



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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Health problems following a non-surgical sterilization
procedure for women

RIVM Letter report 2016-0061
A.W. van Drongelen et al.



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Colophon

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Analyse van klachten na sterilisatie met Essure[®] in Nederland Gezondheidsproblemen na een niet chirurgische sterilisatie-ingreep bij vrouwen

Het RIVM heeft klachten geanalyseerd van vrouwen die zijn gesteriliseerd met Essure[®]. Dit zijn metalen veertjes die via de baarmoeder in beide eileiders worden gebracht waardoor deze na ongeveer 3 maanden dichtgroeien. Het voordeel van deze sterilisatiemethode is, in vergelijking met de traditionele afsluiting van de eileiders, dat er geen chirurgische ingreep voor nodig is.

Het aantal gemelde klachten komt van ruim 1,5 procent van de circa 30.000 vrouwen die in Nederland met Essure[®] zijn behandeld. De meest genoemde klachten zijn pijn en vermoeidheid. Bij de pijnklachten gaat het vooral om de buik, de rug en het hoofd. Daarnaast worden hevige bloedingen tijdens en tussen de menstruatie, stemmingswisselingen, geheugenverlies en concentratieproblemen gemeld. Het werkelijke aantal vrouwen met klachten is onbekend.

Veel vrouwen geven aan dat deze klachten hun dagelijks leven negatief beïnvloeden. Ze voelen de veertjes zitten of ervaren beperkingen bij het bewegen. Verder kunnen ze de dagelijkse taken en de zorg voor kinderen vaak minder goed uitvoeren. Er zijn ook vrouwen die aangeven dat hun relatie lijdt onder de ontstane problemen. Bij 16 procent van de vrouwen die klachten gemeld hebben, is Essure[®] verwijderd naar aanleiding van de klachten. 38 procent van de vrouwen in dit onderzoek heeft een afspraak gemaakt om dat te laten doen.

De klachten zijn gemeld nadat hieraan via diverse kanalen aandacht is besteed. De Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG) heeft de resultaten van de analyse medisch geëvalueerd. Sommige klachten zijn mogelijk toe te wijzen aan de plaatsing van Essure[®], zoals bepaalde pijnklachten. Bij andere klachten is het moeilijker om een direct verband te leggen omdat er ook andere zaken van invloed kunnen zijn, zoals stoppen met de pil waardoor menstruatieklachten kunnen verergeren. Daarnaast komen verschillende klachten, bijvoorbeeld gewichtsschommelingen en urinewegproblemen, ook met enige regelmaat voor bij vrouwen die geen Essure[®] hebben.

De gemelde klachten komen van vrouwen die tussen 2001 en 2016 het implantaat hebben gekregen. Hun gemiddelde leeftijd was 37 jaar op het moment van de sterilisatie.

Kernwoorden: Essure[®], hysteroscopisch, sterilisatie vrouw, implantaat, gezondheidsproblemen, klachten, bloeding, pijn, verwijderen

Synopsis

Analysis of complaints in the Netherlands on Essure®

Health problems following a non-surgical sterilization procedure for women

The RIVM has analyzed the complaints reported by women sterilized using Essure®. Essure® is a sterilization method where two metal coils are placed into both fallopian tubes through the cervix and uterus, provoking those to become blocked after approximately 3 months. In comparison with the traditional sterilization methods, the advantage of the Essure® method is that no surgical procedure is required.

The complaints that were received came from more than 1,5 percent of the 30.000 women who are estimated to have been sterilized using Essure® in the Netherlands. Probably not all women with health problems have submitted a complaint; therefore, the actual number of women with health problems is unknown. The most frequently mentioned health problems are pain and tiredness. The pain is reported to be located mainly in the abdomen, back, and head. In addition, heavy bleeding during and between menstruations, mood swings, memory loss and concentration problems are also reported frequently.

Many women indicated that these health problems negatively affect their daily life. They feel the coils in their body and often experience limitations when moving. They are often less able to adequately perform their daily tasks and take care of their children. There are also women that indicated that their relationship was negatively affected by the health problems. In 16 percent of the women in this study, Essure® has been removed because of the health problems and 38 percent of the women have made an appointment to have Essure® removed.

The complaints were submitted, among other reasons, because the media attention on problems experienced by women following sterilization using Essure®. The Dutch Society of Obstetrics and Gynecology (NVOG) contributed to the interpretation of the results from this study. Some health problems can be directly related to Essure®, for instance some kinds of pain. For other health problems it is more difficult to establish a direct link, because other factors may influence the health problems as well. For instance, heavier menstruation may also be explained by the fact that women stopped taking oral contraceptives following sterilization using Essure®. Furthermore, there are other health problems such as weight changes and urinary tract problems that are also regularly experienced by women not sterilized with Essure®.

Women that submitted a complaint were sterilized using Essure between 2001 and 2016. Their mean age at implantation was 37 years.

Keywords: Essure®, hysteroscopic, female sterilization, implant, health problems, complaints, bleeding, pain, removal

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Introduction

1.1 General

Female contraception can be achieved by non-permanent methods, like oral contraceptives and intra-uterine devices, or by permanent methods. Permanent sterilization can be accomplished by blocking the fallopian tubes via a laparoscopic and hysteroscopic sterilization. The sterilization methods described below are applied in the Netherlands. It is estimated that 10.000 women are sterilized in the Netherlands each year. There is no good registrationsystem for sterilizations in the Netherlands so exact data on sterilization is lacking [1].

1.1.1 *Laparoscopic sterilization*

A laparoscopic sterilization is a surgical procedure in which two small incisions are made in the abdomen to insert a laparoscope (camera) in one of the incisions and the instruments for the sterilization itself in the other. Laparoscopic sterilization can be achieved via surgical, mechanical, or electrical methods (Table 1 and Appendix 1) [2-8]. These procedures require general anesthesia which might be a risk for the patient. Complications are rare after a laparoscopic sterilization (less than 1 in 1000). Women can experience shoulder pain (due to use of carbon dioxide), abdominal pain, blood loss (due to damage to the uterus) and a feeling of weakness (due to operation/anesthesia) after the procedure, which is temporary. Also wound complications, an infection, fever and damage to the intestine/bladder can occur due to the laparoscopic sterilization [2,3]. Besides, surrounding organs (i.a. small intestine) can be burned during electrocoagulation. This risk is higher when using unipolar forceps compared to the use of bipolar forceps [3].

Table 1: Comparison of laparoscopic and hysteroscopic sterilization [8]

	Laparoscopic	Hysteroscopic (Essure®)
Experience	+/- 40 years	13-14 years
General anesthesia	Yes	No
Local anesthesia	No	Possibly
Invasiveness	Invasive	Minimal-invasive
Policlinic placement	No	Yes
Immediate reliability	Yes	No
Recovery period	Several days	One day
Control after 3 months needed	No	Yes
Risk of failure of the procedure	Minimal	+/- 5-10%
Possible side effects	<ul style="list-style-type: none"> - Infection - Blood loss - Abdominal pain - Shoulder pain - Damage intestine /bladder 	<ul style="list-style-type: none"> - Infection - Blood loss - Pain - Weight fluctuations - Mood swings - Skin irritation
Pregnancies after successful procedure	2-5/1000	0-4/1000

1.1.2 Hysteroscopic sterilization

Hysteroscopic sterilization is a non-surgical procedure that does not require general anesthesia. An implant is placed in the fallopian tubes via the cervix and uterus. Currently, Essure® is used for hysteroscopic sterilization. In addition, several new methods are being tested in trials (Altasea® and Ovalastic®) (Table 1, Appendix 1).

Essure® implants, manufactured by Bayer (Essure® was originally developed by Conceptus Inc.. In 2014 Conceptus Inc. was acquired by Bayer), are coils which are inserted via the cervix and uterus into the fallopian tubes (Figure 1, Appendix 1). A device is used to deliver the implants into the fallopian tubes where the implant is expanded and anchors itself. This procedure usually takes less than 10 minutes [9]. After inserting the coils, connective tissue develops around the coils via a natural immune response, leading to a complete blockage of the fallopian tubes in approximately 3 months (Figure 1). A test is needed to confirm that the coils are correctly positioned and the fallopian tubes are indeed completely blocked, e.g. using a radiographic test called hysterosalpingogram (HSG), X-ray or ultrasound.

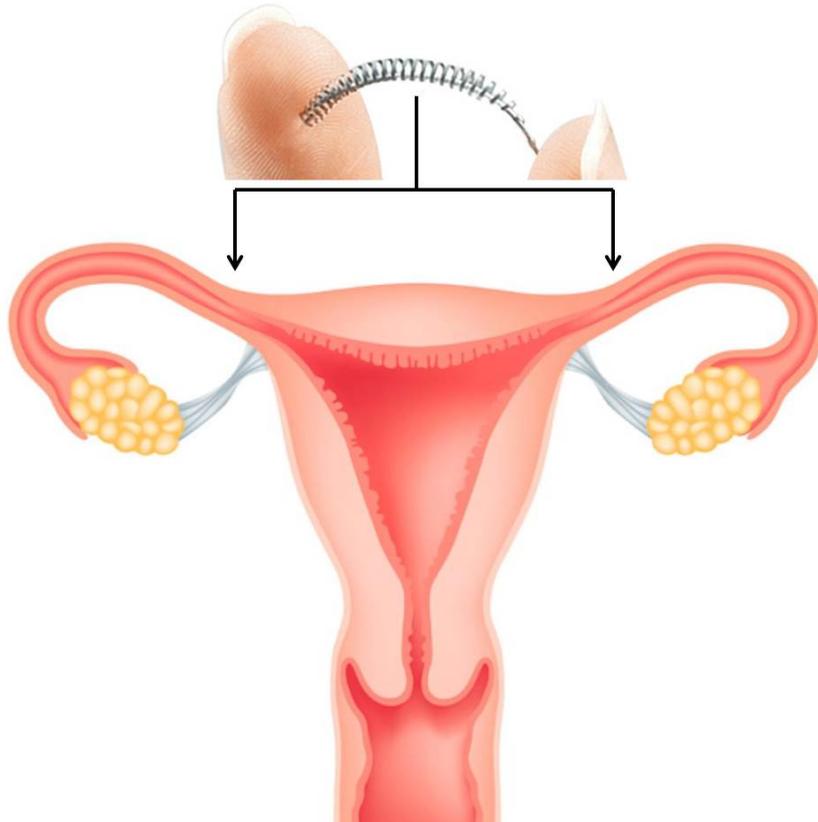


Figure 1: Essure method: A coil is inserted into the fallopian tubes via the cervix and uterus. Tissue develops around the coils, leading to a complete blockage of the fallopian tubes.

