BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	Draft
Article Type:	Original research
Date Submitted by the Author:	n/a
Complete List of Authors:	Catinon, Mickaël; MINAPATH Développement, Roux, Elisabeth; Minapath Développement Auroux, Aline; IRCELYON UMR 5256, CNRS, Université Claude Bernard Lyon 1 Trunfio-Sfarghiu, Ana-Maria; Univ Lyon, INSA-Lyon, CNRS UMR5259, LaMCoS Lauro-Colleaux, Carole; Laboratoire Technipath Watkin, Emmanuel; Laboratoire Cypath Sournies, Gilles; Natecia Gynecology Unit Vincent, Michel; Minapath Développement
Keywords:	GYNAECOLOGY, OBSTETRICS, REPRODUCTIVE MEDICINE

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Confirmation of the predominant role of Sn in a pathology linked to Essure implants: A study of 18 cases with the same pathological process

M Catinon[1], E Roux[1], A Auroux[2], AM Trunfio-Sfarghiu[3], C Lauro-Colleaux[4], E Watkin[5], G Sournies[6], M Vincent[1]

mcatinon@minapath.com ; eroux@minapath.com ; aline.auroux@ircelyon.univ-lyon1.fr ; ana-maria.sfarghiu@insa-lyon.fr ; carole.lauro-colleaux@technipath.fr ; emmanuel.watkin@cypath.fr ; sournies.gilles@wanadoo.fr ; mvincent@minapath.com

[1] Minapath Developpement, Insavalor CS : 52132, 69603 Villeurbanne, France.

[2] IRCELYON UMR 5256, CNRS, Université Claude Bernard Lyon 1, 69626 Villeurbanne, France

[3] Univ Lyon, INSA-Lyon, CNRS UMR5259, LaMCoS, F-69621 Villeurbanne, France

[4] Laboratoire Technipath, 41 allée des Cyprès, 69760 Limonest, France

[5] Laboratoire Cypath, 201 Route de Genas, 69100 Villeurbanne, France

[6] Natecia Gynecology Unit 28 Avenue Rockfeller 69008 Lyon, France

Competing interests

"All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; Michel Vincent is Chief Executive Officer of Minapath Développement. Mickaël Catinon and Elisabeth Roux are employees of Minapath Développement; no other relationships or activities that could appear to have influenced the submitted work."

Authorship

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

* Corresponding author

Michel Vincent
MINAPATH Développement
56 Boulevard Niels Bohr,CEI2, CS : 52132
69603 Villeurbanne Cedex France
Phone: +33 (0)6 37 39 97 47
E-mail: mvincent@minapath.com

Word count: 4983 words

ABSTRACT

Objective: To examine associations between local and systemic symptoms and the wear of the tin weld of Essure implants.

Design: study of a series of cases.

Settings: Two French hospitals.

Participants: Eighteen patients explanted by hysterectomy and salpingectomy for removal of their Essure implants between September 2019 and July 2020, have had a common anatomopathological process.

Main outcome measures: anatomopathological examination by optical microscopy and mineralogical analysis of the fallopian tube or uterine horn with scanning electron microscopy coupled with energy dispersive X-ray (SEM-EDX). Evaluation of local and systemic symptoms with a questionnaire. Examination of blood metal assays (nickel, chromium, and tin).

Results: anatomopathological examination highlights granulomas, fibrosis, adenomyosis, nonspecific inflammation, cysts and myomas in the Fallopian tubes, uterine horns, or both and mentions the presence of foreign bodies in seven cases. SEM-EDX analyses showed, systematically, the presence of tin particles integrated in the wall, generally in clusters, and with a size ranging from about one micron to several dozen microns. The questionnaire shows that the most frequent local symptoms were pelvic pain, urinary disorders, bleeding, and pains during intercourse. The most common systemic symptoms were: asthenia, visual disturbances, amnesia, giddiness, dorsal pains, headaches, and joint pains. The majority of local and systemic symptoms decreased after explantation, but sometimes incompletely. Before explantation, high levels of nickel, tin and chromium were observed in 11/17, 1/7 and 2/17 patients. After explantation, tin levels were high in 3/11 patients.

Conclusions: Local clinical symptoms of bleeding and pains could be for a great part linked to the wear of the tin weld, whereas systemic symptoms and sphincter disorders could be linked to a chronic organotin intoxication. Indeed we suppose that the slow leaching of the tin particles disseminated in uterus tissue and body can lead to the formation of more toxic components.

KEY WORDS: ESSURE implant, tin weld, wearing, local dissemination, tin particles, organotin

Article Summary

1) Many patients with Essure devices request the removal of these implants due to persistent adverse effects.

2) Eighteen patients explanted between September 2019 and July 2020 benefited from a common anatomopathological study protocol.

3) Each patient have an anatomopathological examination, a mineralogical analysis of the fallopian tube or uterine horn, a questionnaire and a blood metal assays.

4) Tin particles were found in all the biopsies analyzed.

5) The symptoms could be for a great part linked to the wear of the tin weld.

Strengths and limitations of this study

1) Patients have benefited from a new anatomopathological protocol specially designed to search for mineral particles in their uterine biopsies after explantation of their Essure contraceptive implants.

2) The mineralogical analysis highlighted, systematically, the presence of particles mainly composed of tin in the uterine biopsies of the patients included in the study.

3) The measurement of local and systemic symptoms for each patient, before and after implant removal, shows a significant reduction of symptoms in most cases.

4) The retrospective study of patients makes it difficult to study blood metal assays that have not been done systematically.

5) The results of this study allowed us to develop the hypothesis that there is a causal relationship between Essure implant's tin solder corrosion and local and systemic symptoms of the patients.

INTRODUCTION

In 2002, a novel hysteroscopic sterilization device was put on the market after review and premarketing approval by the US Food and Drug Administration (FDA): the ESSURE System (initially marketed by Conceptus, a start-up later bought by Bayer Healthcare, Whippany, New Jersey, in 2013). The ESSURE device is made of an internal spring made of steel (iron, chromium and nickel) associated with terephthalate polyethylene (Dacron) and an external spring made of Nitinol (nickel and titanium) to help maintain the device in the fallopian tube. Polyethylen fibers were used to produce a fast inflammatory response with macrophages, fibroblasts, foreign body giant cells and lymphoplasmocytes, designed to induce fibrosis and tubal occlusion in each fallopian tube, to prevent fertilization [1,2]. Three months after placement of the device, women underwent hysterosalpingography to confirm implant placement and occlusion, before discontinuing use of other contraceptive methods.

