

Original Article

# Adverse Events Due to Suspected Nickel Hypersensitivity in Patients with Essure Micro-Inserts

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**ABSTRACT** **Study Objective:** To review reported adverse events associated with suspected nickel hypersensitivity and subsequent clinical outcomes in patients with Essure implants and to evaluate the correlation of nickel allergy-related adverse events with positive results of nickel patch testing.

**Design:** Case series (Canadian Task Force classification II-3).

**Measurements and Main Results:** Reports of suspected nickel hypersensitivity reported from 2001 through July 21, 2010, were collected from de-identified data obtained from the MAUDE (Manufacturer and User Facility Device Experience) database and reports to the manufacturer directly from treating physicians, and published results for the 650 patients in the Phase II and Pivotal trials. Clinical outcomes and symptom resolution, when available, were obtained from de-identified information provided by the treating physicians to the manufacturer. Patients were not directly contacted for the study, and patient files were not reviewed. Patch testing was performed at the discretion of the treating physicians. Results were reported as positive or negative, without mention of the method or brand of patch testing used.

**Conclusion:** Even considering the possibility of underreporting by several orders of magnitude, the reported incidence of adverse events suspected to be related to nickel hypersensitivity in patients with Essure micro-inserts is extremely small (0.01%). The incidence of confirmed nickel reactions is even smaller. This very low incidence of clinical reactions is consistent with data from other nickel-containing implantable devices and is reassuring, raising the question of whether nickel reactions are clinically relevant in the use of nitinol-containing micro-inserts for hysteroscopic sterilization. *Journal of Minimally Invasive Gynecology* (2011) 18, 475–482 © 2011 AAGL. All rights reserved.

**Keywords:** Allergy/allergic; Hives; Itch; Nickel; Rash; Sensitive/sensitivity

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Nickel is currently the most common contact allergen in the industrialized world and is a leading cause of contact dermatitis, especially in female individuals [1]. In the United States, the rate of nickel allergy has increased in the past de-

cade. The most recent data from the North American Contact Dermatitis Group, who patch tested approximately 25,626 male and female patients from 1992 to 2004, showed a steady increase in nickel sensitivity, from 14.5% in 1992 to 18.8% in 2004. Further, they showed that women demonstrated a consistently higher percentage of nickel sensitivity than men. From 1992 to 2004, the positivity rate in women ranged from 18% to 24% [2]. If there were concordance between this reported positivity to nickel patch testing and clinical reactions to a nitinol-containing micro-insert, with more than 400 000 Essure devices implanted, the expected number of patients exhibiting nickel sensitivity would range from approximately 72 000 to 96 000. However, this was not observed. To explain this vast discrepancy, a thorough review of the physiologic effects of the use of nickel alloys

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in medical devices is presented so that the practicing gynecologist may benefit from the research and experience of colleagues in other medical specialties who have dealt with reactions to analogous devices.

## Materials and Methods

Reports of suspected nickel hypersensitivity reported from 2001 through July 21, 2010, were identified from adverse events reported to Conceptus Inc (Mountain View, CA), de-identified data were obtained from the MAUDE (Manufacturer and User Facility Device Experience) database, and the results for 650 patients in the Phase II and Pivotal trials were obtained from reports to the manufacturer directly from treating physicians and the published results of the Phase II and Pivotal trials. Clinical outcomes and symptom resolution, when available, were obtained from de-identified information provided by the treating physicians to the manufacturer. Patients were not directly contacted for this study, and patient files were not reviewed. Patch testing was performed at the discretion of the treating physician. Results were reported as positive or negative without mention of the method or brand of patch testing used.

## Results

Sixty-three reports of suspected nickel hypersensitivity were identified. Of 20 patients who underwent patch testing, 13 tested positive and 7 tested negative. Review of these

reports revealed a lack of correlation between suspected nickel allergy and reported adverse events. A summary of the 63 reports of suspected nickel hypersensitivity is shown in Fig. 1.