1.1.3 Situation around Essure® in the Netherlands

In the Netherlands, Essure® has been implanted in approximately 30.000 women since 2002 [10,11]. Up until 2016, only a limited number (<1%) of women indicated that they experienced health problems after implantation of Essure®. Severe associated health problems sometimes led to the removal of the Essure® implants. The Landelijk Meldpunt Zorg (National Health Care Report Centre, LMZ) received complaints from women and forwarded those to the Dutch Health Care Inspectorate (IGZ). The complaints were related to the problems that women experienced during or after implantation. In the complaints, the health problems most often mentioned were back pain, abdominal pain, muscular pain, joint pain, bleeding, and tiredness. Other complaints mentioned broken implants and problems during implantation [12]. The LMZ also received complaints from women that indicated they had a nickel allergy. Currently, the manufacturer warns for a possible allergic reaction to nickel, but nickel allergy is not a contra-indication in Europe for sterilization using Essure®.

In 2014, the IGZ noticed a slight increase in the number of complaints concerning Essure®. Therefore, the IGZ requested additional information from the manufacturer concerning the reports on incidents received worldwide, in Europe and in the Netherlands. Moreover, the IGZ contacted the Dutch Society of Obstetrics and Gynaecology (NVOG) to obtain information about the clinical experiences with Essure®.

On March 7, 2016, the Dutch TV program "Radar" was dedicated to the problems that women experienced with the Essure[®] sterilization method. In this program, women suffering from health problems following implantation of Essure[®] were interviewed. Following this program, IGZ published an appeal on their website dedicated to Essure[®]. The IGZ appealed women that experienced problems following Essure[®] placement to report their problems to LMZ. This website also indicated that RIVM was going to perform a study into the health problems reported to LMZ.

1.2 Scope

Following the appeal of the IGZ and the TV program, the IGZ requested the RIVM to perform a study into the complaints related to the Essure[®] sterilization treatment that women reported to the LMZ. This study included complaints reported to the LMZ both before and after (from March 7th 2016 until April 18th 2016) this appeal and the TV program Radar.

Main question:

Are there trends in the medical issues women experienced following Essure[®] sterilization? This general question was specified in the following sub-questions.

Sub-questions:

- Which health problems did women experience following Essure[®] sterilization?
 - Which problems did women experience following a procedure during which events occurred?
 - Which problems did women experience following a procedure without events?
- After what period of time following Essure[®] sterilization did the problems start?
- What is the frequency of occurrence of the problems following Essure[®] sterilization?
- For how many women, with health problems following Essure[®] sterilization, was a diagnostic examination performed and what were the outcomes of such examination?
- How many women had their Essure[®] implants removed and what effect did this have on the problems that these women experienced? How were the Essure[®] implants removed (together with the fallopian tubes or also with the uterus)?
- What influence did the health problems have on the daily life of these women (e.g. employment, sport, family life)?
- How often are there other causes than the Essure[®] sterilization for developing the problems that were reported?
 - What are these other causes?
- How many women who experienced health problems reported to have a nickel allergy?

2 Methods

2.1 Received complaints

Complaints received in two periods were included in this study, namely complaints reported following the appeal of the Dutch Health Care Inspectorate (IGZ) and the TV program of March 7th 2016 (March 7th until April 18th) and complaints which were submitted before this period. Complaints analyzed in this study were exclusively obtained from the LMZ. Women could contact the LMZ, either by submitting a web-based form or by telephone. After submission of a web-based form, LMZ contacted by telephone the person that submitted the form. The inclusion of submissions following the appeal of the IGZ and the TV program continued until the number of submissions returned to the level existing before the appeal following the TV program.

A list with specific questions to be asked by LMZ was developed to obtain the information necessary to answer the sub-questions as far as possible. The completed complaints were a combination of the information initially submitted by the women and the information added by the workers of LMZ following the telephone contact with the women. IGZ received the complaints from LMZ and then forwarded them to the RIVM, if women agreed to have their complaint included in the RIVM-study.

2.2 Analysis of complaints

The complaints were received as Word documents, containing the information received by LMZ. An MS Excel database was developed, where the information from the complaints on Essure[®] were entered anonymized. Health problems were classified into 7 different categories. Each complaint was evaluated individually and the answers were scored into the database. The variables included data on the health problems reported, the onset time of the problems and the actions taken by the women to solve their problems. The sub-questions to be answered were taken into consideration (see Appendix 2 for description of variables included). The data were analysed using the statistical analysis program SPSS (IBM, Armonk, USA).

The results from anonymized complaints related to Essure[®], which had been received before the TV program by the LMZ, were also included in this study. These complaints were not completed with a specific questionnaire and had not been analysed using the same database. A comparison could therefore only be made between the two sets of complaints on category level.

The results of this study were discussed with the NVOG [13].

Observations from the NVOG on the results are included in this report.

2.3 Literature search

For remarkable findings, a limited search of the scientific literature was performed to check whether such findings had already been reported in the literature. For the literature search, "Essure" was used as the keyword in Pubmed. This search generated 222 results. First, the title of each article was reviewed and scored as applicable if it was expected that the article might describe events during the procedure and/or

health problems. Case reports were excluded. The abstracts from the selected articles were then evaluated. The relevant articles were used, which described the complications during placement and/or the health problems that developed after placement of the Essure[®] in a group of women. Another literature search (in Pubmed as well as Google) was performed to obtain information about sterilization methods other than the Essure[®] method. A literature search was also performed to obtain more information concerning nickel allergy and health problems related to other implants which contain metals.

The main findings were also compared to the information, mainly warnings, precautions and contra-indications, stated in the manufacturer's Instructions for Use (IFU version 1/07/2013 and 11/11/2015), that was provided by the IGZ.

3 Results

In total, the LMZ received approximately 500 complaints related to the Essure[®] implants. Over 400 complaints were received after the appeal of the IGZ and the TV program Radar. Not all women gave permission to use their complaints for this study and therefore 373 complaints received after the appeal and the TV-program were forwarded to the RIVM. The IGZ also received complaints before this period (referred to as “earlier complaints” from here onwards). In 372 of the 373 cases, these complaints included events during the procedure and/or the development of health problems. One woman reported a successful placement of the Essure[®] without the development of health problems. Less detailed information was obtained from the earlier complaints due to i.a. the lack of the specific questionnaire of the LMZ. The following tables and figures are therefore based on the 373 complaints received after the appeal of the IGZ and the TV program.

The women who reported the complaints were born between 1961 and 1988. The earliest Essure[®] implantation reported was in 2001 and the latest in 2016, while most placements took place in 2012 (Figure 2). The average age at the time of implantation was 37 years, with the youngest woman being 24 years old and the oldest 50 years.

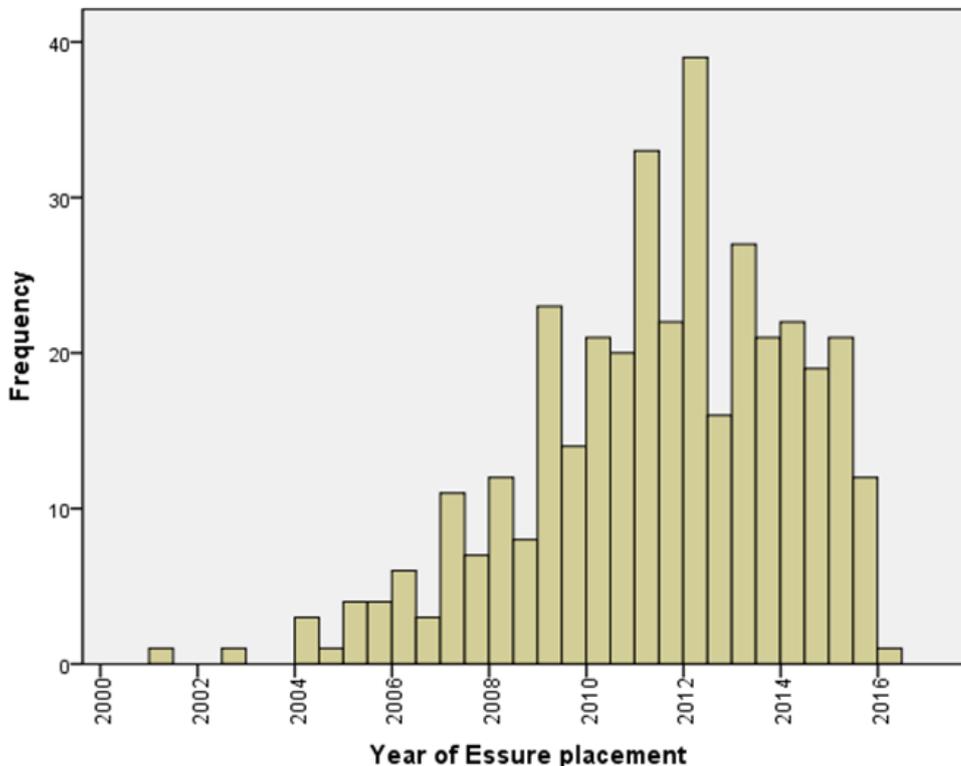


Figure 2: Year of Essure[®] placement

In the following paragraphs, the events during or directly following placement and health problems after placement as reported by the women are described. Since more than one event or health problem was often reported by one woman, the total number of events and health problems can be more than the total number of complaints and therefore more than 100%, as the percentages are calculated using the number of complaints.

3.1 Events during Essure[®] implantation

261 women (70%) reported that events occurred during the placement (Table 2).

