

# Conflict of interest disclosure

- ◆ None of the authors have any conflict of interest with the pharmaceutical industries related to the studied products.

# Preamble

- ◆ Presentation focused on the scientific findings from a large epidemiologic study.

JAMA | **Original Investigation**

# Association of Hysteroscopic vs Laparoscopic Sterilization With Procedural, Gynecological, and Medical Outcomes

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**IMPORTANCE** Safety of hysteroscopic sterilization has been recently questioned following reports of general symptoms such as allergy, tiredness, and depression in addition to associated gynecological results such as pelvic pain, perforation of fallopian tubes or uterus, and unwanted pregnancy.

**OBJECTIVE** To compare the risk of reported adverse events between hysteroscopic and laparoscopic sterilization.

**DESIGN, SETTING, AND PARTICIPANTS** French nationwide cohort study using the national hospital discharge database linked to the health insurance claims database. Women aged 30 to 54 years receiving a first hysteroscopic or laparoscopic sterilization between 2010 and 2014 were included and were followed up through December 2015.

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# Context

- ◆ Safety and effectiveness of Essure® device have been recently called into question<sup>1</sup> following reports of adverse events:
  - various general and non-specific symptoms
    - ❖ migraine, depression, suicide attempts, fatigue, allergy or hypersensitivity reactions, autoimmune diseases, thyroid disorder, and death
  - gynaecologic events
    - ❖ persistent pain
    - ❖ perforation of the uterus or fallopian tubes due to device migration
    - ❖ abnormal bleeding
    - ❖ additional sterilization procedure, salpingectomy or hysterectomy to remove the device
    - ❖ pregnancy

<sup>1</sup> <https://www.fda.gov>; <http://www.hc-sc.gc.ca>; <http://www.rivm.nl>; <http://ansm.sante.fr>.

# Context: literature review

- ◆ Observational cohort studies examining the safety and effectiveness of Essure® devices in comparison with laparoscopic sterilization
  - 3 studies (2 in the USA<sup>1</sup> and 1 in France<sup>2</sup>) published in 2015-2016
  - Essure® vs laparoscopic sterilization
    - ❖ Less immediate surgical complications
    - ❖ More reoperation for a second sterilization
    - ❖ Pregnancy: inconsistent results
    - ❖ Less hysterectomy
- ◆ Limitations of existing data
  - Insufficient number of women with Essure® to study rare adverse health outcomes
  - No data regarding general health outcomes

<sup>1</sup>Mao et al, BMJ 2015; Perkins et al, Gbstet & Gynecol 2016

<sup>2</sup>Fernandez et al, Eur J Obstet & Gynecol & Reprod Biol 2015

# Objective

- ◆ To investigate a possible role of hysteroscopic sterilization, a nationwide cohort study comparing women with Essure® versus laparoscopic sterilization was conducted in France

# Methods: data sources, study population

- ◆ Comparative cohort study
- ◆ National hospital discharge linked to health insurance databases
- ◆ Study population
  - Inclusion criteria
    - ❖ Women aged 30 to 54 years
    - ❖ First Essure® or laparoscopic sterilization between January 2010 and December 2014
- ◆ Follow-up
  - From the first Essure® or laparoscopic sterilization
  - To December 31, 2015

# Methods: outcomes

- ◆ Immediate surgical and medical complications
- ◆ Outcomes at 1 and 3 years of follow-up
  - Gynaecologic events
    - ❖ Fallopian tubal disorder: salpingectomy, complication related to implants
    - ❖ Uterine disorder: hysterectomy, abnormal vaginal bleeding, endometrectomy/curettage, myomectomy
    - ❖ second sterilization procedure
    - ❖ pregnancy
  - General health outcomes
    - ❖ Allergy, autoimmune diseases, thyroid disorder
    - ❖ Medication consumption (analgesics, antimigraines, antidepressants, benzodiazepines)
    - ❖ Outpatient visits
    - ❖ Sickness absence
    - ❖ Suicide attempts
    - ❖ Death



# Methods: statistical analyses

- ◆ Description of baseline characteristics according to type of sterilization (Essure<sup>®</sup> vs laparoscopic sterilization)
- ◆ Comparison of risk of outcomes between both groups
  - Adjusted Cox models to take into account differences in baseline characteristics
    - ❖ Age
    - ❖ Socio-economic characteristics
    - ❖ Marker of alcohol abuse, marker of tobacco use, psychoactive substance use, marker of obesity
    - ❖ Medical history: diabetes, cardiovascular diseases, history of allergy, suicidal attempt
    - ❖ Gynaecologic and surgical history
    - ❖ Concomitant medications (analgesics, antimigraines, antidepressants, benzodiazepines)

