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Full length article

Potential release of toxic metal elements from Essure® device in symptomatic patients: First results of the French Ablimco cohort

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ABSTRACT

Objective: Many patients with Essure® devices request the removal of these implants due to persistent adverse effects. The pathophysiology remains unknown, but a corrosion of the implants in the *in-vivo* environment leading to metal ion release may be suspected. The implants consist of polyester fibers, nickel-titanium alloy and other metals including chromium. The purpose of this study is to deliver the first results on the concentrations of nickel and chromium (two potential toxic metal elements) in peritoneal fluid and in the fallopian tube tissue during laparoscopic removal of Essure®.
Study design: In this prospective observational study conducted in a French academic research hospital (University hospital of Lyon), nickel and chromium concentrations were determined in the fallopian tube tissue and peritoneal liquid from symptomatic patients with Essure® by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) analysis in a PerkinElmer NexION 350.
Results: Significant metal element concentrations were showed in the peritoneal fluid. There was also a differential concentration in the fallopian tube tissue with higher concentration close to the implant then lower at a distance from this implant. There was a correlation between the concentrations of the two metals.
Conclusion: The presence of nickel and chromium in the fallopian tube tissue and the peritoneal fluid raises the question of a possible relationship between the symptoms attributed to Essure® implants and the dissemination of potential toxic metals due to galvanic corrosion of the devices.

Introduction

Since the decision to halt sales of the Essure® implants for permanent birth control in December 2018 (Bayer©, Leverkusen, Germany), many patients have complained of unspecific symptoms, such as gynecological disorders (pain, menorrhagia), but also broad extrapelvic symptoms (persistent asthenia and fatigue, heart palpitations, tinnitus, pruritus, joint and / or muscularis pain, skin rashes, digestive disorders) [1]. Several studies have shown an improvement in symptomatology and quality of life after Essure® removal in symptomatic patients [1,2]. The question arises as to what is the pathophysiology of these local and systemic adverse events. One of the hypotheses could call into question the responsibility of release of toxic metal elements from Essure® devices. Each implant weighs approximately 45.5 mg and has a complex composition of metal elements: iron, alloy of nitinol (55 % nickel and 45 % titanium), 316-stainless steel, chromium, platinum, iridium, and tin-silver welds.

A few rare case reports had shown a nickel sensitization quickly after Essure® placement (a few days to a few weeks) with generalized erythematous eruption and pruritus. After Essure® removal, the positive nickel patch test completely resolved [3,4]. However, no study has been able to show a nickel allergy several months to several years after implant placement [5].

We hypothesized that there could be a release of potential toxic metal elements from Essure® with diffusion in the fallopian tube tissue as well as inside the peritoneal cavity. We aimed to measure nickel (Ni) and chromium (Cr) concentrations (the two major toxic metal elements present in the implants) during the removal of Essure® in symptomatic patients.

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Material and methods

This monocentric prospective cohort study (the French Ablimco cohort) was conducted from August 2018 to February 2020 at the University Hospital of Lyon. This study was approved by the Ethics Committee and was registered under the identification number clinical trials.gov identifier: nct03281564. In the Ablimco cohort, the primary objective was to evaluate the symptom resolution after laparoscopic Essure® removal (previously published [1]) and the secondary objective was to investigate the potential release of metal ions from the Essure® implants. The present paper presents the first results of this ongoing project about the concentrations of Ni and Cr in peritoneal fluid and in the fallopian tube tissue. Correlation between the release of Ni and Cr as well as correlation between metal elements concentrations and the length of time since Essure® placement was also investigated.

Peritoneal fluids and fallopian tubes were obtained during laparoscopic Essure® removals. All informed patients with adverse effects possibly related to Essure® implants and with an indication for laparoscopic removal of the implants were included. Exclusion criteria were as follows:

- Refusal to participate in the study,
- Lack of spontaneous peritoneal fluid at the beginning of the laparoscopic procedure,
- Inability to understand the information during the pre-operative consultation.