Table 2: Events during Essure[®] placement

Events during placement	% of total (n=373)
Events during procedure	70% (n=261)
Painful placement	56%
Other events	42%
<i>Nauseous or dizzy</i>	8%
<i>Placement only on one side</i>	6%
<i>Fallopian tube perforation</i>	1,1%
<i>Breaking of implant</i>	0,5%
<i>Other</i>	31%

A wide variety of events were reported. More than half of the women (56%) experienced pain during the placement. In 42% of the women other events occurred, like for instance nausea or dizziness (8%). In approximately 6% of the women the placement was so difficult that only one Essure[®] implant was placed and a second procedure was needed to achieve a complete sterilization. Nearly one third of the women (31%) reported events that were not listed as a separate option in the database and were therefore scored as 'other'. 'Other' was often scored when it was only indicated that the placement was difficult without further description. It was not clarified in the complaints if the events were due to the experience of the gynecologist, the anatomy of the patient or to other causes.

Comparing this to literature, two studies on Essure[®] (including a so-called Phase II study) described that around 70% of the women experience pain during the placement [14,15]. In our study, this percentage was slightly lower (56%). On the contrary, a Phase III study (which is also used for the manufacturer's IFU) described that 13% experienced pain during the placement and 30% experienced cramping [16]. This Phase III study also reported nausea as a postoperative symptom in 11% of the women, which is slightly higher than the 8% in our study [16].

Six women (~2%) reported events which were related to perforation of the fallopian tube or breaking of the implant. Given this low number, no reliable comparison could be made between the incidence and type of health problems experienced by women who had such events vs. those who had not. Moreover, reporting of these events might not be

accurate, since women might not always be aware of these type of events that occurred during placement.

3.2 Onset time of health problems

The onset time is the time between placement of the implant and the moment the health problem(s) started. In 232 complaints (62%), the general onset time when the first health problems appeared was mentioned. A wide variation (0-9 years) in onset time was observed (Figure 3, left histogram). On average, it took 7 months for the first health problems to appear. The health problems arose within the first month after placement in 40% of the women, and 90% of the women encountered problems within the first year. The onset time per type of health problem can be found in Appendix 3.

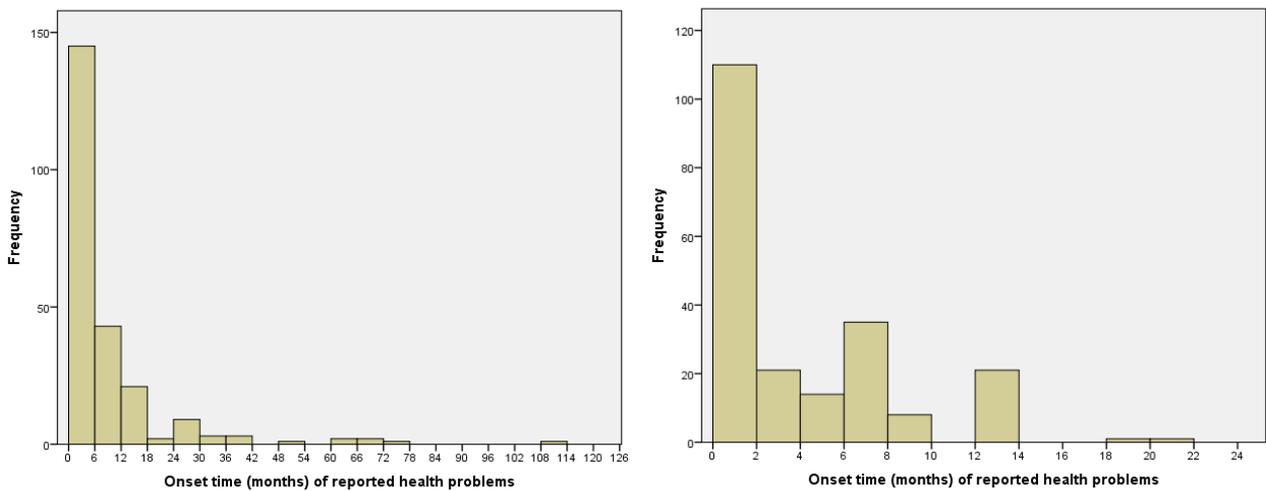


Figure 3: Onset time (in months) of reported health problems. Whole range (left histogram) and detail of the first 24 months after placement of Essure® (right histogram).

3.3 Type of health problems following Essure[®] implantation

The women that submitted a complaint reported a wide range of physical and psychological health problems. Therefore, the health problems were classified into categories. Most women experienced health problems related to pain (94%), psychological issues (91%) and bleedings (54%). In addition, allergy-related health problems (36%), gastro-intestinal/liver (27%) and kidney/urinary tract (23%) health problems were reported. Most women (90%) also reported a wide variety of health problems that were classified in a separate category "other problems" (Figure 4 and Appendix 4).

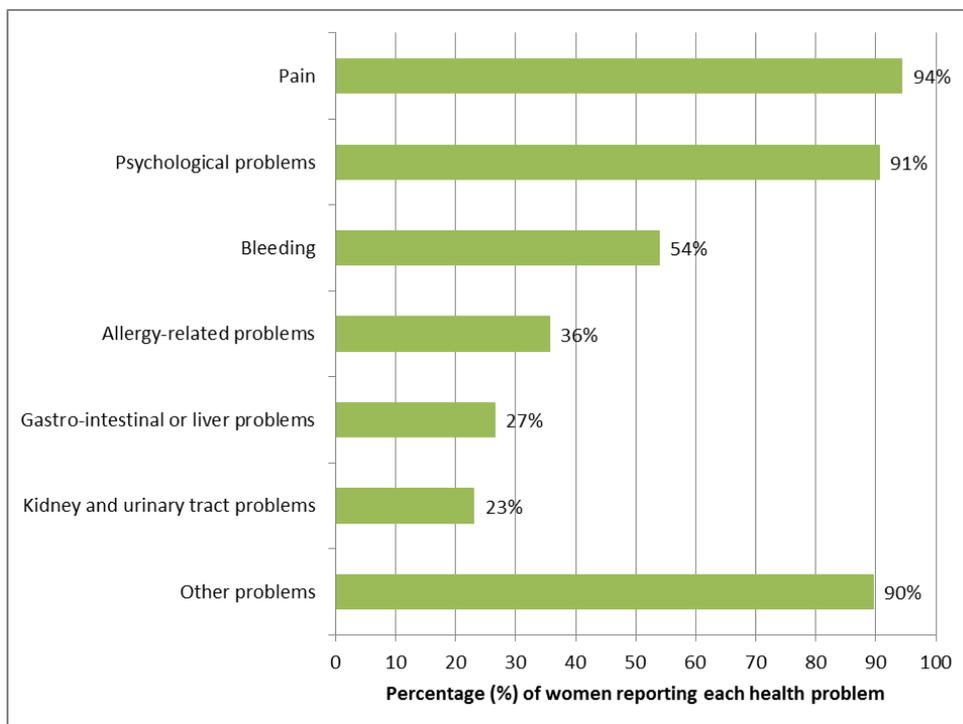


Figure 4: Percentage of women experiencing each category of health problems following Essure[®] placement.

The health problems and the trends thereof observed are comparable between the complaints received after the appeal of IGZ and the TV program and the earlier complaints, although the rates of occurrence differ.

The NVOG recognizes most of the health problems, since they are often reported by women during policlinic visits [13].

3.3.1 Pain

In total, 352 women (94%) experienced pain after the implantation of Essure[®] (Table 3). Abdominal pain was described most often (51%), followed by back pain (49%). Also pain in the head, pelvis/hips and legs were frequently mentioned. Additionally, 31% of the women experienced joint pain (arthralgia), whereas muscle pain, cramps and radiation to the legs were described by approximately 10% for each. Women also felt more pain during ovulation (23%), menstruation (16%) or coitus (13%).

Table 3: Pain related health problems following Essure® placement

Health problem	% of total (n=373)
PAIN	94% (n=352)
During ovulation	23%
During menstruation	16%
During coitus	13%
Abdomen	51%
(Lower)back	49%
Head	31%
Pelvis/hips	28%
Legs	23%
Groin	13%
Breasts	9%
Knees	3%
Other location	22%
Arthralgia	31%
Muscle pain	13%
Cramps	12%
Radiating to legs	11%

Eventhough pain is frequently reported in this study, pain is less commonly mentioned in the literature. A Phase III trial described pain during menstruation, coitus and ovulation in only 6%, 4% and 3% of the women, respectively [17]. This difference in occurrence rate might be explained by the different populations. Our study consist only of women who reported health problems, while a Phase III study contains women with and without health problems after the placement of the Essure® implants.

According to the NVOG, gynecologists see perforations due to the Essure® or kinked coils once in a while during the confirmational check after 3 months, during diagnosis of the health problems, or during removal of the implants. This might induce pain-related health problems in for example the abdomen and the lower back [13]. On the other hand, a correlation is more difficult to find for more chronic pains, like arthralgia as stated by the NVOG.

3.3.2 *Psychological issues*

Most women (91%, n=338) experienced health problems classified in this study as psychological (Table 4). 70% reported tiredness, around 40% reported mood swings or emotional imbalance, and around the same percentage reported memory loss or concentration problems. Approximately 20% of the women reported depressive feelings and an equivalent percentage of women experienced changes in body weight. Changes in body weight were in this study classified as "psychological problems", although other causes are possible, including, but not limited to, hormonal changes.

Table 4: Psychological issues following Essure® placement

Health problem	% of total (n=373)
PSYCHOLOGICAL COMPLAINTS	91% (n=338)
Tiredness	70%
Mood swings or emotionally out of balance	40%
Memory loss or concentration problems	39%
Depressive feelings	21%
Increase/decrease of weight	20%
Insomnia	17%
Loss of libido	15%
Other	37%

Remarkably, psychological issues are hardly mentioned in literature [16,17].