The device offered clear advantages, namely the absence of incision and the possibility to insert intravaginally the implant without general anesthesia and in an ambulatory setting. The outer coil and inner coil were linked by a tin solder. Some incidents of nickel allergy were rapidly noticed [3-5], and pain [6-8], migration [9-11] , contraceptive failure [12] have also been noted, but at the same time studies comparing hysteroscopic versus laparoscopic sterilization were in favor of microinsert implantation [13-15].

In 2015 a sudden increase of patient-reported adverse effects surrounding the ESSURE implant was observed [1, 16]. The driving forces for the sudden increase in adverse event reporting starting in 2013 remain unclear. Pharmacovigilance through online community outreach and mobile reporting applications may have played a role [17]. In France, which was the largest market among European countries with about 200 000 women, three associations of patients have been created and represent more than three thousand women. There is a marked tendency towards salpingectomy or hysterectomy treatment of many affected women. In 2018 a retrospective French study based on data from hospitals and the health safety agency compared 71303 women sterilized by Essure implant and 34 054 sterilized by tubal ligation [18]. The Essure implant technique was associated with a higher risk of gynecological complications one and three years after implantation; however there was no difference for systemic symptoms. A September 2019 FDA report about biological responses to metal implants includes a discussion about ESSURE implants [19], principally centered on nickel hypersensitivity as a proposed explanation for ESSURE intolerance. [3-5].

We recently published in 2020 a study based on ten explanted cases, discussing a dysfunction of the implant at the level of the tin weld [20]. We made four proposals: 1/ to always perform a hysterectomy with salpingectomy because we frequently found tin particles in the uterine horns, 2/ to systematically look for tissue lesions at the weld level during anatomopathological examination, 3/ to perform a mineralogical analysis by SEM-EDX for chemical identification of the particles in fallopian tubes and/or horns, and 4/ to monitor tin blood levels. The purpose of our study is to examine associations between local and systemic symptoms and the wear of the tin weld of Essure implants. Each patient have systematically a new anatomopathological protocol specially designed to search for mineral particles in their fallopian tube or uterine horn with a mineralogical analysis by SEM-EDX, correlated with a clinical questionnaire before and after axplantation and, sometimes, a blood metal assays.

PATIENTS AND METHODS

Study design

This is a retrospective study of a series of 18 cases.

Patient population

Eighteen women aged 36 to 56 years (median and mean: 49 years old), implanted for a duration of 44 to 178 months (median: 89, mean: 94), who requested removal of their ESSURE implant and underwent salpingectomy and hysterectomy. All the patients having benefited from the anatomopathological protocol designed to study the effects of wear on the tin solder were systematically included in the study between September 2019 and July 2020.

Every woman gave an informed consent agreeing to the observation of her specimen in an individual research context with SEM-EDX analysis (MC, ER, and AMS) and to a grouping of cases for publication.

Patient and public involvement

Patients participated in the research but were not involved in the design, conduct, reporting or dissemination plans of the research.

Anatomopathological protocol

The process has been elaborated by our pathologist partners (EW, CL)**.** Seventeen analyses were made by the same medical and pathologist team (GS, and CL); one other center received the anatomopathological protocol beforehand. For the preparation of biopsies, it was recommended that the Essure implant not be removed by the surgeon, so as to make it possible during the macroscopic anatomopathological examination to locate the Essure implant within the fallopian tube, and to open longitudinally the tube and horn without altering the implant and ablate it without stretching it if possible. A longitudinal fallopian tube and/or uterine horn section was prepared in front of the implant, as well as a transversal section at the weld level and at the distal extremity of the implant, in addition

to classical sampling of horn and uterus tissue. Finally the implants were put into a dry flask, with identification of each side. The pathologist sent a paraffin block for mineralogical analysis of the specimen showing the most granulomatosis or inflammatory lesions and if possible foreign bodies identification.

Preparation for scanning electron microscopy coupled with energy dispersive X-ray (SEM-EDX) study

Two 5µm thick histological sections were made from the paraffin block. The first one was subjected to HES coloring and placed on an optical slide. The second was deposited on a double-sided adhesive carbon disc (diameter 25 mm) as described in our recent article [20], which also describes the SEM analysis conditions.

Particle analysis protocol

The goal of the mineralogical analysis was to look for any mineral particles coming from the Essure implant weld in the tube or horn samples. All the histological sections were firstly observed with a low magnification (x50) for identifying high density clusters of particles. Field analyses were then performed on these clusters and as well possibly on granulomatosis or inflammatory lesions. For each biopsy, **at least 30 particles** were analyzed on at least three fields. On each field, the analyzed particles were sampled by the operator and classified into different particle families based on the EDX spectra.

Clinical data

All patients were interviewed by one or two clinicians (GS, MV). Patients were solicited with an evaluation form to assess the level of tolerability of each local or systemic symptom on a scale from 0 to 10, before explantation and after at least three months from explantation. One patient did not respond to the questionnaire.

Blood metal measurements were not systematically performed. The levels were measured by ICP-MS for nickel in plasma, for chromium in total blood, and generally for tin initially in plasma before explantation and total blood after explantation.

RESULTS

A/ Pathological analysis by optical microscopy and SEM-EDX (Figure 1 and table 1 and 2)

The pathological study by optical microscopy (Table 1) shows that all women presented some granulomas (17/18 patients) or fibrosis (1/18) identified in the fallopian tube (9/18), uterine horn (6/18) or both (3/18). We also observed adenomyosis (14/18), nonspecific inflammatory signs (10/18) and foreign bodies (7/18 patients). Various other lesions such as cysts and myomas were observed. Mineralogical analysis showed for each patient some particles of size between one and several dozen microns, often in clusters, in the fallopian tube or horn not far from the wall (Figure 1). Table 2 shows that the presence of tin-based particles was observed in all samples by EDX analysis. Tin was sometimes associated with silver. Some calcium particles were also found, corresponding most often to calcium phosphate and more rarely to calcium oxalate. We observed also some particles of titanium, platinum, silver, and steel (FeCrNi).

B/ Clinical results (tables 3 and 4, Figures 2 and 3)

Seventeen patients responded to the questionnaire. The most frequent local symptoms before explantation, irrespective of perceived intensity, were: pelvic pains (13/17 patients), urinary sphincter disorder (12/17), bleeding (11/17), pains during intercourse and genital prurit (9/18), and symptoms linked to microbian urinary infection (8/18). For 17 patients there was a global improvement in the intensity of symptoms after explantation. (Figure 2). The most frequent systemic symptoms were asthenia, visual disturbances (15/17), dizziness and back pains (14/17), headaches and joint pains (13/17). Figure 3 shows a significant decrease of all systemic symptoms after implant removal.