## Positive Patch Test Results

### *Micro-Inserts Removed and Symptoms Resolved*

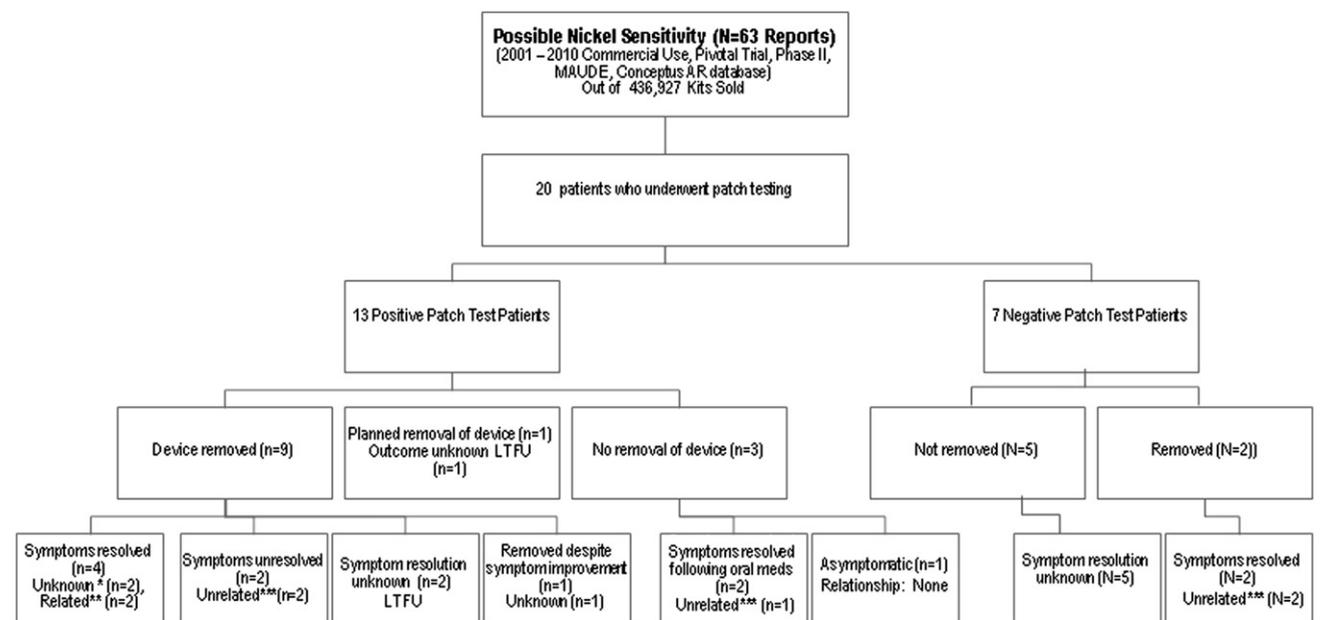
In 9 of the 13 patients who tested positive on the patch test, the micro-device was removed. Symptoms resolved in 4 of the 9 patients. Of these 4 patients, 1 experienced symptoms of rash and itching, and another experienced increased asthma. In these 2 patients, the treating physician judged the symptoms to be directly related to the micro-inserts. In the other 2 patients, it remains unclear whether the symptoms were related to the micro-inserts because of their unusual nature; 1 patient experienced swelling in 1 leg after the procedure. She underwent patch testing, and was found to be positive for nickel allergy. The devices were removed, and the leg swelling resolved within a month. The other patient reported nausea for several months after the procedure. Results of a nickel allergy test were positive. The devices were removed laparoscopically via bilateral salpingectomy, and the nausea reportedly resolved soon thereafter.

### *Micro-Inserts Removed and Symptoms Unresolved*

Two patients who tested positive for nickel allergy did not experience symptom resolution after micro-insert removal.

**Fig. 1**

Reports of suspected nickel hypersensitivity. LTFU = lost to follow-up; NA = data not available.