According to the NVOG, it is difficult to relate these problems to the Essure® implants since some of these mentioned health problems are common among women of the same age in the overall population (e.g. change in weight). The NVOG also indicated that a combination of some of these symptoms are seen as well in other diseases like Lyme disease and chronic fatigue syndrome [13]. Based on the assumption that older women may be more likely to experience these kind of psychological problems, we investigated whether there were age differences between women reporting psychological problems vs the overall population of women in this study or women not reporting psychological problems. This comparison was only done for those women reporting both psychological problems and the onset time of those problems. Based on the available data, there was no clear age difference between these groups of women (Appendix 5).

3.3.3

Bleeding

201 women (54%) reported health problems related to bleeding (Table 5). These problems consisted of increased or heavy blood loss during menstruation (37%), irregular bleeding/breakthrough bleedings (20%) and blood loss during coitus (5%).

Table 5: Bleeding problems following Essure® placement

Health problem	% of total (n=373)
BLEEDING	54% (n=201)
Increase or heavy blood loss during menstruation	37%
Irregular bleeding or breakthrough bleeding	20%
Blood loss during coitus	5%

In a Phase III study, 38% of the women reported a recurrent heavier menstrual flow [17]. This is in the same range as our findings (37%). In

the same study, an irregular menstruation was experienced by 15% of the women and bleedings between menstruations by 19% [17]. Our study revealed irregular menstruation and/or breakthrough bleedings in 20% of the women. These data are difficult to compare since we combined both health problems in one category and the population in these two groups is different since a Phase III study is a prospective cohort study and the current study contains only women with health problems after placement of the Essure® implants.

According to the NVOG, increased or heavier blood loss during menstruation does not have to be related to the Essure® implants but can be related to the fact that women stop using oral contraceptives or Mirena® after confirmation of the sterilization. Women often start with these methods of birth control as a treatment for bleeding problems, since these methods might reduce blood loss by 30% as specified by the NVOG [13]. When stopping any of these treatments after confirmation of complete sterilization with Essure®, the menstrual flow can become heavier again. It is not explicitly asked in this study whether women used birth control before Essure® placement and if this treatment was stopped after confirmation of the sterilization. Additionally, some women had children, which may be another cause of heavier menstrual flow, since menstrual flow often changes after giving birth. Also bleeding disorders may occur during perimenopause [13]. Moreover, breakthrough bleedings can be caused by perforation due to Essure® [13].

3.3.4 Allergy-related health problems

Allergy-related health problems were reported by 36% (n=133) of the women (Table 6). Itchy skin (16%) was the most frequent problem, followed by problems in the eyes (e.g. red or thick eyes, 10%), rash (8%) and eczema (6%). Although all women reporting eczema could be expected to report itchy skin as well, this was not always the case; therefore, the two types of health problems were kept separate.

Table 6: Allergy-related health problems following Essure® placement

Health problem	% of total (n=373)
ALLERGIES	36% (n=133)
Itching skin	16%
Allergic complaints in eyes (e.g. red, dry or thick eyes)	10%
Rash	8%
Eczema	6%
Other	3%

Some allergy-related health problems might be due to a nickel allergy. Essure® implants contain nickel, which might result in problems after placement if patients are allergic to nickel. In our study, 19% (n=71) of the women reported to have a nickel allergy and 9% (n=35) suspected to be allergic to nickel (e.g. they reported to only tolerate gold or silver). In Europe, around 20% of the population has a nickel allergy, with only a limited variation between countries. The prevalence of a nickel allergy is slightly higher in women compared to men [18-20]. Therefore, the

percentage of women in this study with a nickel allergy falls in the same range as the average of the European population (including men and women).

Results from this study show that half of the women who reported to have a confirmed or suspected nickel allergy experienced allergy-related problems while the other half did not. On the contrary, only 30% of the women without nickel allergy experienced allergy-related problems (Table 7). It is not known how many women with a nickel allergy do not develop health problems. Therefore it is not possible to conclude that having a nickel allergy is related to a higher chance of experiencing allergy-related problems after placing of Essure[®]. But it can be concluded that women who experience allergy-related problems more frequently have a nickel allergy compared to women who do not suffer from allergy-related problems.

Table 7: Percentage of allergy-related problems in women with, without or with a suspected nickel allergy.

		Allergy-related problems	
		No	Yes
Nickel allergy	No (n=267)	70%	30%
	Suspected (n=35)	51%	49%
	Yes (n=71)	48%	52%

The 2013 and 2015 versions of the IFU state: "Persons allergic to nickel-titanium may suffer an allergic reaction to the micro-insert". In the English section of the IFU for the US-only, a more elaborate statement is given: "The Essure micro-insert includes nickel-titanium alloy, which is generally considered safe. However, *in vitro* testing has demonstrated that nickel is released from this device. Patients who are allergic to nickel may have an allergic reaction to this device, especially those with a history of metal allergies. In addition, some patients may develop an allergy to nickel if this device is implanted. Typical allergy symptoms reported for this device include rash, pruritus, and hives."

In none of the current IFUs a nickel allergy is described as a contra indication.

Allergy to metal in implants is well known for orthopaedic implants. For orthopaedic implants, sensitivity to chromium, cobalt and nickel has been observed. Stainless steel in orthopaedic implants can contain approximately 10% nickel [21]. Problems that are considered to be related to metal allergy for orthopaedic implants are eczema, swelling, delayed wound healing, pain and even implant loosening [22,23].

In the Australian registry, "metal sensitivity" is indicated for approximately 6% of the revision surgeries for hip implants and 1% for shoulder implants [22,24]. An enquiry among German orthopaedic surgeons indicated that complications related to allergy are rare [25]. It is also indicated that, although metal sensitivity may develop, only 1% of the arthroplasty patients exhibit symptoms.

The need and method used for the diagnosis of a nickel allergy before the placement of orthopaedic implants is debated. The usual patch skin test does not always indicate nickel allergy, whereas the lymphocyte transformation test (LTT) is considered more accurate, but more complex to perform [22]. It has been established that the frequency of

occurrence of metal sensitivity decreases with increasing age. The frequency of metal sensitivity among women under 40 years of age is estimated to be 23 %, whereas this drops to 1% for the age group over 60 years [25].

The occurrence of allergy-related problems after implanting orthopaedic implants cannot be considered to be similar to the occurrence after placing Essure[®]. Orthopaedic implants, like hip and knee replacements, have a considerably higher weight than the Essure[®] coils and abrasive wear will lead to small particles being generated. This debris can lead to allergic and other reactions. The inner coil of Essure[®] is made of stainless steel and PET-fibers. The outer coil is made of nitinol, which is an alloy of titanium and nickel [26], and therefore, nickel will be in contact with the tissue of the patient. It is unknown how quickly nickel reacts or is released from the coil.

As there is still uncertainty about the mechanisms of allergy-related problems for orthopaedic implants and there is also no clear mechanism for allergy related problems for Essure[®], it cannot be established what types of problems of the Essure[®] coils can be attributed to nickel allergy. In literature, metal allergy and its consequences are mainly studied for orthopaedic implants, and not for implants used in the uterus or fallopian tubes.

According to the NVOG, it is difficult to confirm that an allergy-related problem is caused by a nickel allergy or an a-specific inflammation. A nickel allergy is not included as a contraindication in the NVOGs guideline for sterilization [27]. Gynecologists in the Netherlands are currently investigating the application of Essure[®] in women with a nickel allergy. A conclusion cannot be drawn at this moment since this study is not completed yet. Despite the fact that there is no causal relation demonstrated between a nickel allergy and allergy-related problems, gynecologists warn their patients that there is a low chance of allergic problems if they have a nickel allergy.

3.3.5 *Gastro-intestinal or liver health problems*

Approximately one fourth of the women (n=99) experienced health problems related to the gastro-intestinal tract or liver. These health problems were often not described in detail in the reported complaint but, when specified, they were mainly: altered stool (constipation or thin stool), strange taste, and bile problems.

The NVOG does not recognize all these health problems in relation to Essure[®]. For example, a strange taste is not frequently mentioned by their patients and cannot be explained by the NVOG.

3.3.6 *Kidney and urinary tract health problems*

From the women who experienced kidney and urinary tract problems (23%, n=86), problems related to urinating (less/often or difficult, 9%), bladder infection (7%), and incontinence (7%) were reported most frequently (Table 8).

Table 8: Kidney and urinary tract health problems following Essure® placement

Health problem	% of total (n=373)
KIDNEY AND URINARY TRACT COMPLAINTS	23% (n=86)
Problems with urinating (often/less, difficult)	9%
Bladder infection	7%
Incontinence	7%
Other	1%

For some health problems, such as a bladder infection and pain during urinating, the relation with the Essure® implants is considered limited by the NVOG, as these type of problems are common in the Dutch population. Women come to the outpatient clinic with these problems on a daily basis [13].

3.3.7 *Other health problems*

Besides the health problems classified in the categories above, 90% of the women (n=334) deal with other problems ranging from a tingling feeling in e.g. limbs (20%) to excessive sweating (18%) and swollen abdomen (17%) (Table 9). It is unknown if there is a relation between these health problems and the Essure® implants.

Table 9: Other type of health problems following Essure® placement

Health problem	% of total (n=373)
OTHER COMPLAINTS	90% (n=334)
Tingling (hands, feets, legs and arms)	20%
Excessive sweating	18%
Swollen abdomen	17%
Menopause complaints	16%
Hair problems (e.g. hairloss)	14%
Arrhythmia	11%
Vaginal secretion (e.g. much secretion)	11%
Fungal infections (vaginal or other)	11%
Vision problems	11%
Feeling the implant	9%
Other	27%

3.4 **Influence on daily life**

The health problems experienced by the women in this study often have a considerable impact on their daily life. Three-quarter (75%, n=280) of the women reported that the health problems that developed after the placement of Essure® had an impact on their daily lives in one or more ways (Table 10), while 25% of the women did not provide any information on this question. A large number of women encountered problems related to work (39%), ranging from having difficulties with certain tasks, e.g. standing for a prolonged period of time, to not being able to work at all. One third of the women experienced a major impact on their relationship and/or family life. There are, for example, women

who describe that they cannot participate in activities with their children anymore or who were recently divorced, in which their health problems played a role. Most likely, health problems like pain and tiredness are considered to contribute to a large extend of the problems they encounter in their daily life.