Surgical approach

In all cases, peritoneal fluid sampling was collected at the beginning of the laparoscopic procedure in order to determine Ni and Cr levels.

The surgical procedures were performed by laparoscopy according to two previously published techniques (chosen by the surgeon) [6,7]:

- through a longitudinal incision of the tuba with traction on the implant to remove it completely followed by a bilateral salpingectomy [6],
- or through a mini-cornuectomy followed by bilateral salpingectomy [7].

Essure® Implants and the fallopian tubes were separately sent to the Trace Element Analysis Laboratory of Lyon Hospital.

Analysis in trace element analysis laboratory

The analyses were carried out at the level of the surrounding tissue around the Essure®, and for each case on the proximal part of the fallopian tube, on the distal part of the fallopian tube, and finally in the peritoneal fluid (Fig. 1).

ICP-MS analysis

Ni and Cr concentrations were determined by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) analysis (PerkinElmer NexION 350X) in kinetic energy discrimination (KED) mode. The instrument was operated using helium as the collision cell gas. Quantitative analysis was performed by using external calibration and an internal standard, Rh^{103}. A drying step (overnight in an oven at 80 °C then 3 h at 105 °C and samples are weighed in element-free Teflon vessels) followed by an acid digestion (1 mL concentrated suprapure HNO_3 at 60 °C overnight) were required to measure Ni and Cr concentrations in the fallopian tube tissue. The vessel was rinsed with 1 mL of (deionized water / HNO_3 0.1 % v/v). Results were expressed as μg of Ni and Cr per gram of dry tissue.

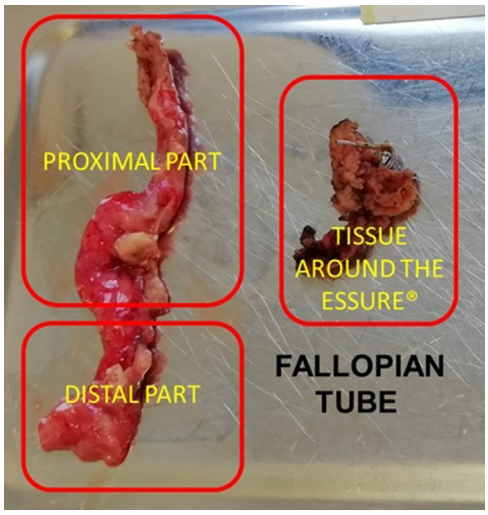

Fig. 1. The different parts of the tubal analysis.

Statistical analysis

Since there are no data in the literature about the concentrations of Ni and Cr in peritoneal fluid and in the fallopian tube tissue, we couldn't calculate the sample size.

Continuous quantitative characteristics were described using median, interquartile range (IQR), and extreme values. Qualitative variables were described using percentages and counts. Comparisons of continuous variables were performed by the Mann-Whitney test and the correlations were evaluated using the Spearman's rank correlation coefficient. Statistical analyses were performed using MedCalc software, version 12.1.

Results

Patients

A total of 37 patients were included. The median age (min-max) at the time of Essure® removal was 48.3 years old (24.9–57.3). The median length of time between Essure® placement and removal was 6.4 years (1.8–11.9). Pre-operative reported symptoms are given in Table 1.

Concentrations of metal elements in the fallopian tube tissue

For Ni and Cr, a gradient of concentrations was observed with declining levels from tissues surrounding the implants to the distal parts of the fallopian tube. Concentrations in the tissues surrounding the Essure® were 4.12 (IQR: 0.52–6.68) and 12.72 μg/g of dry tissue (4.09–17.53) for Ni and Cr, respectively. In the distal parts of the fallopian tube tissue, concentrations were 0.35 (0.24–0.56) and 1.35 μg/g of dry tissue (1.00–2.23) for Ni and Cr, respectively (Fig. 2). All comparisons were significant at $p < 0.05$. A significant correlation was also observed between Ni and Cr concentrations (rho = 0.792, $p < 0.0001$) (Fig. 3).