\*\*Unknown\* relationship to nickel  
 \*\*\*Related\* to nickel  
 \*\*\* Unrelated\* to nickel  
 LTFU – lost to followup

One of the 2 demonstrated symptoms of arthritis and pelvic pain more than 2 years after Essure implantation. At laparoscopy, 1 of the devices was observed to have perforated the fallopian tube, and the contralateral device had perforated the uterus and was lodged in the myometrium. The devices were removed, with improvement of pain but persistence of arthritis. The other patient experienced rash and hives 4 years after Essure placement. Allergy testing was positive for nickel. Although she experienced no symptoms for 4 years after placement until the recent episode, the devices were removed; however, the symptoms did not resolve. In both cases, the treating physician judged the symptoms to be unrelated to the nickel in the micro-inserts.

#### ***Micro-Inserts Removed and Symptom Resolution Unknown***

In 2 patients the devices were removed; however, no additional information could be gathered to assess resolution of symptoms. One patient experienced nausea, shivering, and pain after placement of the Essure devices, which was performed at the same time as removal of etonogestrel implants. Nine months later, the patient underwent laparoscopic bilateral salpingectomy because of persistent intermittent 1-sided pain in the iliac region. Pathologic analysis was unremarkable. Symptom resolution is unknown because the patient was lost to follow-up. In another case, reported anonymously via MedWatch, Essure was placed in a patient with a known nickel allergy. No symptoms were reported. The device was removed at the patient's request. Relationship to nickel remains unknown; however, in the absence of any symptoms, it cannot be determined whether any reaction to nickel occurred.

#### ***Micro-Inserts Removed Despite Symptom Improvement***

One patient underwent micro-insert removal despite improvement of symptoms. She initially reported pain 1 day after Essure placement, and underwent diagnostic laparoscopy, which revealed no abnormalities. On the evening of the laparoscopy, the patient experienced increased pain, hives, and rash. She was treated with diphenhydramine, and the symptoms improved. Despite improvement, the physician removed the micro-devices via laparoscopic cornual resection and bilateral salpingectomy. The pathologist identified leukocytes and eosinophils within the specimen, and postoperative skin testing revealed nickel allergy. Because the symptoms had resolved by the time the devices were removed, it could not be determined whether there was a true hypersensitivity reaction of clinical significance.

#### ***Micro-Insert Removal Planned But No Further Information Provided***

One patient with a confirmed nickel allergy experienced constant pain, which increased with menses. The physician was planning micro-insert removal; however, despite

attempts to collect additional data, no follow-up information was provided.

#### ***Micro-Inserts Not Removed***

In 2 patients in whom nickel allergy was not suspected before the procedure, the micro-inserts were placed, and the patients developed symptoms. Patch testing yielded positive results; however, the Essure devices were not removed. One patient experienced a rash after Essure placement, which was treated with methylprednisolone. The rash was "nearly resolved" at 3-month follow-up hysterosalpingography, after which time the patient was lost to follow-up. She was able to rely on Essure for contraception, and the possible relationship to nickel allergy remains uncertain. The other patient underwent placement of the micro-inserts, and after several weeks, a skin test was positive for nickel allergy. She claimed to have developed a skin reaction as a result of the Essure devices, and requested that the devices be removed. She was treated with diphenhydramine. The treating physician judged that the symptoms were not related to the micro-inserts but planned to remove them anyway. Of note, a third patient with positive results of a nickel allergy test remained asymptomatic. This patient underwent testing before the Essure procedure, and notified her physician of symptoms the day after the procedure.

A detailed description of findings in patients with positive patch test results is given in [Table 1](#).

#### ***Negative Patch Test Results***

Of 7 patients with negative patch test results, 5 experienced rash, hives, or itching; 1 experienced tingling and swollen lips; and 1 experienced pain at 2 years after Essure placement. None of these symptoms in the 7 patients were deemed related to the micro-inserts. In 2 patients, the micro-inserts were removed. One patient underwent a complete hysterectomy because of medical reasons unrelated to the Essure devices, and symptoms resolved despite negative results of a patch test. The patient who experienced itching after Essure placement subsequently underwent hysterectomy and salpingectomy, after which the symptoms resolved. The 5 patients who did not undergo micro-insert removal were treated conservatively with antihistamines or steroids.

