) parameters of a uterine environment cannot be mimicked in simulated uterine solutions. This paper discusses the results obtained during X-ray diffraction (XRD) and scanning electron microscopy (SEM) analyses.

2. Material and methods

2.1. Investigated samples

GyneFix IUDs consist of 99.99% pure copper sleeves, which are 5 mm long and 2.2 mm in diameter with a wall thickness of 0.3 mm. The 0.01% of impurities present consists mainly of Ag (50 ppm), Fe (10 ppm) and Ni, Zn, Se and P (5 ppm). Depending on their suture position, the tubes are present in two different shapes. The middle tubes are cylindrical, while the end tubes are pinched cylinders (Fig. 1E–G). The former are named O-shaped tubes while the latter are referred to as U-shaped tubes. In total, 11 tubes from three different IUDs, corroded in utero up to 150 months, were analyzed by both XRD and SEM. All samples could be classified depending on a combination of the following parameters: the origin of the sample, the shape and its inside/outside orientation. An overview of the analyzed samples is listed in Table 1. After removal of the uterus, samples were carefully rinsed with distilled water and stored in a sterile environment until the measurements were performed.

2.2. XRD experiments

XRD patterns were carried out at BM28 (XMaS) end-station at the European Synchrotron Radiation Facility (Grenoble, France) [9]. Diffraction rings were recorded with a Mar CCD 165 camera (Mar USA Inc., Evanston, IL, USA), oriented at an angle of 45° to the input beam with its surface at 130±0.5 mm from the sample surface. The X-ray beam was incident at 10° to the sample surface resulting in an elliptical beam footprint. Dimensions of the beam were set to 1 mm wide and 1.15 mm long by adjusting the vertical slit height. The monochromator was set to 8 keV (λ=1.5498 Å).

In order to examine the inner surface of a copper GyneFix sleeve, the sleeves were opened longitudinally with a utility knife (degreased with 2-propanol). The half cylinders were mounted on a sample stage carousel with the inside or the outside surface pointed toward the incoming X-ray beam.

A diffraction pattern of a new GyneFix® sleeve was recorded at the University of Warwick with an X'Pert PRO diffractometer (PANalytical, Almelo, The Netherlands). The instrument produces Cu-Kα radiation (λ=1.5498 Å) selected by a curved Ge-monochromator. Reflections were recorded by a PIXcel® solid-state detector (PANalytical, Almelo, The Netherlands).

2.3. SEM experiments

Scanning electron micrographs were recorded with a Phenom-FEI bench top scanning electron microscope (Phenom World BV, The Netherlands). Backscattered electron (BSE) images were collected using 5 kV electrons and a solid-state detector.

Table 1
Overview of analyzed samples according to the position of the copper tubes on the IUD

Nr.	Sample	Residence time in utero (months)	Shape	Orientation
1	DCM W27	144	U	Inside
2	DCM W27	144	U	Outside
3	DCM W27	144	O	Inside
4	DCM W27	144	O	Outside
5	DR W24	150	U	Inside
6	DR W24	150	U	Outside
7	BF W134	98	U	Inside
8	BF W134	98	U	Outside
9	BF W134	98	O	Inside
10	BF W134	98	O	Outside
11	Cu-REF	0	O	Inside/outside

3. Results

3.1. XRD patterns

XRD patterns of a new GyneFix sleeve (Fig. 2, top) confirm the purity of the raw material from which the IUD was manufactured. The middle and bottom diffraction patterns of Fig. 2 correspond respectively to the inside and outside of an O-shape sleeve. These diffractograms show the presence of solely copper (Cu) and cuprite (Cu_2O).