Regarding the questionnaire scoring for each patient, in the majority of cases there was a decrease in the total scores, sometimes modest. Three patients had unchanged total systemic symptom scores (among them patients 10 and 11 who had no symptoms before explantation). The eight patients who had urinary infections had a mean systemic score of 88.5 whereas the 9 patients without infection had a mean score of 44.8 (Mann and Whitney test; p=0.0037).

C/ Metal blood level measurements (Table 5)

Before explantation, the plasmatic nickel levels were above the superior limit (SL) in 11/17 patients, and so were the plasmatic tin level in 1/9 patient and the total blood chromium level for 2/17 patients. After explantation the total blood tin level was still higher than SL in 3/11 patients, and in three cases we observed a higher total blood tin level after explantation compared to the plasma level before explantation.

DISCUSSION

We pre-established and applied an anatomopathological protocol to a series of 18 patients who underwent surgery to remove their Essure implants. The use of this protocol followed by a mineralogical analysis of uterine biopsies enabled us to systematically detect tin-based particles in the fallopian tubes and uterine horns. These results are correlated with an anatomopathological examination, a questionnaire and, sometimes, a blood metal assays in order to examine associations between local and systemic symptoms and the wear of the tin weld of Essure implants.

Limitations

The results of blood tests are incomplete due to the retrospective nature of our study. In fact, the patients did not systematically carry out this type of examination. For symptom collection, the intensity scale from 0 to 10 is filled in by the patients. There may be a bias in the perception of pain that may be dependent on the patient. One patient did not respond to the questionnaire.

A/ Anatomopathological and mineralogical analysis by SEM-EDX

These results confirm those of our preliminary study in which there was no specific anatomopathological examination [20]. In that study, the reason why half of the specimens did not show tin particles is probably because the biopsies studied were far from the implant weld. The sampling made in the present study, at the implant weld level, explains the systematic observation of (most often) granulomatosis or (in one instance) fibrosis lesions. Indeed, a 2001 preliminary study of pathological effects of implants on fallopian tube and uterine tissue on 33 women [2] showed that there were foreign body granulomatosis reactions in 26 of 47 fallopian tubes studied and a chronic inflammatory reaction in 42 of them.

However, a US retrospective study on 126 explanted women observed an inflammatory aspect in only 59 cases, of which 31 were in association with giant cells and a chronic lympho-plasmacytic reaction [21]. Finally, a French study on 90 explanted patients found that 28 had fibrosis signs, and only 14 had inflammatory salpingitis and 10 had a macrophagic reaction [22]. A preclinical animal study on pigs by Conceptus Inc. showed by optical microscopy the presence of foreign bodies in fallopian tubes, without chemical identification [23].

Indeed SEM-EDX analysis was necessary for identifying particles coming from worn tin solder. The identification of granulomas at the uterine horn level for nine women suggests a diffusion of particles from the fallopian tubes or a partial implant migration, justifying the recommendation for systematically associating a hysterectomy to salpingectomy. This diffusion of particles is confirmed with the observation (unpublished) by our team of an implanted patient with a rectovaginal inflammatory granulomatosis nodule for which SEM-EDX analysis identified granulomatosis reaction with some tin particles.

Adenomyosis was an associated condition in 15/18 cases. This pathology, easily identified by Magnetic Resonance Imagery and linked to a uterine traumatism, could have been induced by the Essure implants [24]. SEM-EDX observation allowed the identification of particles for all patients whereas

optical microscopy only identified foreign bodies in 7/18 cases. This proves the interest of SEM-EDX use for eliminating all granulomas related to foreign bodies. The other identified particles come from other Essure implant parts: the steel internal spring (iron, chromium and nickel) or the nitinol external spring (nickel and titanium). However steel particles were rarely observed. It is possible that nickel could be present in the form of nanoparticles that cannot be observed by our SEM with the magnification used for analysis. Indeed an inductively coupled plasma mass spectrometry (ICP-MS) tissue study [25] of the elements chromium and nickel showed the presence in fallopian tube and uterine tissue of a density gradient between the juxta implant zone and the more distal zone, suggesting that a release of these two metals did occur. Unfortunately, no study of the presence of tin in the same tissues was performed, either by ICP-MS or by SEM-EDX analysis. Chromium, nickel and titanium particles coming from joint prostheses are considered biocompatible. This is the case for example with hip prostheses, even if some particles are observed in loco-regional nodes [26]. Similarly, the nitinol implants widely used in vascular endoprostheses are considered to be well tolerated despite a long term leaching [27,28]. The calcium particles frequently observed in our study could be linked to a beginning of endogenous calcification from uterine inflammatory tissues. Thus it seems possible that an important part of the inflammatory and fibrosis process observed in the fallopian tubes and uterine horns could be attributed to tin particles predominantly coming from tin weld wearing [20], even though one cannot eliminate a possible role for chromium and nickel nanoparticles.

B/ Clinical data

For the studied patients, the median time between implantation and explantation was about 90 months, i.e. seven and a half years. In previous studies, the frequency and importance of symptoms have been found to increase with the time elapsed since implantation [29]. After a median follow up time of 29 months, 689 implanted women out of 924 (74%) responded to a satisfaction questionnaire about symptoms. Of those, only 100 (15%) reported disabling symptoms, most often local. The same questionnaire sent to 577 patients after a median follow up time of 144 months (12 years) resulted in

157 out of 317 respondents (49.5%) reporting disabling symptoms, and 51 (16%) undergoing implant removal.

An improvement in clinical data and quality of life has been reported in all explantation studies [30-33]. The screening questionnaire with scores between 0 and 10 about the level of symptoms before and after explantation was completed after an individual interview about symptoms by at least one clinician for all patients. It took into account the most frequently reported local and systemic symptoms. One patient did not respond to the scoring questionnaire. Two patients signaled that they had no symptoms but asked for implant removal in relation to information found on social networks. However the placebo hypothesis for explaining the regression of local symptoms on the great majority of patients (14/17) can be eliminated in light of the large-scale French data analysis comparing Essure implant and tubal ligation cohorts [18]. The difference between the two cohorts has been studied for the incidence of new local surgery procedures, but also systemic symptoms such as auto-immune disease, thyroid disorders, allergies, antalgic, antimigraine, antidepressant or benzodiazepine treatments, medical check-ups, death, new disease, suicide attempts. More than 5% of Essure implanted women (5.6%) needed another local surgery, compared to only 1.7% of the patients treated by ligation.