A detailed description of findings in patients with negative patch test results is given in [Table 2](#).

#### ***Discussion***

Implants in a wide range of medical applications are composed of alloys that contain nickel. Thus, the mechanism that creates the potential for adverse reactions to implants that contain metals in practical applications is worth noting [3]. Metal ions are haptens with a high immunogenic potential, with Ni<sup>2+</sup> representing the most common contact allergen that primarily affects the skin. Common manifestations are

Table 1

Positive nickel allergy patch test results in 13 patients

Patient/Incident identifier	Time from procedure to symptom onset	Symptoms	Intervention	Treatment results	Comment
Micro-inserts removed; symptoms resolved (n = 4)					
AR-07499-J73H	Postprocedure	Swelling of 1 leg	Devices removed	Symptom resolved	Not known whether related to nickel
AR08545-OXR9	6 Months	Nausea	Devices removed	Symptom resolved	Not known whether related to nickel
AR-09946-HR3P	Postprocedure	Rash and itching	Referred to dermatologist; devices removed	Symptoms resolved	Related to nickel allergy, per treating physician
AR-13311-5Z8V	1 Year	Increased symptoms of asthma	Referred to allergist; devices removed	Symptoms resolved	Related to nickel allergy, per treating physician
Micro-inserts removed; symptoms unresolved (n = 2)					
AR-11220-SWVS	2+ Years	Arthritis, pelvic pain	Devices removed	Symptoms unresolved	Not related to nickel allergy, per treating physician
AR-15158-BYXK	4 Years	Rash and hives	Devices removed	Rash unresolved	Not related to nickel allergy, per treating physician
Micro-inserts removed; not known whether symptoms resolved (n = 2)					
AR-04054-VLB3	Postprocedure	Nausea, shivering, discomfort sometimes associated with iliac pain on right side	Devices removed	Not known	Not known whether related to nickel
AR-05122-OFDG	≤5 Days	Not known	Devices removed	Not known	Not known whether related to nickel
Micro-inserts removed despite symptom improvement (n = 1)					
AR-05145-XK32	1 Day	Pain, rash, hives	Diphenhydramine; devices removed	Symptoms improved	Not known whether related to nickel
Micro-inserts removed; no further information provided (n = 1)					
AR061341	Not known	Constant pain increasing with menses	Device removal planned	Not known	Not known whether related to nickel
Micro-inserts not removed (n = 3)					
AR04668	1–3 Days	Rash	Methylprednisolone and steroids	Rash nearly resolved at 3-month follow-up hysterosalpingography	Not known whether related to nickel
AR-08745-6NRD	1 Month	Skin reaction	Oral medication	Not known	Not related to nickel allergy, per treating physician
AR050597	Not applicable	No symptoms	None	Not applicable	Patient had confirmed nickel allergy but no symptoms

**Table 2**

Negative nickel allergy patch test results in 7 patients

Patient/Incident identifier	Time from procedure to symptom onset	Symptoms	Intervention	Treatment results
Micro-inserts removed; symptoms resolved (n = 2)				
AR-08870-L3N3	Postprocedure	Total body itching	Devices removed	Symptom resolved
AR-09555-VNL1	1–2 Months	Generalized overall itching	Antihistamines; devices removed	Symptom resolved
Micro-inserts not removed (n = 5)				
AR03469	4 Weeks	Rash and hives	Prednisone and diphenhydramine	Symptoms resolved
AR050911	3 Weeks	Rash	No information available	Not known
AR-07620-84R4	2 Weeks	Tingling, swollen lips	Prednisone	Not known
AR-08018-FKR2	1 Day	Hives, itching	Referred to dermatologist	Not known
AR-15044-HZ3L	2 Years	Pain	Referred to allergist and specialist	Not known