Concentrations of metal elements in the fallopian tube tissues were characterized by high interpatient variability, particularly for the tissue around the Essure® implants. In this segment, the ratio of minimum to maximum concentration is between 1:54

(0.46–25.06 μg/g of dry tissue) and between 1:125 (0.08–10.06 μg/g of dry tissue) for Cr and Ni, respectively.

Concentrations of metal elements in the peritoneal fluid

In peritoneal fluid, Ni and Cr concentrations were 2.24 μg/L (IQR: 0.32–3.67) and 5.39 μg/L (2.22–8.68 μg/L), respectively. As observed in the fallopian tube tissue, there were (i) a significant correlation between Ni and Cr levels (rho = 0.756, $p < 0.0001$) (Fig. 3) and (ii) a high interpatient variability.

No correlations were found between the levels of metal elements and the length of time between Essure® placement and removal ($p = 0.09$ and $p = 0.06$ for Cr and Ni, respectively) (Fig. 4)

There were also no relationships between the levels of metal elements and reported fatigue, psychological disorders, or pain in joints (the three main symptoms); all p-values were non-significant (Table 2).

Table 1
Pre-operative reported symptoms in the cohort of 37 patients. Data are presented as number of patients (and as percentages).

Reported symptoms	Number of patients (%)
Fatigue	24 (64.8 %)
Psychological disorders	22 (59.4 %)
Pain in joints	19 (51.3 %)
Poor concentration/ lack of focus	18 (48.6 %)
Heavy menstrual bleeding	17 (45.9 %)
Abdominal pain	15 (40.5 %)
Muscularis pain	13 (35.1 %)
Headaches	13 (35.13 %)
Skin rash	8 (21.6 %)
Heart palpitations	8 (21.6 %)
Back pain	7 (18.9 %)
Pain in legs and hips	6 (16.2 %)
Digestive disorders	6 (16.2 %)
Dysmenorrhea	5 (13.5 %)
Tinnitus	5 (13.5 %)
Hair loss	3 (8.1 %)
Itching	1 (2.7 %)
Dyspareunia	1 (2.7 %)

Discussion

Essure® implants were recently removed from the world market with many non-answered questions [1]: which patient should benefit from the removal of the implants? How can we explain the non-gynecological symptoms such as asthenia or pain in joints? What is the exact pathophysiological mechanism which could lead to these adverse effects?

The Essure® implants have a complex composition of different metals.

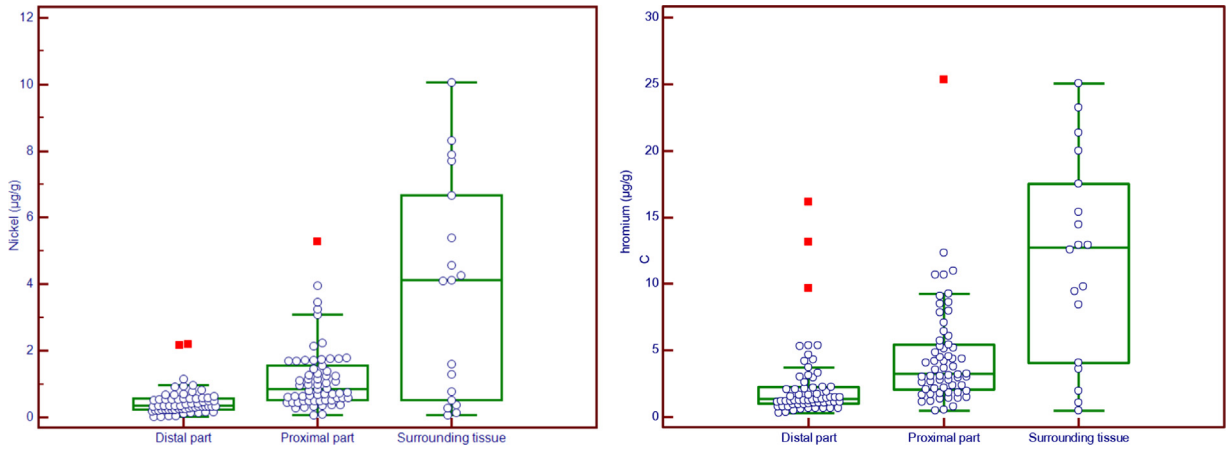

Fig. 2. Concentrations of nickel (left) and chromium (right) in the different parts of fallopian tube tissue. The surrounding tissue is the tissue around the Essure®.