Table 10: Overview of influence on daily life

Influence on daily life	% of total (n=373)
Influence on daily life	75% (n=280)
Work-related problems	39%
Relation and/or family problems	34%
Problems with daily tasks (e.g. at home)	24%
Mobility problems (e.g. during walking, biking, sports etc)	22%
Lack of social activities and happiness (incl burnout)	9%
Other	29%
Influence not mentioned	25%

3.5 Visiting doctor/specialist and diagnosis

Around 90% (n=335) of the women visited a doctor for their health problems (Appendix 6) and 21% explicitly mentioned to have visited a gynecologist. 53% of the women who reported their problems have undergone some kind of diagnostic testing such as control of the position of Essure[®] (9% of the women), blood test (22%) or a wide variety of other tests (37%) like MRI or echo (without further specifying if this was done to control the position of the implant or for another medical reason). From those women who mentioned the outcome of the tests, half of them received a diagnosis while in the other half nothing was found. It was not clarified if the diagnosis was related to the Essure[®] or not.

In a fair number of cases, the complaints indicated that visits to the doctor were mainly related to the occurrence of health problems and treatment or diagnosis thereof, and not directly related to problems with the implants. Therefore, no direct relationship between visiting doctors and undergoing examinations and Essure[®] could be established. It is difficult (for the physicians) to link the health problems that women experienced to the implants due to the type of problems that the women report, since the reported health problems are common and can be related to a lot of other causes.

Perforation of i.a. fallopian tube after the placement of the Essure[®] implants was reported by 10 women (3%). In 4 of them, perforation was recognized during placement of Essure[®] while in the other 6, perforation was only revealed later after doctor's examination. This percentage is difficult to compare with literature since a wide variety of percentages are described in literature. Al-Safi et al evaluated the Essure[®] complaints of women in the FDA's Manufacturer and User Facility Device Experience (MAUDE) database [27]. This is a database in which patients as well as manufacturers, health professional and healthcare centres can submit complaints on all kind of devices. Since multiple persons can submit complaints in this database it is possible

that one event is reported several times (e.g. by a patient and a doctor). For Essure[®], perforation was described in 20% of the events in the MAUDE database. On the contrary, a Phase II and Phase III study report a perforation rate of 3% and 1% respectively [15,16]. This variation in occurrence rate might be explained by the different populations. The MAUDE database consist only of women who reported health problems, while a Phase II/III study contains women with and without health problems after the placement of the Essure[®] implants. The NVOG mentioned that they observe perforations after placement of the Essure[®] once in a while. Therefore, perforation might be underreported in our study. This underreporting of perforations may be due to the fact that this was not asked literally in the questionnaire used by the LMZ and women might often not remember this event.

3.6 Removal of Essure[®]

The Essure[®] implants were removed in 16% (n=60) of the women (Table 11). Of these women, 53 indicated that a single or both the fallopian tubes were removed together with the Essure[®]. Since the Essure[®] implants become fully embedded in tissue that develops in the fallopian tube after insertion, it is difficult to remove the Essure[®] implants while maintaining the fallopian tubes intact. Therefore, it is expected that the fallopian tubes are removed in 100% of the women. The uterus was removed together with the fallopian tubes in a quarter of the women, and the ovary was removed in two women. The implants were removed between 2010 and 2016, on average 4 years after placement, ranging from two weeks to over 13 years after placement (Figure 5).

From the women who had the implants removed, 23% (n=14) reported to be fully recovered after the removal while 48% (n=29) is still recovering. One out of 10 women did not notice any improvement/relief of their health problems after the removal. From 18% (n=11) of the women it is unknown if they recovered after the removal of the implants. There was a slightly different prevalence of health problems before removal of Essure[®] among the women who recovered vs women who did not recover after the removal (Appendix 7). For instance, 51% (n=18) of women who did not recover reported allergy-related problems before removal, while none of the women in the group that recovered did. It is hard to interpret this data. This may indicate that allergy-related problems are, at least in the short term, not solved by removal of Essure[®]. It might also be possible that women with a nickel allergy are more aware of allergy-related problems and link this quicker to the Essure[®] implants. Besides, small particles might still be present after removal of the Essure[®] implants or the allergy-related problems might have another cause than the implants and therefore the health problems remain after removal of the implants.

On the contrary, bleeding before removal was more prevalent in the group of women that recovered vs the other group. However, results from such a descriptive analysis should be interpreted with caution.

At the time of reporting to LMZ, 38% (n=140) of the women with health problems had an appointment planned for the removal of the Essure[®]

implants and 8% (n=31) explicitly mentioned they were considering the removal of the implants.

Table 11: Removal of Essure® and outcome after removal

	% of total (n=373)
Essure removed	16%
<i>One fallopian tube removed</i>	1%
<i>Two fallopian tubes removed</i>	13%
<i>Uterus removed</i>	4%
<i>Ovary removed</i>	1%
Removal Essure planned	38%
Removal Essure considered	8%
Removal not mentioned	38%

	% of removed (n=60)
Recovered after removal Essure	23%
Still recovering after removal Essure	48%
Not recovered after removal Essure	10%
Unknown	18%

	Time after which Essure was removed (months)
Mean	49
Standard deviation	35
Minimum	0,5
Maximum	157

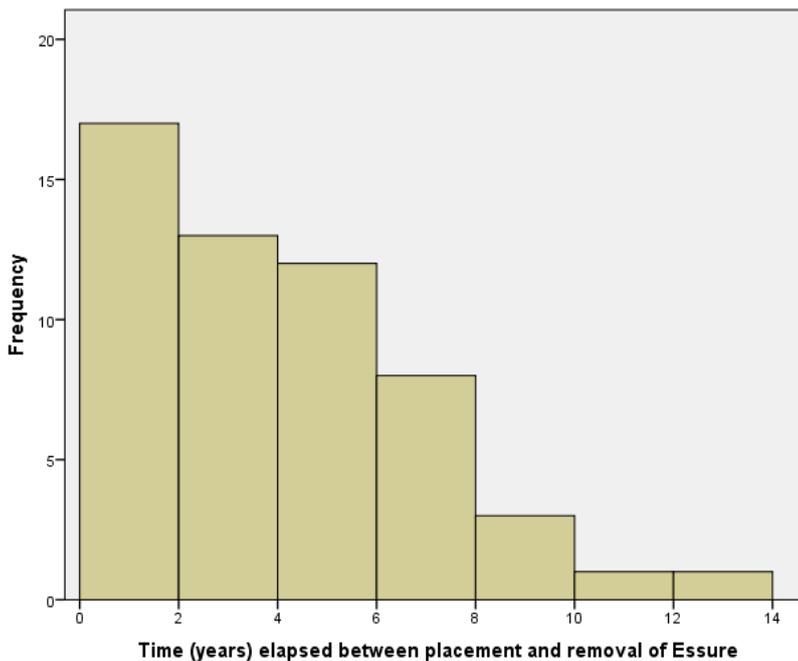


Figure 5: Time (years) elapsed between placement and removal of Essure®

4 Discussion and conclusions

4.1 Discussion

4.1.1 *General/method*

In the Netherlands, there are approximately 30.000 women sterilized by the Essure[®] method. In this investigation, data were extracted from 373 complaints submitted to the LMZ related to problems with the Essure[®]. The number of health problems can be assumed to be higher in the total population of Essure[®] users since it is not expected that all women experiencing health problems have reported this to LMZ. On the other hand, by far, most women do not report health problems after the Essure[®] treatment. Lastly, the NVOG notified that the Dutch Facebook page for Essure[®] problems advised women to report as many health problems as possible so that the chance that gynecologists would remove the implants would be higher. This might have some influence on the data from this study. Eventhough women often indicate that they want the Essure[®] implants removed it should be noted that the removal is a complex procedure and it is not guaranteed that the Essure[®] will be completely removed (sometimes small particles remain) or that the health problems resolve.

4.1.2 *Implementation of the Essure[®] method*

According to the NVOG, the Essure[®] sterilization method has been implemented gradually in the Netherlands. Gynecologists first received training and their performance had to be observed before they were allowed to apply this method independently. In the Netherlands, gynecologists were trained to assess HSG and X-ray pictures and to recognize perforations. In addition, there is a panel of experts that can be consulted in case of complications or e.g. doubts about X-ray pictures.

In the USA, the Essure[®] method was implemented differently compared to the Netherlands, according to the NVOG [13]. Al-Safi et al, evaluated the complaints about Essure[®] in the MAUDE database (a USA based database). 20% of the complaints in the MAUDE database were related to perforations [27]. On the contrary, the perforation rate was around 2% in Phase II and III studies which were also (partially) conducted in the USA [15,16] but presumably in a more controlled setting. Thirteen percent of the complaints in the MAUDE database described unintended pregnancies, while this was only reported by 1 woman (0.3%) in our study. The Phase II and III studies did not observe any unintended pregnancies.

4.1.3 *Association between Essure[®] and health problems*

The RIVM discussed the results with the NVOG and IGZ to evaluate which health problems could be related to the Essure[®] implants. The NVOG indicated that breakthrough bleedings and pain-related problems, especially in the abdomen and lower back, could be linked to the Essure[®] implants. A heavier menstrual flow, instead, was most likely caused by stopping with the contraceptive pill after a confirmed sterilization, as contraceptive pills are known to reduce blood loss during menstruation. In addition, some health problems like pain during

urinating and weight changes are common in women and are therefore not likely to be linked to the Essure[®]. It is difficult to determine the relationship between Essure[®] and the more general health problems reported. Besides, the health problems sometimes develop after a long period. Due to the long onset time, it is difficult to determine whether these health problems are related to Essure[®] or not. For example, one woman reported that the first health problems appeared after 9 years. Currently, the NVOG investigates if the health problems resolve after the removal of the Essure[®] implants to give insight into the relation between Essure[®] implants and the health problems.