contact hypersensitivity with hand eczema, generalized dermatitis, and urticaria [3]. Transition metals such as nickel have an ionic radius too small to be antigenic but can act as a hapten (a low-molecular-weight determinant group that of itself is nonimmunogenic but becomes so when placed on a larger molecule) when its partially filled d-shell oxidizes to an electropositive cation, enabling interaction with tissue protein. There is increasing evidence that the actual immunogenic form of nickel is the trivalent ion,  $\text{Ni}^{3+}$ , rather than the traditional  $\text{Ni}^{2+}$  [1].

How does nickel become a clinically relevant allergen? It is not triggered by dietary intake. The mean oral intake of nickel from the diet per person is estimated to be 150 to 900  $\mu\text{g}/\text{day}$  [4]. In a meta-analysis of systemic contact dermatitis after nickel introduced orally into the body, it was estimated that 1% of patients allergic to nickel would develop a systemic reaction to a normal diet of nickel, and that 10% would react to nickel intake levels of 0.55 to 0.89 mg [5]. Insofar as toxicity, not allergenicity, the maximum recommended tolerable amount of nickel administered in a human being via intravenous fluids is 0.5  $\mu\text{g}/\text{kg}/\text{day}$ , or approximately 7  $\mu\text{g}/\text{kg}$  in an adult weighing 70 kg [6].

Nickel allergic contact dermatitis is generally characterized by delayed-type hypersensitivity. After sensitization via contact, a reaction can develop from even minor contact with  $\text{Ni}^{2+}$ -containing metals. Reactions associated with implants are typically type IV hypersensitivity cell-mediated reactions that occur via skin contact and elicit lymphocyte T-cell action. The microenvironment of the lymphocytes involved determines the variation in tissue-related allergic reactions [7].

Patch testing is the standard for diagnosis of nickel allergic contact dermatitis, and most commonly entails placing 2.5% or 5% concentrated nickel sulfate in petrolatum on the skin for 48 hours. The skin is examined 72 to 96 hours later for a local reaction [8]. For delayed-type hypersensitivity (type IV) that generally characterizes nickel allergic

responses, diagnostic tests in patients with symptoms of dermatitis include open patch, closed patch, lymphocyte transformation, and macrophage migration inhibition tests. Patients with eczema can be tested using oral provocation [1]. On the skin, contact urticants go through the epidermis and react with preformed specific IgE molecules, causing the subsequent release of histamine and other cell-bound mediators of inflammation. Consequently, immediate-type hypersensitivity to nickel can be diagnosed in vitro using the radioallergosorbent test, which uses radiolabeled anti-IgE to recognize the IgE antibodies in a patient's serum. In vivo, reaction to the skin-prick test for immediate-type allergy is visible on the patient's skin [1].

Approximately 80% of patients with positive patch test results have a clinical history of metal sensitivity [7]. However, patch testing is not always a reliable predictor of a systemic nickel allergic reaction. A large percentage of the population that tests positive on the nickel sulfate skin-patch test remains asymptomatic and exhibits no noticeable signs of nickel allergic hypersensitivity. Conversely, many who report sensitivity actually test negative on skin patch testing. The validity of self-reported nickel allergy is low, and tends to overestimate the true prevalence of nickel allergy. Josefson et al [9] observed that fewer than 60% of patients who self-report allergy to nickel were actually positive when patch tested. A commercially available lymphocyte transformation test (Orthopedic Analysis, LLC, Chicago, IL) has recently been developed, with claims to accurately predict allergic reactions to nickel-containing alloys used in implant surgery. However, the company's own disclaimer states that issues of sensitivity and specificity remain unresolved, as well as how implant performance is related to positive reactivity results [10].