In our experience, local symptoms with pelvic pains were the most frequently reported ones, ahead of urinary sphincter troubles and intercourse pain; all of these were significantly improved by explantation. If the pains and bleeding can be linked to local inflammation and adenomyosis, the frequency of urinary leaks (12/17), associated in four cases with troubles of the anal sphincter, suggest a neurogenic factor independent of uterine inflammation. Among the four cases with anal sphincter troubles, one patient needed a neurostimulation and was completely cured after explantation. However, it also seems plausible that the tin weld corrosion inducing inflammatory granulomatosis could also be responsible, along with adenomyosis, for the pelvic and intercourse pains and bleeding.

About systemic symptoms, the median follow up time between implantation and explantation of more than 7.5 years confirms the need to have a new large-scale study on the French data [18] with a minimal follow-up time of five years. It is interesting to compare the total screening results of patients with or without urinary infections and systemic symptoms: the mean systemic symptom score of patients with infection was 88 whereas the other patients without infection had a mean score of 44. One other patient has been diagnosed with multiple sclerosis after two neurologic symptoms, diplopy followed by abnormal movements of the arm, signs which are compatible with organotin intoxication [34].

C/ Metal measurments. The measurements were realized by ICPMS dosage, taking into account 100 healthy control subjects [35]. For nickel dosage, the frequency of levels higher than SL was important compared with studies on nickel-rich stainless steel. A first study on nickel alone, 9 to 15 years after implantation of hip prostheses, did not show any significant difference for 12/13 patients compared to 30 healthy subjects. The mean nickel levels reported were 0.28 µg ± 0.24 µg/l. Only one patient, a 78 year old man with two hip prostheses, had a high level of 3.1 µg/l but related to a renal insufficiency [36]. On the other hand, a chromium and nickel level study on 20 patients who had hip prostheses for more than ten years and 20 controls showed a significant difference for those two elements, but without levels that exceeded the SL [37]. The nickel values were between 0.26 and 0.33 µg/l. If some neurologic symptoms have been observed related to chromium-cobalt intoxication in metal-metal prostheses [38], we do not know of systemic symptoms linked to stainless steel hip implants. In some studies nickel and chromium are found to have a low risk of neurotoxic symptoms [39,40]. However other studies discuss a possibility of nickel neurotoxicity [41,42]. The frequent occurrence of high levels of nickel in the blood for Essure implants, compared to their very rare occurrence for hip prostheses, is probably linked to the high vascularization of the uterine horn tissue, with adenomyosis, in sharp contrast with the bone support of hip prostheses.

Partial tin dosages confirm the higher sensitivity of dosages on the total blood specimen, due to a large portion of micro or nanoparticles being positioned within blood cells. Based on this, we recommend looking for tin overloading by performing dosage on total blood. At the present time we were unable to locate, in France, a biological laboratory able to study organotin levels, which could help to understand symptoms.

Indeed it is tin which could be responsible for a great part of the general symptoms of the patients. Among them, 11/17 agreed to realize a new dosage of tin in total blood after explantation, and in 3/11 the tin level was higher than SL. In our recent experience, tin dosage on total blood before explantation can be very high, up to four to five times the superior limit.

D/ The strong suspicion of a chronic organotin intoxication

This hypothesis seem plausible. Three points have to be discussed: 1/ an incorrect estimation in preclinical studies of the importance of tin leaching by the implant weld; 2/ a possible transformation in the body of inorganic tin into organotin; and 3/ the similarity of symptoms of implanted patients and organotin intoxication victims.

1/ An underestimation of the importance of tin release by the weld into the body compared to oral diet intake.

Tin may be found in the body in three principal forms: tin ions, metallic or inorganic tin, and organotin.

Inorganic tin is widely used in fruit or vegetable juice cans, in the form of tin chloride salt, as an antioxidant and color-preserving additive (E512). Some cases of intoxication have been reported in the literature, involving a contamination of the steel can with tin [43,44]. Inorganic tin tolerance has been reviewed in 2018 by the European agency for food safety [45]. The maximum tolerable daily dose (MTD) was decreased from 140 mg a day to 40 mg, a level above which patients begin having gastric symptoms. It was estimated that the daily diet intake from additives was under 1.3 µg/ day and that the 95 percentile maximum exposure could be 11 µg/day. At the same time, the daily intake of

inorganic tin from the diet, outside of canned juice additives, was estimated in various studies to be 1 to 8 mg/day [34]; 0.2 to 1mg according to Rudel and Shaeffer [46,47]; and 0.18 mg in the United Kingdom according to Winship [48]. Moreover it is established that the proportion of mineral tin absorbed from the gastro-intestinal tract is very low, about 1 to 2% [34]. So the approximate penetration of inorganic tin in the body is about 25 µg/day. A Conceptus document submitted to the French medical safety agency in 2004 (Annex 1) showed that the implant weld observed by SEM after immersion for six months in a salted serum bath had a very important corrosion on 25-50 % of the surface at 3 months and 100% at six months whereas no implant rupture was observed. The report's authors considered that the absence of rupture after six months was sufficient to achieve fallopian tube fibrosis and sterilization. Moreover, chemical tests measuring implant corrosion were made for tin, chromium and nickel in salt baths over a six months survey. The release of tin ions was up to 25 µg/day, two hundred times more than for nickel and one thousand times more than chromium. The importance of tin release had to be minimized according to the report's authors if we compare this release to the daily diet tin intake "of 100mg/day per os". However this daily tin intake of 100 mg does not correspond to the usual daily intake which is only about one mg, and the comparison ignores the very low absorption of tin by the gastrointestinal tract. In fact the release of tin into the body by the Essure implant was at least of the same order of magnitude as that arising from the diet daily intake. The major corrosion of the tin weld has recently been confirmed by Aslam [49] by a galvanic corrosion study in a bath with phosphate buffer saline (PBS) and formol. Nickel release was 10 ppb after 1000 hours, with a stabilization over time, whereas tin release increased from 200 ppb to 300 ppb between 500 and 1000 hours without apparent stabilization. Major weld corrosion was also observed by SEM analysis.