Some gynecologists observed a layer of sediment on the metal coils during the removal of the implants, according to the NVOG. Currently, gynecologists investigate why this sediment forms and what is the possible consequence. The time span after which this sediment is formed is still unknown. Although the formation of this sediment might be a cause of some of the health problems, it is not likely to explain all the health problems observed in this study.

The influence of a nickel allergy on the development of health problems is also unknown. Overall, more research would be needed to establish a causal relationship between Essure[®] and the reported health problems including the effects of a nickel allergy. Also the likelihood to recover after removal of the implants should be investigated.

4.1.4 *Position NVOG about Essure[®]*

The NVOG does not see a reason to be negative regarding Essure[®] as a sterilization method despite the fact that some women report health problems after its placement. For some women, the Essure[®] method is a better choice compared to other, more conventional sterilization methods that also bring along some risks. For example, the Essure[®] sterilization method is less risky compared to invasive methods for women who had multiple operations in the abdominal area. In addition, most women do not experience health problems after the placement of Essure[®]. A case-by-case weighing of the risks and benefits of Essure[®] compared to alternative methods should be done. In addition, the NVOG considers it important to inform their patients adequately about the possible health problems after placement of the Essure[®] implants. The NVOG suggests that more extensive studies (e.g. randomized clinical trials) are needed when new products are used in a large population.

4.2 **Conclusions**

Complaints were received from approximately 500 women who were sterilized with Essure[®] implants. This corresponds to more than 1.5% of the total amount of women sterilized with Essure[®] in the Netherlands. A wide variety of health problems were reported. The average reported onset time of health problems was 7 months, ranging between 0 and 108 months. The most frequently reported health problems were pain (94%), psychological issues (91%) and deviant bleedings (54%). In our study population, there was a slightly higher frequency of allergy-related problems in women who reported to be allergic to nickel compared to women without this allergy. In approximately three quarters of the women, the health problems had a considerable influence on the women's daily life, mainly related to work, family/relationship and daily duties. The Essure[®] implants were removed in 16% of the women, with

almost one quarter of these women recovering from their health problems after the removal. 38% of the women have planned to have Essure[®] removed.

For some of the health problems (e.g. abdominal pain and breakthrough bleeding) there could be a possible relationship with the Essure[®]; for other health problems (e.g. weight changes and urinary tract problems), this link is less likely.

Eventhough some women experience health problems after the placement of Essure[®], this method might be beneficial for some women since no general anesthesia and operations are needed which is the case for laparoscopic sterilization. There is no long term study conducted into the relation between the Essure[®] implants and the development of health problems. This study indicates that there is a trend in health problems which the women experience after the placement of the implants but based on the available data it is not possible to determine if there is a causal relation between the health problems and the Essure[®] implants.

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Appendix 1: Overview of sterilization methods for women available in the Netherlands

Laparoscopic sterilization (surgical) [3-7]	
Surgical methods	
Tubectomy	Surgical removal of the fallopian tube
A variant of the three methods below can be applied during a caesarian operation	
Pomeroy	A chromic tie is placed around a loop of the fallopian tube after which 1-2 cm is excised.
Irving method	A segment between 2 ties is resected. Afterwards, one end is attached to the back of the uterus and the other end is buried in the surrounding connective tissue.
Uchida method	A vasoconstrictive solution is injected in the tubal mucosa. A part of the sub-serosa is dissected and 2 cm of muscular part is resected. One end retracts in connective tissue and the other end is exteriorized to peritoneal cavity.
Mechanical methods	
Bands/rings	A ring is placed around a loop of the fallopian tube. The ring contracts after release and closes the tube. The loop undergoes necrosis and separates from the healthy part of the tube.
Hinged clips	A clip is compressed around the fallopian tube. Only a small part of the tube is damaged.
Electrical methods	

Hysteroscopic sterilization (non-surgical)	
Essure [®] implants	A coil is inserted into the fallopian tube. The tube is blocked due to tissue growth around the coils.
Altaseal [®] implants	A stainless steel implant is placed in the fallopian tube and closes the tube immediately (Currently only applied in clinical trial)
Ovalastic [®] implants	A flexible rubber implant is placed in the fallopian tube and closes the tube immediately (Currently only applied in clinical trial)
Electrocoagulation with bipolar forceps	The fallopian tube is grasped by 2 forceps through which a current passes, which damages at least 3 cm of the tube.

Appendix 2: Description of the variables in the database

Type of data	Variable prefix	Variable explanation	Variable name	Type of variable	Possible values/format
Administrative data	ADM_	Notification number	ADM_NR_NOTIFICATION	numeric	1 up to last notification
		Follow up number LMZ	ADM_LMZ_NR	numeric	8 digit code
		Registrar	REGISTRATOR	string	text (initials)
		Date of notification	ADM_DATE_NOTIFICATION	numeric	format DD/MM/YYYY
		Date of birth	ADM_DATE_OF_BIRTH	numeric	format DD/MM/YYYY
		Date of Essure placement	ADM_DATE_ESSURE	numeric	format DD/MM/YYYY - if there are multiple dates (e.g. between 2013-2014), take the average - if only the month is mentioned, take the 15th as the date - start of 2016 =
		Age of woman when Essure was placed	ADM_AGE_ESSURE	numeric	in years
In which hospital was the Essure placed?	ADM_HOSPITAL	string	text		
How did the procedure go	PROC_	How long did the placement take?	PROC_TIME	numeric	in minutes
		Was the placement painful?	PROC_PAIN	numeric	1 (=YES), 0 (=NO), blank (= unknown)

Type of data	Variable prefix	Variable explanation	Variable name	Type of variable	Possible values/format	
		<i>If so, how long did it last?</i>	PROC_PAIN_TIME	numeric	in days	
		Where there any other complications?	PROC_OTH_COMPLICATION	numeric	1 (=YES), 0 (=NO), blank (= unknown)	
		<i>If so, fallopian tube perforated?</i>	PROC_OTH_COMPLICATION_PERFORATION	numeric	1 (=YES), 0 (=NO), blank (= unknown)	
		<i>If so, adhesion?</i>	PROC_OTH_COMPLICATION_ADHESION	numeric	1 (=YES), 0 (=NO), blank (= unknown)	
		<i>If so, breaking of implant?</i>	PROC_OTH_COMPLICATION_BREAK	numeric	1 (=YES), 0 (=NO), blank (= unknown)	
		<i>If so, placement on one side only?</i>	PROC_OTH_COMPLICATION_ONESIDE	numeric	1 (=YES), 0 (=NO), blank (= unknown), Second placement can be added at PROC_TREAT_AND	
		<i>If so, other?</i>	PROC_OTH_COMPLICATION_OTH	numeric	1 (=YES), 0 (=NO), blank (= unknown)	
		<i>If so, nauseous and/or dizzy?</i>	PROC_COMPLICATION_NAUSEOUS_DIZZY	numeric	1 (=YES), 0 (=NO), blank (= unknown)	
		<i>If other, which ones?</i>	PROC_OTH_COMPLICATION_OTH_TXT	string	text	
		Treatment after procedure with complications				
		<i>Sterilisation with other methods</i>	PROC_TREAT_OTH_STERILIZATION	numeric	1 (=YES), 0 (=NO), blank (= unknown)	
		<i>Novasure treatment</i>	PROC_TREAT_NOVASURE	numeric	1 (=YES), 0 (=NO), blank (= unknown)	
		<i>Other?</i>	PROC_TREAT_OTH	numeric	1 (=YES), 0 (=NO), blank (= unknown)	
		<i>If other, which ones?</i>	PROC_TREAT_OTH_TXT	string	text	

Type of data	Variable prefix	Variable explanation	Variable name	Type of variable	Possible values/format
		Result after procedure with complications	PROC_RESULT	string	text
Complaints	COMP_	Time till start of complaints (if not specified per individual complaint)	COMP_TIME	numeric	in months (or blank if unknown)
		Allergic complaints	COMP_ALLERGIC	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Latency time</i>	COMP_ALLERGIC_TIME	numeric	in months (or blank if unknown)
		<i>Allergy for products (e.g. shampoos, parfume)</i>	COMP_ALLERGIC_PRODUCTS	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Eczema</i>	COMP_ALLERGIC_ECZEMA	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Rash</i>	COMP_ALLERGIC_RASH	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Itching skin</i>	COMP_ALLERGIC_ITCHING	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Allergic complaints in eyes (e.g. red, dry or thick eyes)</i>	COMP_ALLERGIC_EYES	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Urticaria</i>	COMP_ALLERGIC_URTICARIA	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		Bleeding	COMP_BLEED	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Latency time</i>	COMP_BLEED_TIME	numeric	in months (or blank if unknown)
		<i>Increase or heavy blood loss during menstruation</i>	COMP_BLEED_MENST	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Irregular bleeding or breakthrough bleeding</i>	COMP_BLEED_IRREGULAR	numeric	1 (=YES), 0 (=NO), blank (= unknown)
<i>Blood loss during coitus</i>	COMP_BLEED_COITUS	numeric	1 (=YES), 0 (=NO),		

Type of data	Variable prefix	Variable explanation	Variable name	Type of variable	Possible values/format
		<i>Location</i>	COMP_BLEED_LOCATION	string	blank (= unknown) text
		<i>How often (interval between two bleeding episodes)</i>	COMP_BLEED_INTERVAL	numeric	in days (or blank if unknown)
		<i>Duration of bleeding</i>	COMP_BLEED_DURATION	numeric	in days (or blank if unknown)
	Gastro-intestinal or liver complaints		COMP_GI	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Latency time</i>	COMP_GI_TIME	numeric	in months (or blank if unknown)
		<i>Thin stools</i>	COMP_GI_THIN_STOOL	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Bile problems</i>	COMP_GI_BILE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Liver problems</i>	COMP_GI_LIVER	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Constipation</i>	COMP_GI_OBSTIPATION	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Strange taste in mouth (e.g. metal taste)</i>	COMP_GI_TASTE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Smelly breath</i>	COMP_GI_SMELLY_BREATH	numeric	1 (=YES), 0 (=NO), blank (= unknown)
	Kidney and urinary tract		COMP_KIDNEY_URINE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Latency time</i>	COMP_KIDNEY_URINE_TIME	string	in months (or blank if unknown)
		<i>Adrenal exhaustion</i>	COMP_KIDNEY_URINE_ADRENAL EXHAUSTION	numeric	1 (=YES), 0 (=NO), blank (= unknown)