The concern about hypersensitivity and adverse reactions to the nickel content of implantable devices with regard to ion release or leaching is of critical importance. Nickel alloys that commonly come in contact with the skin must

Table 3

Material composition of components of Essure micro-insert

Component	Material	Composition
Outer coil	Chromium-doped nitinol (nickel-titanium)	55% Nickel, 44% titanium, trace chromium
Inner coil, thread coil	316L Stainless steel	~62.5% Iron, 17.6% chromium, 14.5% nickel
Stopper band, platinum band, platinum ring, bump	Platinum-iridium	90% Platinum, 10% iridium
Solder	Tin-silver	95% Tin, 5% silver
Fiber	PET polyester, white	≥92% Polyester, <5% titanium dioxide, <3% fiber lubricants

be differentiated from biological nickel-containing alloys, and the physiologic reactions are qualitatively distinct. Nitinol is an alloy composed of a mixture of nickel and titanium, with the proportion varying with each implantable device. It is commonly used in surgical implants such as orthopedic staples, vena cava filters, dental devices, and intravascular stents because of its unique shape-memory and good biocompatibility [5]. Because cardiac devices are exposed to the bloodstream, they should be most likely to release detectable blood levels of metal ions and initiate a hypersensitivity reaction [3]. In fact, hypersensitivity reactions to the materials used in endovascular devices represent only uncommon reactions that may lead to local or systemic complications subsequent to implantation [7]. Worldwide each year, more than 1.5 million percutaneous coronary revascularization procedures are performed, most involving intracoronary stent implantation. Intracoronary stents made of 316L stainless steel contain approximately 12% nickel in addition to other potentially sensitizing metals such as chromium and molybdenum. These metals may be eluted by surrounding blood and body fluids [10]. Nitinol-associated nickel allergy cases are rare, with a risk factor of approximately 1 in 17 000 heart and endovascular devices. This may be explained in part because in physiologic solution, nitinol forms a titanium oxide coating along with a surface layer of calcium phosphate that is thought to minimize leaching and protect against nickel hypersensitivity [11].

Results from an in vitro study measured the nickel release from nitinol (NiTi), CoCrNi, and NiCr alloys common in vascular stents suggest that metal ion release from the studied alloys was insufficient to activate expression of cellular adhesion molecules on endothelial surfaces or to stimulate cytotoxicity. Although nitinol had the highest concentration of nickel in the studied alloys, it had the lowest nickel ion release [7]. This may help explain the low observed rate of hypersensitivity reactions.

The use of nickel-containing devices for closing cardiac defects has been exceptionally well tolerated, with more than 50 000 devices placed worldwide. The rate of nickel-related adverse events associated with these devices is exceedingly low when taking into account the aforementioned observed prevalence of dermal sensitivity [3].

The Amplatzer septal occluder (AGA Medical Corp, Golden Valley, MN) is one such device used for closing

cardiac defects that uses nitinol. An in vitro study in which the release of Ni<sup>2+</sup> was measured after immersion in physiologic Hank's solution demonstrated a titanium oxide coating that forms and is later covered by a calcium-phosphate layer. In vivo, endothelialization of the surface of the Amplatzer device is complete in 3 months [3]. Analysis of the Ni<sup>2+</sup> release of Amplatzer occluders revealed 3-fold increased serum levels (1.50 ng/mL) from baseline (0.47 ng/mL) at 1 month after implantation, which returned to preimplantation levels at 12 months [12].

Coronary artery in-stent restenosis has been associated with nickel allergy in some studies, whereas others have not been able to confirm such an association [13]. One study found that 10% of individuals with significant in-stent restenosis at 6 months had positive adverse reactions to nickel or molybdenum in patch tests despite all having negative patch-test results for 316L stainless steel [14]. Another study found that only repeat in-stent restenosis was associated with positive metal patch test results, whereas other smaller studies have not confirmed an association [10].