2/ A possible transformation of inorganic tin into organotin after ionic corrosion. Tin in ionic form can combine with carbon atoms to form organotin compounds. Those compounds are largely used in the industry for plastics, but also insecticides, wood preservatives, antifouling paints for boat hulls and repulsives. The industrial process for organotin synthesis requires high temperatures (about 200°C)

and special reagents [43]. However organotin may also be produced without such high temperatures from inorganic tin within ecosystems in relation with microbiota [49-51]. Moreover, redox reactions at normal temperature have been described to allow the transformation of inorganic tin into organotin by contact between tin coming from corrosion and organic molecules such as acetylcholine, via a methylation process [52]. The probability that inorganic tin absorbed by the gastrointestinal tract could be transformed into organotin was considered as impossible by Blunden [43] because of the very low digestive absorption of inorganic tin, which is rapidly eliminated with feces, and because the transformation process of inorganic tin into organotin by microbes is very slow and impossible to complete during the short amount of time spent by the inorganic tin in the body. However, in the case of the Essure implant, the tin mineral particles observed in the uterine tissue are present for several years in contact with the uterine biotope [53], and further subjected to infections [54], as attested by the frequency of genito-urinary infections among our cases. Such a mechanism of transformation of inorganic metal into more toxic organometal compounds by the biotope has also been described for mercury [55]. The fact that patients having had urinary infections have a higher score on symptom intensity than patients without infections is in favor of this hypothesis. Finally if we take in count this possibility of inorganic tin transformation into organotin in the body, over a period of several years during which the implant weld slowly undergoes corrosion, we can suspect that systemic symptoms, and some local symptoms such as sphincter troubles, observed on patients can correspond to the symptoms of organotin intoxications.

3/ Organotin toxicity has been known since 1954, following the French sanitary scandal of Stalinon [56]. This organotin based medication was prescribed in France for treating furunculosis. Animal and human clinical trials had been largely insufficient and led to the sale of highly toxic organotin capsules, resulting in about 100 deaths and more than 100 cases of severe injuries. Patients presented cerebral and meningeal edemas and intracranial hypertension. Several survivors had severe paraplegias with motor and sphincter troubles. Another cluster of organotin intoxication cases was observed in the 1990s in South China where more than a thousand were poisoned by misusing organotin contaminated

industrial lard as cooking oil [57]. Other observations have been reported more often in an occupational context [58-60], sometimes with psychiatric symptoms. Brain Magnetic Resonance Imaging (MRI) noted defects in the white matter [61, 62]. Cima [34] details neurologic symptoms linked to organotin toxicity: hearing loss, visual disturbances, headaches, involuntary hand movement episodes, diplopia, giddiness, amnesia, polyneuropathy, calculation ability impairment, delayed sensomotor polyneuropathy. Many of these symptoms are frequently mentioned in the complaints of Essure implanted patients. Among the 18 cases in our study, one patient was diagnosed with multiple sclerosis after two types of symptoms: diplopia and involuntary unilateral hand movements, both of which occur with organotin toxicity. Finally, the neurologic bladder signs could be interpreted as organotin toxicity symptoms. Another physiopathological hypothesis of toxicity linked with tin weld corrosion, despite the small ponderal level of tin (1.9 mg in each solder according to Bayer) is the possibility of nano-toxicity mechanisms. Indeed the persistent wear of tin particles over the years could induce the production of nanoparticles. We know that the toxicity of nanoparticles is not directly linked to the weight of metal, but rather proportional to the exchange surface between metal particles and biological tissue, with an increase of toxicity level by factors of up to a thousand for the same weight [63].

Of course these results have to be confirmed by other SEM-EDX analyses conducted by other teams. A study on a random sample of several hundred implanted patients with a follow up interval of at least five years, with a common questionnaire about local and systemic symptoms and measurements of the plasmatic levels of nickel and total blood levels of tin and organotin, could confirm this strong suspicion, especially if combined with new mineralogical analyses by SEM-EDX if patients needed to be explanted. A great number of patients report continuing symptoms after explantation, which could be linked to a dissemination of particles in the body before explantation. We recall the case of a patient with a rectovaginal granulomatosis nodule within which tin particles were identified, confirming the transport of such particles outside the uterus. The persistence of a high tin blood level, as was the case

for three patients of our study, could form the basis to propose a prospective clinical trial with treatment by a chelating agent [64].

CONCLUSION

We demonstrate for the first time that inflammation observed under granulomatosis form in fallopian tubes and uterine horns, following Essure implant implantation, is not principally linked to polyethylene fibers but also to corrosion of tin solder. This tin solder is a specific feature of the Essure implant among commonly implanted devices. No SEM-EDX chemical study was performed on the particles observed in fallopian tubes during animal experiments and in clinical preliminary studies. The local symptoms of pain and bleeding in implanted patients have to be linked to this dysfunction of the implant, with on one hand granulomas at the contact point with worn solder, and on the other hand, horn adenomyosis.

The systemic clinical syndrome that slowly appears in some implanted women can concern up to 50% of patients after five years and is compatible with chronic organotin toxicity syndrome. Several mechanisms are evoked for explaining organotin formation from inorganic tin solder corrosion: redox processes in presence of molecules such as acetylcholine, a possible role of the genitourinary microbiota, or mechanisms of nano-toxicity. The diffusion of particles to the uterine horns makes it advisable to systematically propose a hysterectomy associated to salpingectomy. A random sample study of about a thousand implanted women for at least five years, combining a clinical inquiry, metal blood level measurements, and tissue mineralogical analysis by SEM-EDX in case of explantation, seems to us necessary in order to completely validate our hypothesis. Moreover, if most patients see improvements in clinical condition after explantation, sometimes the persistence of symptoms could be linked to the persistence of tin particles in the body. A prospective clinical trial with metal chelating agents could be proposed for patients whose symptoms persist.

On a broader scale, this study confirms the interest of SEM-EDX analysis, which is a precious tool in preclinical biomaterial studies as well as in the search for identifying the causal agent of many granulomatosis diseases often considered as idiopathic. It is because of SEM-EDX analysis, which had not been previously used in preclinical trials and explanted tissue analysis, that tin imputation could have been evoked.

ACKNOWLEDGEMENTS

All patients included in the study for their collaboration and responsiveness.

"Association de Lutte contre le Cancer Thoracique et les Minéralopathologies" (ALCTMP) chaired by Doctor JF. ALEX, for the subsidy granted in aid of publication and for the advances of mineralogical analysis costs allocated to certain patients.

The mutual insurance companies "Pacifica", "Macif", "Banque Populaire et Caisse d'Epargne" (BPCE) for covering the cost of mineralogical analyses for certain patients.

A. BOUCHARDON and B. SMATTI of the "Centre d'Imagerie Quantitative Lyon-Est" (CIQLE) for the management and preparation of samples for SEM analysis.