Cuprite is an intermediate in the dissolution process of copper in an uterine environment, necessary for the detachment of the copper ions (Cu^{2+}) from the bulk copper [10,11]. Notwithstanding the complex physicochemical nature of a uterus, it is generally accepted that the production of cupric ions proceeds according to the following reaction mechanism [12]:

$$4Cu + O_2 \rightarrow 2Cu_2O \text{ (a)}$$
$$2Cu_2O + 8H^+ + 2O_2 \rightarrow 4Cu^{2+} + 4H_2O \text{ (b)}$$

However, the importance of uterus-dependent parameters such as pH, partial oxygen pressure, uterine fluid composition and so on should not be neglected as they greatly influence the kinetics of these reactions. Indeed, it is obvious that higher cupric ion concentrations will be observed in uteri with a lower pH and a higher partial oxygen pressure, as confirmed by Mora et al. [12,13]. Although the production of cuprite is impeding the contraceptive efficacy of the IUD by trapping up to 40% of the cupric ions, it is a necessary step in the copper dissolution process and therefore direct proof of both ongoing corrosion and effective operation of the device [14].

When analyzing the XRD patterns from the inside and outside of a U-shaped tube, only copper and cuprite reflections are detected (samples no. 1 and no. 2, diffractograms not shown; samples originate from the same IUD as the O-shaped sleeves shown in Fig. 2).

Although the presence of other corrosion products [$CaCO_3$, $Ca_3(PO_4)_2$, $Cu(OH)_2$, etc.] has been reported in the past [15,16], none of these compounds have been observed. However, we do not discard the possibility that these compounds could be

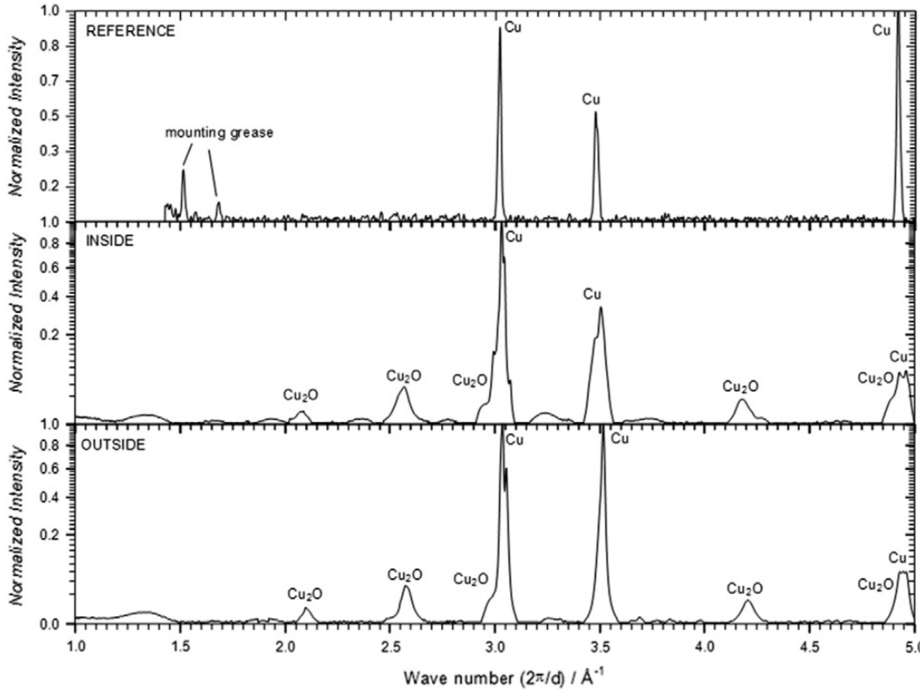

Fig. 2. XRD patterns of an uncorroded reference sleeve (top, sample no. 11) and inside (middle, sample no. 3) and outside (bottom, sample no. 4) of an O-shaped GyneFix® sleeve, both corroded for 144 months in utero. Beside copper (Cu), only cuprite (Cu_2O) was found as a corrosion product.

present in trace amounts. Indeed, they could be hidden in microscopically small regions not detectable by XRD due to its low surface coverage averaged across the X-ray beam footprint. If this would be the case, these contaminants would be present in such small quantity and dimension that their presence would be insignificant compared to Cu_2O. Nevertheless, work presented here was intended to prove or disprove the possibility of hollow tubes to liberate Cu^{2+} ions from both the outside and the inside and not to detect all copper reaction products in a uterine environment, which have otherwise already been reported.