Rigatelli et al [15] reported placing a nitinol-containing atrial shunt in 9 patients with proved nickel allergy. Eight of the 9 patients developed chest discomfort, exertional dyspnea and asthenia, and mild leukocytosis, which was described as a "device syndrome." After 1 week of therapy with prednisone and clopidogrel, the symptoms completely resolved [15]. The authors concluded that nickel allergy is not itself a contraindication to use of a nitinol device to close atrial septal defects and that adverse effects are mild and manageable with low-dose prednisone and antiplatelet therapy. It remains unclear whether in-stent restenosis or complications associated with septal occluders are consequences of nickel or other metal allergy or of some other as-yet undetected cause [7,10].

Documented cases related to nickel sensitivity and metal joint replacement failure are rare. However, eczematous reactions have been reported. One study found that the risk of surgical revision in total hip arthroplasty procedures was not increased in patients with metal allergy [16]. In addition, Schram et al [11] noted that the connection of nickel allergy and failure of metal orthopedic implants and cardiac devices is not clear, citing the existing, mainly retrospective, publications that suggest only an association of nickel allergy with implant failure rather than determine causation.

Patients who are metal-allergic can tolerate orthopedic prostheses that contain the metals to which they are allergic [7].

In orthodontics, nickel is regularly used without complications. In orthodontic wires, nitinol has corrosive properties similar to those of stainless steel [17], and preorthodontic testing for metal allergy is not routinely performed. Although dermatitis at or proximal to the site of dental and orthodontic endoprostheses has been noted in the literature, reactions to prostheses consisting of medical-grade stainless steel alone are rare [5]. There is also evidence that immunotolerance has a role. Dental braces containing high amounts of nickel alloys (e.g., chromium with 60%–80% nitinol) resulted in nickel tolerance in girls who subsequently had their ears pierced compared with high nickel sensitivity in girls who had their ears pierced but who did not previously wear such dental braces. This tolerance may be caused by a mechanism involving low nickel exposure orally over time [18].

By weight, the nitinol alloy used to form the outer coil of the Essure micro-insert is composed of about 55.8% nickel, 44% titanium, and 0.25% chromium, which is comparable to the composition of nitinol in other surgically implanted devices. The nickel ions in nitinol alloys are tightly bound to titanium. Conceptus Corp, the manufacturer of the Essure micro-inserts, uses a chromium-doped nickel-titanium alloy that is processed so that the entire alloy surface is covered with a protective layer of titanium oxide, which acts to minimize nickel ion release. The material composition of the components of the Essure micro-insert are given in Table 3.

A corrosion study analyzed the amount of nickel leached into solution after the Essure micro-insert was placed in saline solution for varying amounts of time and compared that with the average amount of natural nickel ingested daily from food and water (300 µg/day). The study found that the highest measured leaching rate of nickel was 0.14 µg/day, which is approximately 2143 times less than the average human daily intake from food and water [19].

The cyclicity of the hormones of the menstrual cycle may also have a role in the effects observed during insertion of Essure micro-inserts and may regulate expression of nickel hypersensitivity in women. Bonamonte et al [20] noted that dermatologic contact irritation seems to be more prevalent during the premenstrual secretory phase, as noted by a more intense response to patch tests with sodium lauryl sulfate, compared with the follicular phase of the cycle, which is when the Essure device is traditionally placed. During the follicular phase, a temporary protective role in inhibiting the eliciting phase of allergic contact dermatitis is observed. In the days before menstruation, contact dermatitis intensifies [21]. Noting how estradiol induces inhibition of delayed hypersensitivity-type reactions, their study focused on the possibility that ovulation could inhibit contact sensitization mechanisms. Patch tests were performed during the ovulatory and secretory phases and showed a significantly reduced response to the patch tests during the follicular and ovulatory phases. The authors' findings

suggest that the follicular and ovulatory phases of the cycle have a considerable inhibitory role on delayed hypersensitivity-type reactions and that negative responses to patch tests performed during these phases could be false-negative [20]. Patch testing may, therefore, be confounded by the phase of a woman's cycle.