Doctor J. REVERSO-MEINIETTI from the "MEDIPATH" laboratory in Nice for the application of the anatomopathological protocol and Dr CLAVE for the surgical operation.

Professor V. BALTER and P. TELOUK from the "Laboratoire de Géologie de Lyon, Terre, Planètes et Environnement" (LGLTPE), "Ecole Normale Supérieure" (ENS) of Lyon, for the analysis of the elementary composition of an implant and for thinking about metal dosages.

P. GIORGIO and the "Association Générale de l'Internat de Lyon" (AGIL) for assistance with bibliographical research.

Professor H. MAISONNEUVE for his advice.

G. PETITJEAN "Laboratoire Cerba" France for its help in thinking about metal dosages.

D. AMOUROUX (CNRS and University of PAU) for his help in thinking about organotin production in ecosystems.

AUTHOR STATEMENT

All the authors of this article meet the following criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table 1: Description of the patients, the different biopsies analyzed and details of the histological study. ft: fallopian tube; uh: uterine horn.

Patient number	Age	Biopsy	Time before removal (months)	Granuloma	Fibrosis	Non-specific inflammation	Foreign bodies	Adenomyosis	Others
1	49	ft + uh	127	X				X	Cervical epidermal dystrophy
2	52	uh	90	X		X	X	X	
3	49	uh	73	X				X	Dystrophic endometrium
4	56	ft	114	X				X	Myomas
5	52	ft	66	X		X	X	X	Calcifications
6	43	ft	80	X				X	Cystosteanonecrosis
7	46	ft	60	X		X		X	Paratubar cysts
8	48	ft	103	X				X	Myomas
9	36	ft	44	X		X	X		
10	54	uh	178	X		X	X	X	Ovarian and paratubar cysts
11	38	ft + uh	55	X		X		X	Paratubar cyst
12	51	ft	80	X					Myomas
13	45	ft	61		X				Paratubar cysts
14	56	uh	121	X				X	Myomas
15	49	uh	107	X		X	X	X	
16	50	uh	91	X		X	X	X	Paratubar cyst
17	56	ft	162	X		X			Myomas
18	55	ft + uh	89	X		X	X	X	

Table 2: results of the mineralogical analysis of the biopsies. ++++: 75 to 100%; +++: 50 to 75%; ++: 25 to 50%; +: 0 to 25%. ft: fallopian tube ; uh: uterine horn.

Patient number	Sample	tin-based	calcium-based	silicon-based	Steels	Fe comp	Ti comp	Pt comp	AgO	number of particles analyzed
1	ft + uh	++++							+	96
2	uh	++++	+		+					133
3	uh	++++	+							30
4	ft	++++								59
5	ft	++++								40
6	ft	++++								45
7	ft	+++					+	+		40
8	ft	++++	+				+			50
9	ft	++++			+					30
10	uh	++++								30
11	ft + uh	++++								45
12	ft	++				+++				70
13	ft	++++	+		+					32
14	uh	++++								30
15	uh	+++	++	+						47
16	uh	++++								30
17	ft	++	++	+	+		+	+		42
18	ft + uh	++++								45

Table 3: intensity of local symptoms contracted by patients before and after removal of their ESSURE implants. The intensity is measured with a score ranging from 0 (no symptoms) to 10 (very strong symptoms). Patient N°12 lost of follow up.

		1	2	3	4	5	6	7	8	9	10	11	13	14	15	16	17	18	Total score
Genital haemorrhages	**Before**	0	0	8	0	10	5	0	8	10	0	1	4	8	10	1	0	1	**66**
	After	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Pelvic pain	**Before**	4	3	0	8	6	8	10	9	10	3	0	2	0	9	6	6	0	**84**
	After	0	0	0	10	0	0	10	3	6	0	0	0	0	0	0	3	0	**32**
Pain during sexual relations	**Before**	0	0	0	7	5	8	10	8	10	0	0	0	0	7	4	10	0	**69**
	After	0	0	0	10	0	0	0	2	10	0	4	0	0	0	0	0	1	**27**
Microbial urinary infection symptoms	**Before**	1	0	0	9	0	4	2	5	10	0	0	0	0	0	8	6	0	**45**
	After	0	0	0	10	0	0	1	0	10	0	0	0	0	0	0	0	1	**22**
Genital fungus infection symptoms	**Before**	6	0	0	0	0	0	0	5	10	0	0	2	0	0	0	6	0	**29**
	After	0	0	0	0	0	0	0	0	10	0	0	1	0	0	0	0	0	**11**
Urinary sphincter disorders	**Before**	0	2	0	8	0	7	3	10	7	0	0	2	7	5	7	6	6	**70**
	After	0	2	0	9	0	3	10	3	5	0	0	0	4	2	3	2	2	**45**
Anal sphincter disorders	**Before**	0	0	0	2	0	0	10	2	0	0	0	0	0	0	0	0	9	**23**
	After	0	0	0	2	0	0	9	0	0	0	0	0	0	0	0	0	0	**11**
Genital itching	**Before**	0	0	0	6	0	4	9	8	9	0	0	0	3	6	7	6	0	**58**
	After	0	0	0	7	0	0	7	2	9	0	0	0	0	2	0	1	0	**28**
Anal itching	**Before**	0	0	10	4	0	0	10	8	0	0	0	0	0	0	0	6	0	**38**
	After	0	0	0	4	0	0	10	2	8	0	0	0	0	0	0	1	0	**25**
Total score	**Before**	**11**	**5**	**18**	**44**	**21**	**36**	**54**	**63**	**66**	**3**	**1**	**10**	**18**	**37**	**33**	**46**	**16**	
	After	**0**	**2**	**0**	**52**	**0**	**3**	**48**	**12**	**58**	**0**	**4**	**1**	**4**	**4**	**3**	**7**	**4**	

Table 4: intensity of systemic symptoms contracted by patients before and after removal of their ESSURE implants. The intensity is measured with a score ranging from 0 (no symptoms) to 10 (very strong symptoms). Patient N°12 lost of follow up.