Type of data	Variable prefix	Variable explanation	Variable name	Type of variable	Possible values/format
		<i>Bladder infection</i>	COMP_KIDNEY_URINE_BLADDER_INFECTION	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Dark urine</i>	COMP_KIDNEY_URINE_COLOUR	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Incontinence</i>	COMP_KIDNEY_URINE_INCONTINENCE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Problems with urinating (often/less, difficult)</i>	COMP_KIDNEY_URINE_URINATE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
Pain related complaints			COMP_PAIN	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Latency time</i>	COMP_PAIN_TIME	string	in months (or blank if unknown)
		<i>When was the pain worse?</i>			
		<i>During ovulation</i>	COMP_PAIN_OVULATION	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>During menstruation</i>	COMP_PAIN_MENSTRUATION	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>During coitus</i>	COMP_PAIN_COITUS	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Location</i>			
		<i>Pelvis/hips</i>	COMP_PAIN_HIPS	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Legs</i>	COMP_PAIN_LEGS	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Abdomen</i>	COMP_PAIN ABDOMEN	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Head</i>	COMP_PAIN_HEAD	numeric	1 (=YES), 0 (=NO), blank (= unknown)

Type of data	Variable prefix	Variable explanation	Variable name	Type of variable	Possible values/format
		<i>Knees</i>	COMP_PAIN_KNEE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>(Lower)back</i>	COMP_PAIN_BACK	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Groin</i>	COMP_PAIN_GROIN	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Breasts</i>	COMP_PAIN_BREASTS	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Other location</i>	COMP_PAIN_OTH	string	text
		<i>Type of pain (defined as)</i>			
		<i>Arthralgia</i>	COMP_PAIN_TYPE_ARTHRALGIA	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Cramps</i>	COMP_PAIN_TYPE_CRAMP	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Muscle pain</i>	COMP_PAIN_TYPE_MUSCLE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Radiating to legs</i>	COMP_PAIN_TYPE_RADIATING	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Other type</i>	COMP_PAIN_TYPE_OTH	string	text
	Psychological complaints		COMP_PSYCH	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Latency time</i>	COMP_PSYCH_TIME	numeric	in months (or blank if unknown)
		<i>Depressive feelings</i>	COMP_PSYCH_DEPRESSION	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Dizziness</i>	COMP_PSYCH_DIZZINESS	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Intolerant to noises</i>	COMP_PSYCH_NOISES	numeric	1 (=YES), 0 (=NO), blank (= unknown)

Type of data	Variable prefix	Variable explanation	Variable name	Type of variable	Possible values/format
		<i>Increase/decrease of weight</i>	COMP_PSYCH_WEIGHT	numeric	blank (= unknown) 1 (=YES), 0 (=NO), blank (= unknown)
		<i>Loss of libido</i>	COMP_PSYCH_LIBIDO	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Nausea</i>	COMP_PSYCH_NAUSEA	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Tiredness</i>	COMP_PSYCH_TIREDNESS	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Restless feelings</i>	COMP_PSYCH_RESTLESSNESS	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Insomnia</i>	COMP_PSYCH_INSOMNIA	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Mood swings or emotionaly out of balance</i>	COMP_PSYCH_MOODSWINGS	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Memory loss or concentration problems</i>	COMP_PSYCH_MEMORY	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Brain fog</i>	COMP_PSYCH_BRAINFOG	numeric	1 (=YES), 0 (=NO), blank (= unknown)
	Other complaints		COMP_OTH	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Latency time</i>	COMP_OTH_TIME	string	in months (or blank if unknown)
		<i>Adenomyosis</i>	COMP_OTH_ADENOMYOSIS	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Always feeling cold</i>	COMP_OTH_COLD	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Anemia</i>	COMP_OTH_ANEMIA	numeric	1 (=YES), 0 (=NO), blank (= unknown)

Type of data	Variable prefix	Variable explanation	Variable name	Type of variable	Possible values/format
		<i>Brittle nails</i>	COMP_OTH_NAILS	numeric	blank (= unknown) 1 (=YES), 0 (=NO), blank (= unknown)
		<i>Swollen abdomen</i>	COMP_OTH_SWOLLEN ABDOMEN	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Hair problems (e.g. hairloss)</i>	COMP_OTH_HAIR	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Arrhythmia</i>	COMP_OTH_ARRHYTHMIA	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Coughing</i>	COMP_OTH_COUGHING	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Vaginal secretion (e.g. much secretion)</i>	COMP_OTH_SECRETION	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Weakness or asthenia</i>	COMP_OTH_ASTHENIA	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Unwished pregnancy</i>	COMP_OTH_PREGNANCY	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Menopause complaints</i>	COMP_OTH_MENOPAUSE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Tooth problems</i>	COMP_OTH_TEETH	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Fungal infections (vaginal or other)</i>	COMP_OTH_FUNGAL_INFECTION	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Vitamine deficiency</i>	COMP_OTH_VITAMINE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Fluid in uterus</i>	COMP_OTH_FLUID_UTERUS	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Vision problems</i>	COMP_OTH_VISION	numeric	1 (=YES), 0 (=NO), blank (= unknown)

Type of data	Variable prefix	Variable explanation	Variable name	Type of variable	Possible values/format
		<i>Heavier menstruation (if patient is not specific about pain or bleedings)</i>	COMP_OTH_MENSTUATION	numeric	blank (= unknown) 1 (=YES), 0 (=NO), blank (= unknown)
		<i>Excessive sweating</i>	COMP_OTH_SWEATING	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Tingling (hands, feets, legs and arms)</i>	COMP_OTH_TINGLING	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Feeling the implant</i>	COMP_OTH_IMPLANT	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Tinnitus</i>	COMP_OTH_TINNITUS	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Others</i>	COMP_OTH_OTH	string	text (add here complaints not mentioned before)
Influence on daily life	INFL_	<i>Problems with movenents (e.g. walking, biking, doing sports etc)</i>	INFL_MOVE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Work-related problems</i>	INFL_WORK	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Problems with daily tasks (e.g. at home)</i>	INFL_TASKS	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Relation and/or family problems</i>	INFL_RELATION	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Social activities and happiness (incl burnout)</i>	INF_MOOD_HAPPINESS_SOCIAL (inclusief burnout)	numeric	2 (=YES), 0 (=NO), blank (= unknown)
		<i>Others</i>	INFL_OTH	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>If other, which ones?</i>	INFL_OTH_TXT	string	text

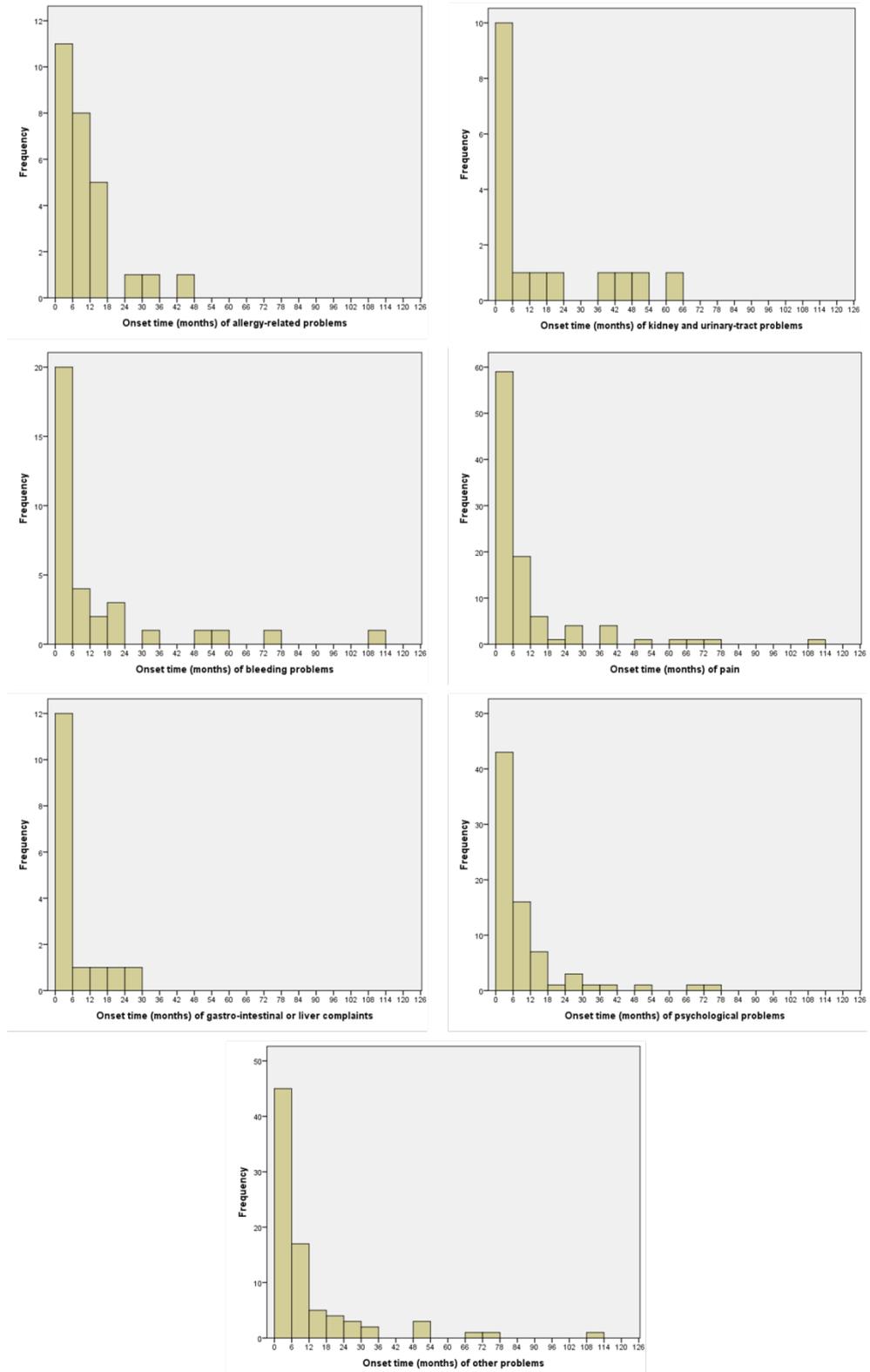
Type of data	Variable prefix	Variable explanation	Variable name	Type of variable	Possible values/format
Action taken	ACT_	No action	ACT_NONE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		Contacted a doctor	ACT_DOCTOR	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		Visited a gynecologist	ACT_DOCTOR_GYNECOLOGIST	numeric	2 (=YES), 0 (=NO), blank (= unknown)
		Other action	ACT_OTHER	string	text
Tests conducted	RES_	Hysterosalpingography	RES_HYSTEROSALPINGOGRAPHY	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		Control position Essure	RES_CONTROL_POSITION	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>If so, through echo</i>	RES_POSITION_ECHO	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>If so, through laparoscopy</i>	RES_POSITION_LAPAROSCOPY	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		Blood test	RES_BLOOD	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		Other	RES_OTH	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>If so, which ones?</i>	RES_OTH_TXT	string	text
		Result after tests: nothing found	RES_RES_NONE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		Result after tests: diagnosis	RES_RES_DIAG	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>If so, which ones?</i>	RES_DIAG_TEXT	string	text
Problems with	IMPL_	<i>Perforation</i>	IMPL_PERFORATION	numeric	1 (=YES), 0 (=NO),