The Essure micro-insert is placed during the early proliferative phase of the menstrual cycle, during which time the immune response is least pronounced. If there were to be any immunologic reaction, it would be blunted, only to emerge again during the late secretory phase just before menstruation. This may explain a delayed response to placement noted in several reports of adverse events, although it is difficult to differentiate these symptoms from those caused by occult perforation of the devices or other inflammatory or infectious process. The incidence of these events is statistically too small to reach clinical relevance.

Review of the medical literature confirms that there are no reliable tests to predict nickel hypersensitivity caused by implantable devices. It has yet to be determined whether adverse reactions to metal-containing implants result from a specific cellular immune response, and confirmation of a type IV hypersensitivity reaction would necessitate biopsy of the affected tissue showing effector T cells and macrophages. Currently, there is inadequate evidence to support such an association; thus, the relationship between systemic reaction and cutaneous allergy is unknown. Nickel allergy determined using patch testing should, therefore, not be an absolute contraindication to the use of biomaterials that contain nickel [3]. The incidence of adverse reactions to implantable nickel alloys is negligible across all known reported devices, and because self-reported reaction to nickel remains an unreliable indicator of nickel hypersensitivity, a history of a reaction to cutaneous exposure to nickel does not necessarily indicate contraindication to use of devices containing nickel-titanium alloy. It has been shown that nickel-sensitive individuals may be safely observed or treated with prednisone, antihistamines, or antiplatelet agents, without having to remove the device [7,15].

Like all of the aforementioned devices, the incidence of reported nickel-related reactions or complications from the Essure micro-insert remains far below the range of 18% to 24% in women with contact nickel allergy. Of the 436 937 Essure kits sold since its commercial release, there have been only 63 reported cases in which nickel hypersensitivity was suspected, or 0.014%, and none in clinical trials. It is safe to assume that these 63 cases represent underreporting of suspected nickel allergy cases. Even if the reporting of adverse effects were to be underestimated by several orders of magnitude, the Essure data demonstrate an almost negligible occurrence of proved nickel-related reactions. The findings of a recent European analysis of 4000 Essure commercial procedures assessing all reported complications found only 2 patients with previously undiagnosed nickel sensitivity who underwent laparoscopic salpingectomy, for an

incidence of 0.05% [22]. Significantly, devices were placed in 25 patients with known nickel allergy, without adverse effects. This further substantiates the lack of correlation between suspected symptoms and nickel allergy in women with Essure micro-inserts and corroborates the findings in the present study as evidenced by the 1 patient with a confirmed positive nickel patch test who was completely asymptomatic.

Similarly, the data from the present study is remarkable in that 6 of 7 patients in the patch test–negative group experienced symptoms that would normally be associated with allergic reactions, that is, itching, hives, rash, and asthma. The mechanism for these symptoms cannot be attributed to an allergic reaction, and raises more questions as to the validity of patch testing and the correlation of symptoms to allergy. In addition, symptoms were reported anywhere from immediately after the procedure to 4 years later, which raises doubts as to whether the reported symptoms were truly allergy-related or if some other mechanism was responsible.

The strengths of this study include the large number of cases. Weaknesses include inherent limitations of any reporting system and the inability to obtain detailed follow-up in some of the patients to better determine the relationship between reported symptoms and true allergy.

## Conclusions

The World Health Organization Uppsala Monitoring Centre system divides case causality into several categories to evaluate suspected adverse drug reactions [23]. The low reported incidence of nickel sensitivity to Essure components combined with the lack of definitive relationship between suspected and proved cases results in a classification of “unlikely,” and suggests that nickel sensitivity may not be a clinically relevant consideration for placement of nitinol-containing micro-inserts. Nevertheless, in patients who have suspected reactions accompanied by positive results of nickel allergy testing, it seems reasonable to first try conservative management with medication. The findings of the present case series and those involving other nitinol-containing devices do not demonstrate any difference in outcome even when the devices were removed from patients in whom nickel allergy was suspected. Ongoing surveillance of potential reports of nickel sensitivity in patients with Essure implants will continue to inform future findings. Review of the current Essure data offers perspective and reassurance to practitioners and their patients insofar as nickel allergy is concerned.

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