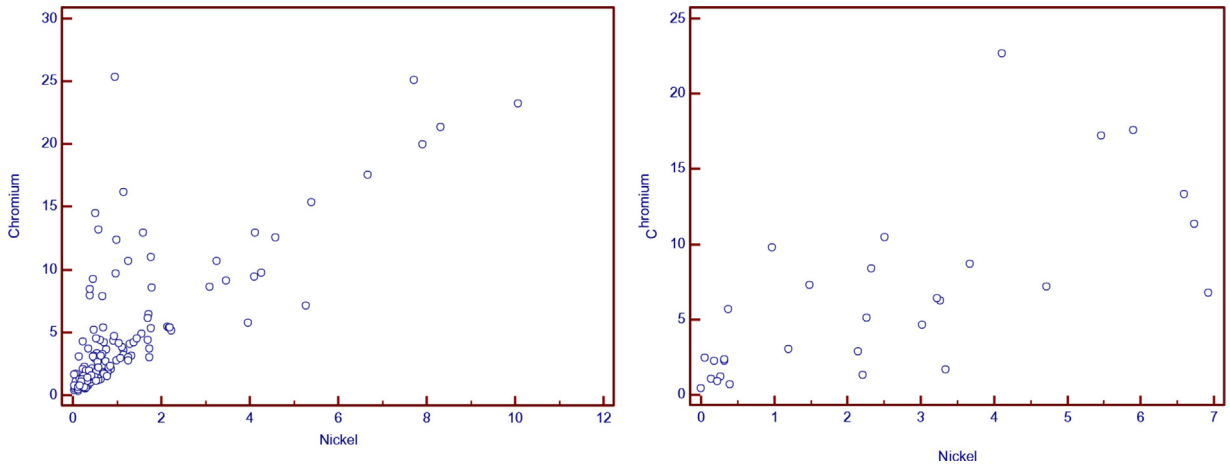

Fig. 3. Correlation between the Ni and Cr concentrations in the fallopian tube tissue (μg/g of dry tissue) (left) and in the peritoneal fluid (μg/L) (right). Spearman's rho = 0.792 and = 0.756, respectively ($p < 0.0001$).