Type of data	Variable prefix	Variable explanation	Variable name	Type of variable	Possible values/format
implant		<i>Migration of implant</i>	IMPL_MIGRATION	numeric	blank (= unknown) 1 (=YES), 0 (=NO), blank (= unknown)
		<i>Breaking of implant</i>	IMPL_BREAKING	numeric	1 (=YES), 0 (=NO), blank (= unknown)
Treatment complaints	TREAT_	Treatment performed	TREAT_PERF	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Medication</i>	TREAT_PERF_MED	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Other</i>	TREAT_PERF_OTH	string	text
		<i>Removal of Essure</i>	TREAT_PERF_REMOVAL_ESSURE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Date removal Essure</i>	TREAT_PERF_REMOVAL_ESSURE_DATE	numeric	format DD/MM/YYYY
		<i>What was removed together with Essure?</i>			
			<i>One fallopian tube</i>	TREAT_PERF_REMOVAL_ESSURE_1TUBE	numeric
		<i>Two fallopian tubes</i>	TREAT_PERF_REMOVAL_ESSURE_2TUBES	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Uterus</i>	TREAT_PERF_REMOVAL_ESSURE_UTERUS	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Ovary</i>	TREAT_PERF_REMOVAL_ESSURE_OVARY	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Novasure conducted</i>	TREAT_PERF_NOVASURE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Result</i>			
		<i>Recovered</i>	TREAT_PERF_RESULT_RECOVERED	numeric	1 (=YES), 0 (=NO), blank (= unknown)

Type of data	Variable prefix	Variable explanation	Variable name	Type of variable	Possible values/format
		<i>Recovering (treatment is performed but it is not known yet if patient will fully recover)</i>	TREAT_PERF_RESULT_RECOVERING	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Not recovered</i>	TREAT_PERF_RESULT_NOT_RECOVERED	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Deceased</i>	TREAT_PERF_RESULT_DECEASED	numeric	1 (=YES), 0 (=NO), blank (= unknown)
	Treatment planned		TREAT_PLANNED	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Medication</i>	TREAT_PLANNED_MED	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Other</i>	TREAT_PLANNED_OTH	string	text
		<i>Removal of Essure</i>	TREAT_PLANNED_REMOVAL_ESSURE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Date removal Essure</i>	TREAT_PLANNED_REMOVAL_ESSURE_DATE	numeric	format DD/MM/YYYY
		<i>What will be removed together with Essure?</i>			
		<i>One fallopian tube</i>	TREAT_PLANNED_REMOVAL_ESSURE_1TUBE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Two fallopian tube</i>	TREAT_PLANNED_REMOVAL_ESSURE_2TUBES	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Uterus</i>	TREAT_PLANNED_REMOVAL_ESSURE_UTERUS	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Ovary</i>	TREAT_PLANNED_REMOVAL_ESSURE_OVARY	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Novasure planned</i>	TREAT_PLANNED_NOVASURE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
	Consider removal of Essure		TREAT_CONSIDER_REMOVAL	numeric	1 (=YES), 0 (=NO), blank (= unknown)

Type of data	Variable prefix	Variable explanation	Variable name	Type of variable	Possible values/format
		No treatment performed and no treatment planned	TREAT_NONE	numeric	1 (=YES), 0 (=NO), blank (= unknown)
Medical history	HIST_	<i>Nickel allergy</i>	HIST_NICKEL	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Suspected nickel allergy</i>	HIST_SUSPECTED_NICKEL	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Other sterilisation method</i>	HIST_OTH_STERILISATION	numeric	1 (=YES), 0 (=NO), blank (= unknown)
		<i>Other</i>	HIST_OTH	string	text
Remarks		Relevant remarks	REMARKS	string	text

Appendix 3: Onset time of the categories of health problems



Appendix 4: Frequency of occurrence of all health problems

	Column Total N %	Count
Pain	94,4%	352
Psychological complaint	90,6%	338
Other complaints	89,5%	334
Bleeding	53,9%	201
Allergies	35,7%	133
Gastro-intestinal or liver complaints	26,5%	99
Kidney and urinary tract complaints	23,1%	86

	Column Total N %	Count
ALLERGIES	35,7%	133
Itching skin	15,8%	59
Allergic complaints in eyes (e.g. red, dry or thick eyes)	10,2%	38
Rash	7,8%	29
Eczema	6,4%	24
Allergy for products (e.g. shampoos, perfume)	2,9%	11
Urticaria	0,3%	1
BLEEDING	53,9%	201
Increase or heavy blood loss during menstruation	36,7%	137
Irregular bleeding or breakthrough bleeding	20,1%	75
Blood loss during coitus	5,1%	19
GASTRO-INTESTINAL OR LIVER COMPLAINTS	26,5%	99
Constipation	4,6%	17
Strange taste in mouth (e.g. metal taste)	4,0%	15
Bile problems	2,9%	11
Thin stool	2,7%	10
Liver problems	1,6%	6
Smelly breath	0,5%	2
KIDNEY AND URINARY TRACT COMPLAINTS	23,1%	86
Problems with urinating (often/less, difficult)	9,1%	34
Bladder infection	7,0%	26
Incontinence	6,7%	25
Adrenal exhaustion	0,8%	3
Dark urine	0,3%	1

	Column Total N %	Count
PAIN	94,4%	352
During ovulation	23,3%	87
During menstruation	16,4%	61
During coitus	12,9%	48
Abdomen	51,5%	192
(Lower)back	48,5%	181
Head	31,4%	117
Pelvis/hips	28,4%	106
Legs	22,8%	85
Groin	12,6%	47
Breasts	8,6%	32
Knees	2,9%	11
Other location	21,7%	81
Arthralgia	30,6%	114
Muscle pain	13,4%	50
Cramps	12,1%	45
Radiating to legs	10,7%	40

	Column Total N %	Count
PSYCHOLOGICAL COMPLAINTS	90,6%	338
Tiredness	70,2%	262
Mood swings or emotionally out of balance	39,9%	149
Memory loss or concentration problems	38,9%	145
Depressive feelings	21,2%	79
Increase/decrease of weight	19,6%	73
Insomnia	17,2%	64
Loss of libido	15,0%	56
Dizziness	12,6%	47
Restless feelings	8,6%	32
Nausea	8,3%	31
Brain fog	7,5%	28
OTHER COMPLAINTS	89,5%	334
Tingling (hands, feets, legs and arms)	20,4%	76
Heavier menstruation (if patient is not specific about pain or bleedings)	18,5%	69
Excessive sweating	18,0%	67
Swollen abdomen	16,9%	63
Menopause complaints	16,4%	61
Hair problems (e.g. hairloss)	13,7%	51
Arrhythmia	11,3%	42
Vaginal secretion (e.g. much secretion)	11,3%	42
Fungal infections (vaginal or other)	11,3%	42
Vision problems	11,3%	42

	Column Total N %	Count
Feeling the implant	8,8%	33
Vitamine defficiency	7,0%	26
Tinnitus	5,4%	20
Tooth problems	4,0%	15
Weakness or asthenia	2,4%	9
Anemia	2,7%	10
Always feeling cold	1,9%	7
Coughing	1,6%	6
Brittle nails	1,3%	5
Unwished pregnancy	0,3%	1

Appendix 5: Age of women at the onset of health problems

	Age		
	n	Mean	SD
All women in the study	229 ^a	38	5
Women without psychological complaints	25 ^a	39	5
Women with psychological complaints	75 ^b	38	5
Women with tiredness	52 ^b	38	5
Women with mood swings or emotionally out of balance	26 ^b	39	3
Women with memory loss or concentration problems	34 ^b	39	4
Women with depressing feelings	19 ^b	38	6
Women with increase or decrease in weight	15 ^b	39	5
Women with insomnia	15 ^b	41	5
Women with loss of libido	12 ^b	37	7
Women with dizziness	8 ^b	38	4

a) number of women for which the age when complaints started (not specified per complaint) is known

b) number of women for which the age when the specific psychological complaint started is known

Appendix 6: Data on medical consultation

	% of total
No contact with doctor/specialist	1%
Visited a doctor/specialist	90%
Visited a gynecologist	21%
Test performed	53%
Control position Essure	9%
<i>Echo</i>	6%
<i>Laparoscopy</i>	1%
Hysterosalpingography	2%
Blood test	22%
Other test	37%

	% of total
Result after tests: nothing found	14%
Result after tests: diagnosis	13%
Perforation	1,6%
Migration of implant	3,8%

Appendix 7: Prevalence of health problems before removal of Essure®