The presence of cuprite on both sides of the IUD sleeve suggests that the reduced space on the inside of a copper cylinder is not limiting the dissolving agent to enter and initiate copper dissolution, even in the extreme case where the copper tubes are compressed (U-shaped cylinders). Consequently, it can be concluded that all the exposed copper surface areas (inside and outside of the sleeves) are participating in the contraceptive action of the IUD. All samples from Table 1 yielded very similar XRD patterns, regardless of the shape (O or U), orientation of the IUD tube or time of residence in utero.

3.2. SEM analysis

Additional information on the corrosion products formed and possible differences on in utero corrosion due to site-specific effects was gained by a morphology study with SEM in BSE mode.

Fig. 3 gives an example of electron micrographs taken on the inside and the outside of the in utero corroded IUDs. A reference micrograph is added for comparison with a new, uncorroded GyneFix sleeve. The micrograph number corresponds with the sample number in Table 1. All micrographs show that all samples have been affected by the uterine fluid and therefore participated in the contraceptive effect of the IUD. However, it seems that not all samples have been corroded to the same extent and resided at time of removal in different stages of the corrosion process. Berthou et al. screened 461 T-shaped IUDs with SEM and concluded that in utero corrosion of Cu-IUDs is a multi-step process [17].

It is noteworthy that all micrographs taken from the different samples, except for the Cu-reference, displayed extensive corrosion. Generally, corrosion is in an advanced stage where damage is no longer restricted to discrete points but had taken place over large areas. However, no ruptures of any of the copper tubes were noticed, even when some devices had been inserted for more than 10 years. Images suggest that the outsides of the investigated samples of the GyneFix tube appear to corrode faster than the inside.

4. Discussion

Studies suggest that a good contraceptive efficacy is obtained with IUDs having a copper surface area of 200 mm^2. Failure rates of TCu200 IUD are in the order of 3.0/100/year after 2 years. When the copper surface area is