		1	2	3	4	5	6	7	8	9	10	11	13	14	15	16	17	18	Total score
headaches	**Before**	9	0	0	8	3	9	9	9	10	0	1	0	8	8	3	8	6	**91**
	After	0	0	0	6	0	3	9	3	5	0	1	0	2	5	2	8	3	**47**
asthenia	**Before**	10	9	9	10	7	8	10	10	10	0	0	3	6	9	8	9	7	**125**
	After	3	7	5	9	1	7	10	2	6	0	0	1	0	5	7	6	3	**72**
alopecia	**Before**	4	8	0	10	3	0	10	7	9	0	0	7	5	9	10	3	0	**85**
	After	1	7	0	8	1	0	10	3	9	0	0	6	2	1	10	2	0	**60**
skin rash	**Before**	7	0	7	3	3	0	7	5	9	0	0	0	5	8	1	1	0	**56**
	After	0	0	2	3	0	0	7	2	7	0	0	0	4	1	0	2	0	**28**
muscle pains	**Before**	10	0	7	8	8	6	10	9	10	0	0	0	8	9	9	1	7	**102**
	After	6	0	4	10	7	3	10	3	10	0	0	0	4	0	6	1	2	**66**
back pains	**Before**	10	5	10	9	0	8	10	7	10	0	1	0	8	10	8	9	6	**111**
	After	8	5	9	10	0	5	10	3	10	0	1	0	5	1	3	7	2	**79**
joint pains	**Before**	10	0	2	8	4	7	10	10	9	0	0	0	9	5	9	8	7	**98**
	After	8	0	2	10	1	3	10	3	6	0	0	0	3	1	5	8	2	**62**
visual disorders	**Before**	8	6	2	5	3	6	10	10	8	0	0	2	6	9	10	9	5	**99**
	After	3	6	0	5	1	2	10	2	5	0	0	1	0	9	8	8	2	**62**
memory disorders	**Before**	8	9	1	6	8	7	10	10	10	0	0	5	8	8	8	9	4	**111**
	After	6	4	0	6	7	5	10	3	10	0	0	5	3	8	8	8	2	**85**
sleep disorders	**Before**	9	9	5	8	0	3	10	9	10	0	1	7	8	9	5	9	6	**108**
	After	0	7	5	7	0	2	10	9	10	0	1	9	3	5	3	7	3	**81**
hearing problems	**Before**	6	0	0	7	6	0	8	8	0	0	0	0	3	0	1	2	0	**41**
	After	5	0	0	6	1	0	8	7	0	0	0	0	0	0	1	1	0	**29**
diziness	**Before**	5	5	2	6	5	4	10	6	2	0	0	4	8	8	6	9	4	**84**
	After	2	2	1	5	5	0	10	2	0	0	0	4	4	4	6	7	2	**54**
Total score	**Before**	**96**	**51**	**45**	**88**	**50**	**58**	**114**	**100**	**97**	**0**	**3**	**28**	**82**	**92**	**78**	**77**	**52**	
	After	**42**	**38**	**28**	**85**	**24**	**30**	**114**	**42**	**78**	**0**	**3**	**26**	**30**	**40**	**59**	**65**	**21**	

Table 5: nickel, tin and chromium concentrations (µg/L) in plasma (p) and whole blood (wb) of patients before and after explantation of their ESSURE implants. Plasma nickel < 1.3 µg/L (95th percentile) (Cesbron A, 2013); Whole blood tin < 0.6 µg/L (95th percentile) (Cesbron A, 2013); Whole blood chromium < 0.87 µg/L (95th percentile) (Cesbron A, 2013).

	nickel		tin		chromium	
	Before (p)	**After (p)**	**Before (p)**	**After (wb)**	**Before (wb)**	**After (wb)**
1	4.8	<0.5	<0.7	0.23	<0.87	
2	2		<0.1	0.31	0.74	
3	2.6		0.1		0.5	
4	1.2			0.34	1.36	
5	1.4				0.65	
6	1.2			0.25	0.68	
7	1		0.17	0.23	0.5	
8	1.4				<0.5	
9	1.2			0.35	<0.5	
10	0.6				2.65	
11	2.3				<0.5	
12	1.8				0.88	
13	0.3		<0.5	0.85	3.2	
14	1.2			0.66	<0.5	
15	3.5		0.32		<0.5	
16		1.4		0.37		<0.5
17	2.3		1.34	0.73	<0.5	
18	1.6			0.33	0.69	

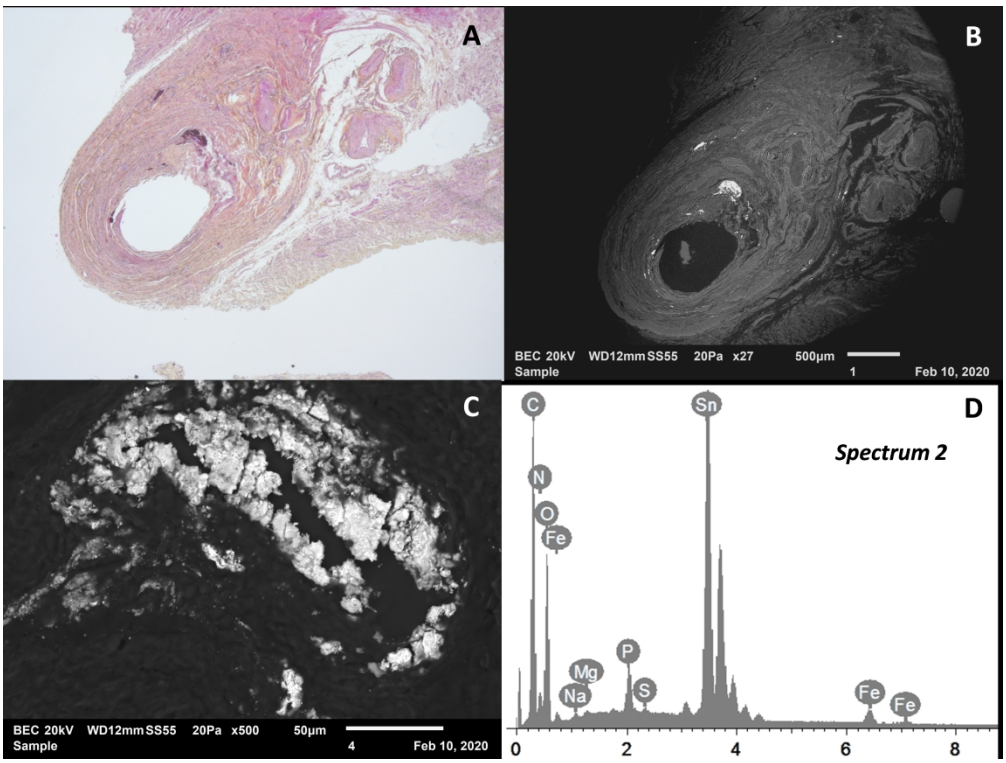

Figure 1: Correlative observation by light microscopy (A) and scanning electron microscopy (B) of the histological section of the fallopian tube of patient no. 6 at x25 and x27 magnification. A cluster was observed at x500 magnification (C) and an EDX analysis was performed. In this field, the 10 particles analyzed have a spectrum similar to the spectrum n°2 presented in figure (D).