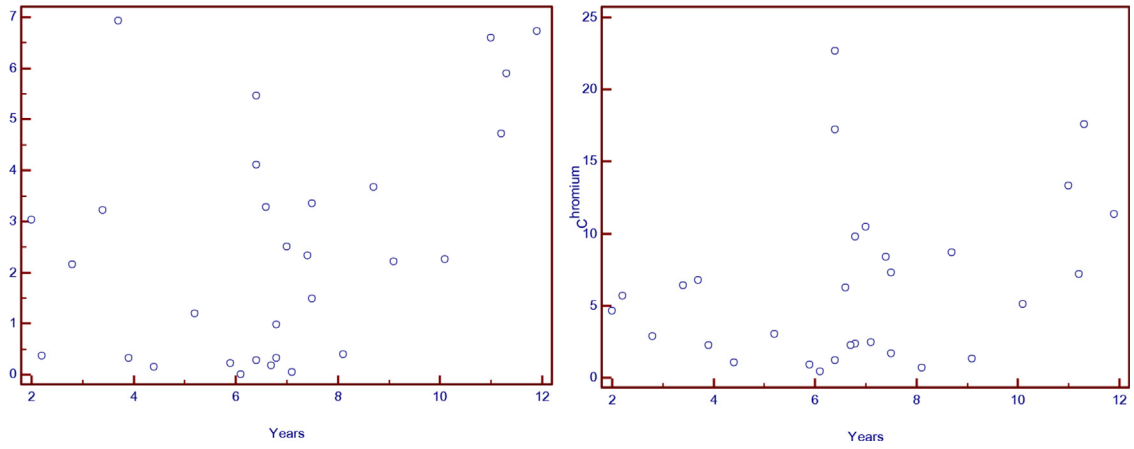

Fig. 4. No correlations were found between concentrations of Ni (left) and Cr (right) in the peritoneal fluid (μg/L) and the length of time between Essure® placement and removal (years) (Spearman's rho, all p-values > 0.05).

Table 2
Association between the main pre-operative reported symptoms and the concentrations of Cr and Ni in the peritoneal fluid. Data are presented as median (and as IQR).

Symptoms		Patients who reported the symptom	Patients who did not reported the symptom	p
Fatigue	Cr	6.32 μg/L (1.95–8.53)	4.87 μg/L (2.46–9.79)	NS
	Ni	2.42 μg/L (0.36–4.2)	1.56 μg/L (0.14–3.02)	NS
Pain in joints	Cr	6.39 μg/L (2.09–8.89)	5.10 μg/L (1.99–8.96)	NS
	Ni	2.51 μg/L (0.99–4.91)	0.97 μg/L (0.26–3.37)	NS
Psychological disorders	Cr	6.39 μg/L (2.29–9.64)	4.63 μg/L (1.82–8.61)	NS
	Ni	2.51 μg/L (0.28–4.36)	2.21 μg/L (0.38–3.59)	NS

According to the manufacturer, there would be a daily *in vitro* release of nitinol of 0.14 to 0.26 μg / day especially during the first weeks after the Essure® placement [5]. The question of a Ni allergy hypothesis or an immune-allergic reaction could arise. However, several clinical studies didn't demonstrate any allergic skin reactions after Essure® procedure: patients with previous proved Ni allergy didn't have a more severe allergic symptomatology few months after Essure® placement. And on the other hand, there was no *de novo* Ni sensitization [5,8]. We know that there is no interest in doing skin tests to look for a Ni allergy since patch-tests are only predictive of allergic skin reactions and did not necessarily correlate with clinically systemic reactions [9].

There are a lot of medical materials with Ni. For example, in the coronary stents used since 1997, all containing alloys with Ni (composition varying from 10 to 35 % of Ni molecules) and no allergic reaction has been documented after the implantation of these devices [10].

The second hypothesis would be a possible corrosion and maybe a galvanic corrosion of the Essure® device. Galvanic corrosion is defined as an electrochemical process in which one metal corrodes preferentially when it is in electrical contact with another, through an electrolyte in its environment [11]. Our study found the presence of potential toxic metal elements in the peritoneal fluid and in the fallopian tube with a differential concentration (higher if closer to the Essure® implants). This is in agreement with a recent study of 10 cases showing a possible degradation of the Essure® weld with dissemination of metal particles in the fallopian tube and uterin horn [12]. There was also a significant correlation between Ni and Cr concentrations in the fallopian tube tissue and in the peritoneal fluid suggesting a complex exchange between these two compartments. Since several metals are in direct contact, galvanic corrosion of the Essure® implants could be the mechanism which may explain our results and the dissemination of metal elements with potential toxicities [9]. We hypothesized that levels of metal elements could be explained by the length of time between Essure® placement and removal. However, in our study the correlations did not reach the significance threshold. It was also hypothesized that patients with high Ni or Cr concentrations in the peritoneal fluid may experience more systemic symptoms, but no clear relationships were found between the three main reported symptoms (fatigue, psychological disorders, or pain in joints) and the levels of metal elements. These results were potentially due to a lack of statistical power, which makes it difficult to draw definitive conclusions (Table 2).