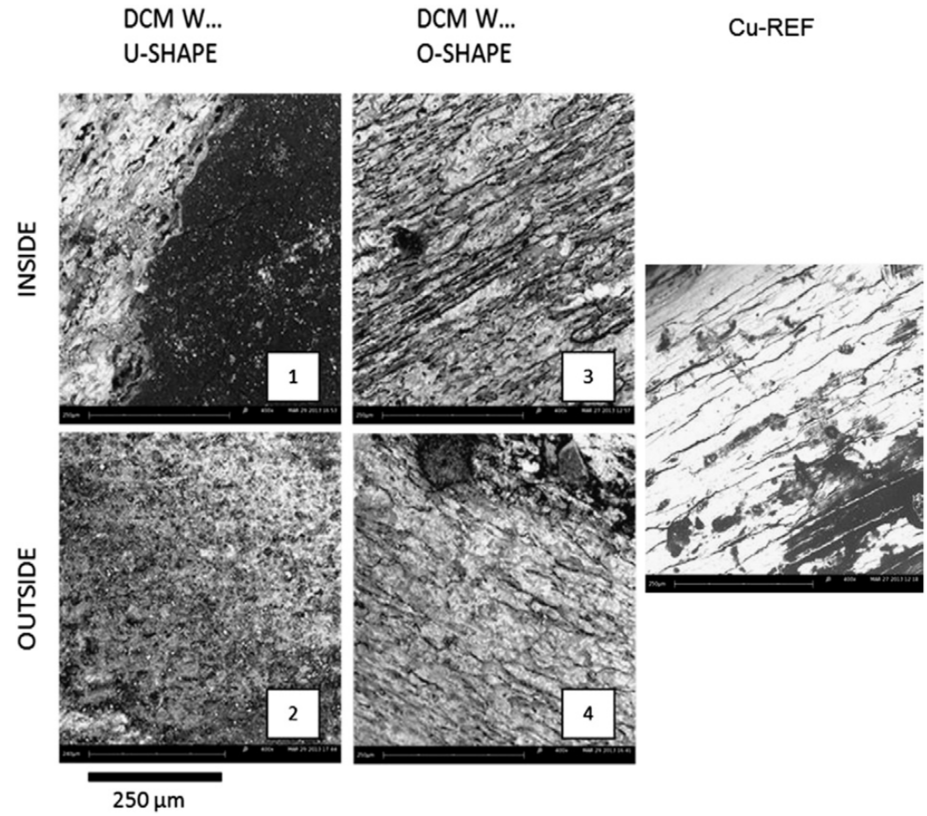

Fig. 3. Micrographs of corroded inner (1 and 3) and outer (2 and 4) surfaces of U-shaped and O-shaped copper tubes. Cu-REF is the micrograph of a new, uncorroded GyneFix sleeve.

increased to 380 mm^2, failure rates are usually less than 1.5/100/year after 2 years. These clinical studies were conducted with copper IUDs provided with a copper wire wound around the stem of the IUD. It is important to distinguish between IUDs with copper wire and the ones that have copper tubes or a combination of the two [7]. The remark by Kosonen is important: "Only in the case of copper tubes is the nominal and the effective surface area the same. When copper wire is used, that part of the wire lying against the plastic body is ineffective and should not be calculated as a part of the effective surface area" [18]. Other researchers confirm these findings: "The portions of the wire winding in contact with the plastic surface give off hardly any copper" [19]. Chantler writes: "It has been shown that there is negligible corrosion of the copper in contact with the plastic core and that this area should be discounted in the calculation of the active surface area of the copper" [20]. Kosonen concludes that up to 40% of the copper wire is 'ineffective' [21]. This research also showed that copper release is lower and the more the winding of the copper wire is tighter. This is the case with high-load copper IUDs such as MLCu375 en TCu380A. Based on this research, the estimated 'effective' copper surface area of the TCu200 IUD is between 120 and 180 mm^2 and that of the TCu380A IUD is between 252 and 340 mm^2.

The current study shows that, with the frameless GyneFix IUD, all surface areas are exposed to the uterine environment. This is a fundamental difference compared to conventional IUDs. Moreover, copper-release studies with the standard GyneFix 330 IUD removed after more than 10 years of use have shown that the copper surface area decreases very little over that period, only 7% after 12 years of use (Contrel Research, data on file). This could explain the high efficacy of the small GyneFix IUD, ~1.0 at 5 years of use, and the absence of increase in annual pregnancy rate.

Furthermore, copper IUDs could be developed that last at least 25 years without decreasing efficacy over time as long as 'open' copper tubes are used as the corrosion process from both sides will only minimally affect the copper surface area. This research also suggests that smaller IUDs could be developed if copper ion release occurs from the outer as well as from the inner side of the copper tubes. It is known that the smaller the size of the foreign body is, the less effect on menstrual blood loss is. Women wearing the small GyneFix 200 IUD usually report a similar bleeding pattern when compared with the bleeding pattern before insertion of the IUD [22]. At the same time, the small surface area optimizes tolerance. This could enhance continuation of use since abnormal bleeding and cramping pain are the two major reasons for IUD discontinuation.

One of the limitations of the study is that only a few samples were examined. However, the corrosion effects were similar in all devices and subgroups studied allowing valid conclusions. Another limitation is that the relationship between protein absorption on copper corrosion and to possible side effects of the IUD (e.g., abnormal bleeding, infection) was not studied. This could be an important research topic for future studies.

5. Conclusion

The site-specific corrosive behavior of three different in utero corroded GyneFix IUDs was analyzed in order to verify whether copper release of the unconventional GyneFix design occurs from the outside as well as from the inside of the copper tubes. XRD indicated the sole presence of cuprite (Cu_2O) as corrosion product on both the inside and the outside of the copper tubes. These results were confirmed by BSE micrographs recorded on the inside, the outside and the cross-section of the IUD. The apparent copper loss from both sides of a GyneFix tubes proves that both sides are a potential copper source and therefore justifies the design of GyneFix. This could be beneficial for women as the IUD could be reduced in size and therefore better tolerated. In turn, the impact on bleeding could also be minimized.

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