855x644mm (144 x 144 DPI)

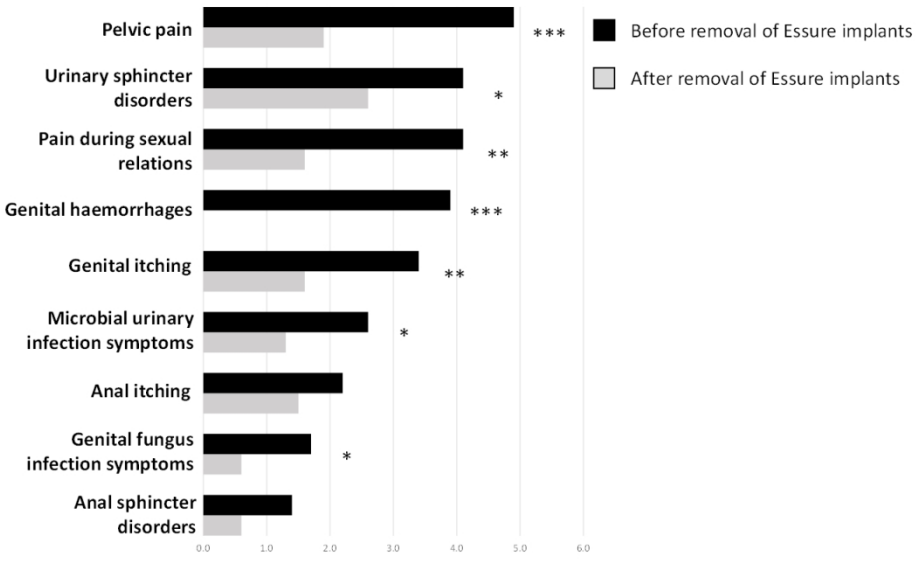

Figure 2: Histogram representing the score for each local symptom before (black histograms) and after implant removal (grey histograms). The results are expressed as averages. A Wilcoxon signed rank test for paired samples was performed for each symptom. $0.05<p<0.1$ (*); $0.01<p<0.05$ (**); $p \leq 0.01$ (***).

242x144mm (150 x 150 DPI)

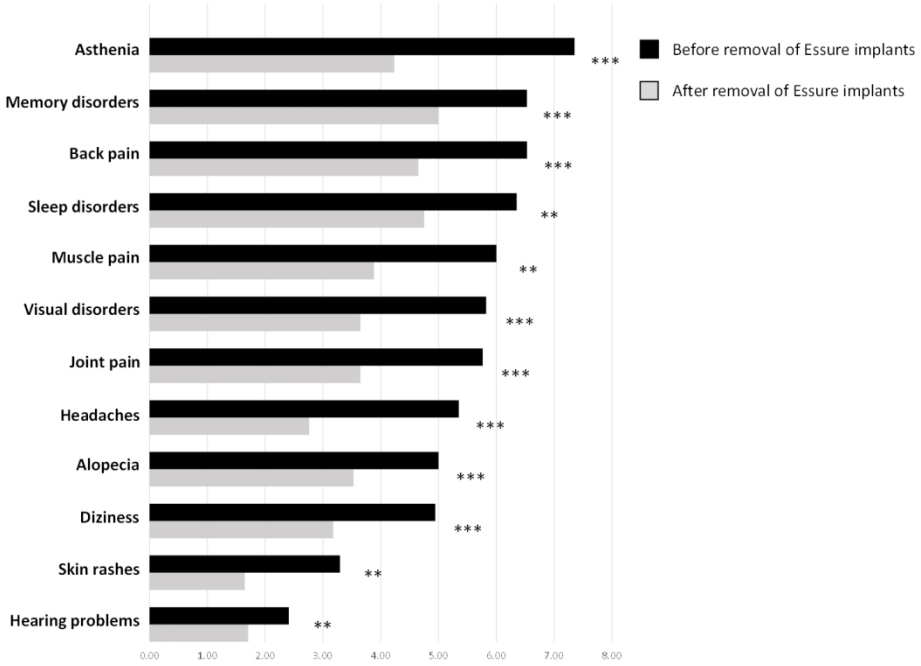

Figure 3: Histogram representing the score for each systemic symptom before (black histograms) and after implant removal (grey histograms). The results are expressed as an average. A Wilcoxon signed rank test for paired samples was performed for each symptom. $0.01<p<0.05$ (**) ; $p \leq 0.01$ (***).

267x190mm (150 x 150 DPI)

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			

Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	5
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5-6
Bias	#9	Describe any efforts to address potential sources of bias	N/A
Study size	#10	Explain how the study size was arrived at	N/A
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	5-6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	N/A
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	N/A
Statistical methods	#12c	Explain how missing data were addressed	N/A
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	N/A
Statistical methods	#12e	Describe any sensitivity analyses	N/A
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed	7-8

		eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	6-7
Participants	#13c	Consider use of a flow diagram	N/A
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	N/A
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	6-8
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	6-8
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
Main results	#16b	Report category boundaries when continuous variables were categorized	6-8
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	#18	Summarise key results with reference to study objectives	8
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	8
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	8-17

Generalisability	#21	Discuss the generalisability (external validity) of the study results	16-18
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

Bias #9

In order to limit bias on the intensity of symptoms, we averaged all responses for a comparison of symptoms before and after implant removal. For the blood test, we have only described the results available to us.

Study size #10

The size of the population was not predefined prior to the study. We decided to stop including patients when we decided to write our article.

Statistical methods #12a

We performed Mann and Whitney test which is a non-parametric test on unmatched data and a Wilcoxon signed rank test for paired samples.

Statistical methods #12b

We carried out tests to compare the intensity of symptoms before and after explantation (wilcoxon signed rank test) and to compare two groups of patients (Mann and Whitney test).

Statistical methods #12c

One patient did not respond to the questionnaire and, logically, was not included in the statistical tests.

Statistical methods #12d

As this is a retrospective study of a series of cases, we did not use a sampling strategy.

Statistical methods #12e

We have not carried out a sensitivity analysis

Participants #13c

Information on the participants is described in Table 1. We did not find it necessary to make a flow diagram.

Descriptive data #14a

This did not seem appropriate for our study.

Main results #16c

This is not suitable for our study