Strenghts of our study are the analysis of several localizations for each case (3 zones at the level of the tube and the peritoneal fluid). However, all of these results should be interpreted with caution. We have not proven the causal relationship but simply highlighted the presence of Ni and Cr. It is not certain that these potential toxic metals are necessarily responsible for the adverse effects. As a result, there are no indications to date to remove implants to all patients, especially in case of non-symptomatic patients [1]. In symptomatic patients, there are also no biological or clinical arguments to prefer hysterectomy with salpingectomy rather than laparoscopic conservative procedure (salpingectomy with traction on the implant or salpingectomy with mini-cornuectomy) [1].

Other studies are still needed to better understand the relationship between levels of toxic metal elements in peritoneal and fallopian tube and adverse events, especially in comparison with a control group (currently underway in our department). These first results are also encouraging to explore the release of other metals like tin or platinum.

Disclosure statement

The authors declare they have no conflict of interest to disclose.

Source funding

None.

Previous presentation details

Part of this study was presented at the 14thJournées Daniel Dargent Congress, at the 29th Gynécologie Obstétrique Pratique Congress and as oral presentation poster at the "7th International Symposium FESTEM (Federation of European Societies on Trace Elements and Minerals)- 35th Annual GMS Meeting", 2–5 April 2019, University of Potsdam (Germany).

References

[1] Chene G, Cerruto E, Moret S, Lebail-Carval K, Chabert P, Mellier G, et al. Quality of life after laparoscopic removal of Essure(®) sterilization devices. Eur J Obstet Gynecol Reprod Biol X. 2019;3(May):100054.
[2] Maassen LW, van Gastel DM, Haveman I, Bongers MY, Veersema S. Removal of Essure® sterilization devices: a retrospective cohort study in the Netherlands. J Minim Invasive Gynecol 2018.
[3] Al-Safi Z, Shavell VI, Katz LE, Berman JM. Nickel hypersensitivity associated with an intratubal microinsert system. Obstet Gynecol 2011;117:461–2.
[4] Lane A, Tyson A, Thurston E. Providing re-essure-ance to the nickel-allergic patient considering hysteroscopic sterilization. J Minim Invasive Gynecol 2016;23:126–9.
[5] Siemons S, Vleugels M, van Eijndhoven H. Evaluation of nickel allergic reactions to the essure micro insert: theoretical risk or daily practice? J Minim Invasive Gynecol 2017;24(Jan (1)):140–4.
[6] Chene G, Vidican P, Azzi C, Carval KL, Chabert P, Beaufils E, et al. How I do . . . laparoscopic removal of Essure(®) device? Gynecol Obstet Fertil Senol 2017;45 (May (5)):316–9.
[7] Chene G, Lebail-Carval K, Azzi C, Chabert P, Mellier G, Lamblin G. How I do . . . laparoscopic removal of Essure(®) device by mini-cornuectomy without fragmentation? (with video). Gynecol Obstet Fertil Senol 2018;46(Jul-Aug (7-8)):608–9.
[8] Raison-Peyron N, Du-Thanh A, Compan C, Perrochia H, et al. Are adverse events attributed to essure associated with nickel sensitization? Dermatitis 2020;31 (Mar/Apr (2)):122–7.
[9] FDA. Biological responses to metal implants. https://www.fda.gov/media/131150/download.
[10] Romero-Brufau S, Best PJ, Holmes DR, Mathew V, Davis MD, et al. Outcomes after coronary stent implantation in patients with metal allergy. Circ Cardiovasc Interv 2012;5:220–6.
[11] https://ansm.sante.fr/var/ansm_site/storage/original/application/114c59313992db5144689be838ed5a36.pdf.
[12] Catinon M, Roux E, Auroux A, Balter V, Fellah C, Trunfio-Sfarghiu AM, et al. Identification of inorganic particles resulting from degradation of ESSURE® implants: study of 10 cases. Eur J Obstet Gynecol Reprod Biol 2020;250 (Apr):162–70.