# Methods: statistical analyses

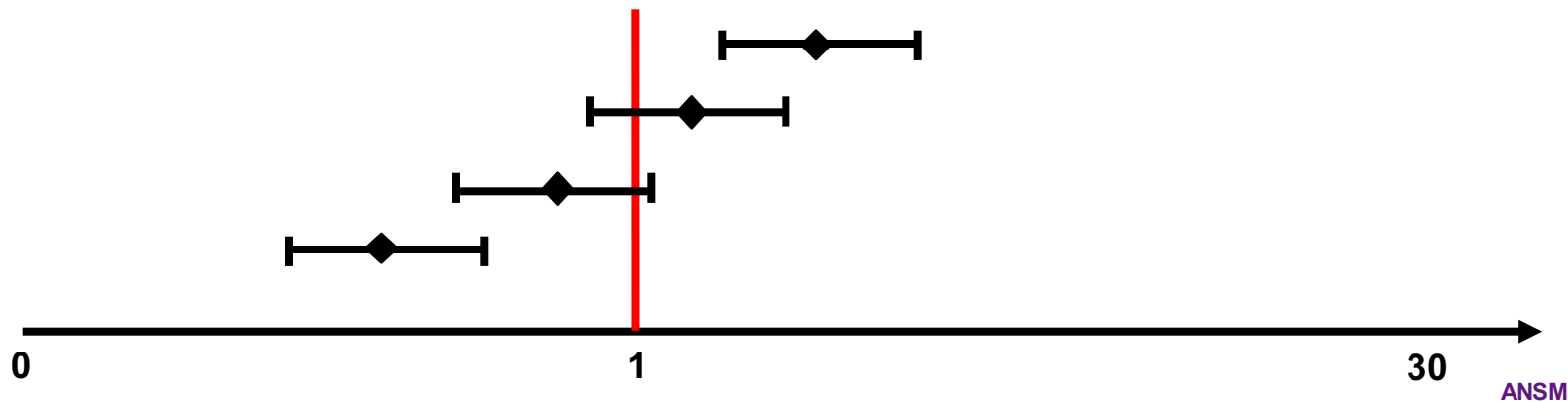
## ◆ Hazard ratio (HR)

$$HR = \frac{\text{Incidence Essure®}}{\text{Incidence laparoscopic sterilization}}$$

## ◆ Interpretation

- HR > 1 → Higher risk in Essure® group
- HR = 1 → No risk difference between groups
- HR < 1 → Lower risk in Essure® group

## ◆ Confidence interval



# Results

# Study population

- ◆ Total population: **105,357 women**
  - **71,303** (67.7%) in Essure® group
  - **34,057** (32.3%) in laparoscopic sterilization
- ◆ Duration of follow-up
  - Mean: 3.3 years

# Baseline characteristics

- ◆ Women in Essure<sup>®</sup> group compared to laparoscopic group:
  - Older (mean age: 41.5 vs 40.8 years)
  - Higher socioeconomic status (supplementary universal medical cover: 7.2% vs 10.0%)
  - Medical history
    - ❖ More likely to have diabetes (4.9% vs 4.6%) and obesity
    - ❖ Less likely to have a history of allergy (9.3% vs 11.1%)
  - Less likely to have gynaecologic history
  - Lower consumption of medications
    - ❖ Analgesics (35.0% vs 36.0%)
    - ❖ Antimigraines (2.6% vs 3.0%)
    - ❖ Antidepressants (8.4% vs 9.5%)
    - ❖ Benzodiazepines (7.6% vs 9.2%)

# Immediate surgical and medical complications

	N (%)		aOR [95% CI] <sup>1</sup> Essure® vs laparoscopic	P-value
	Laparoscopic 34,054	Essure® 71,303		
<b>Surgical complications<sup>2</sup></b>	265 (0.78)	96 (0.13)	<b>0.18 (0.14-0.23)</b>	<b>&lt;0.0001</b>
<b>Medical complications<sup>3</sup></b>	39 (0.11)	41 (0.06)	<b>0.51 (0.30-0.89)</b>	<b>0.02</b>

<sup>1</sup>Adjusted for age, propensity score for sociodemographic characteristics, medicines use, and medical, surgical, gynecologic history.

<sup>2</sup>**Surgical complications** include acute hemorrhage; abdominal injury; complications related to the placement of a prosthesis or implant; debridement, evacuation, ablation of a foreign body; and other surgical complications.

<sup>3</sup>**Medical complications** include acute myocardial infarction and cardiac arrest; stroke; peripheral arterial thromboembolism; deep vein thrombosis/pulmonary embolism; anesthetic/anaphylactic shock; respiratory complications; and infection.

## ◆ In Essure® group compared to laparoscopic group:

- 5 times less likely to have surgical complications
- 2 times less likely to have medical complications

# Gynaecologic outcomes at 1 year

	N (%)		aHRa [95% CI] *†	P-value
	Laparoscopic 34,054	Essure® 71,303		
<b>Gynecologic disorder</b>				
Fallopian tubal disorder‡	80 (0.23)	500 (0.70)	2.98 (2.17-4.10)	<0.0001
Uterine disorder§	510 (1.50)	914 (1.30)	0.85 (0.74-0.98)	0.02
<b>Second sterilization procedure</b>	56 (0.16)	2955 (4.10)	26.0 (17.8-37.9)	<0.0001
<b>Pregnancy¶</b>	138 (0.41)	168 (0.24)	0.70 (0.53-0.92)	0.01

\*Laparoscopic group is the reference group for comparisons.

†Adjusted for age, propensity score for sociodemographic characteristics, medicines use, and medical, surgical, gynecologic history.

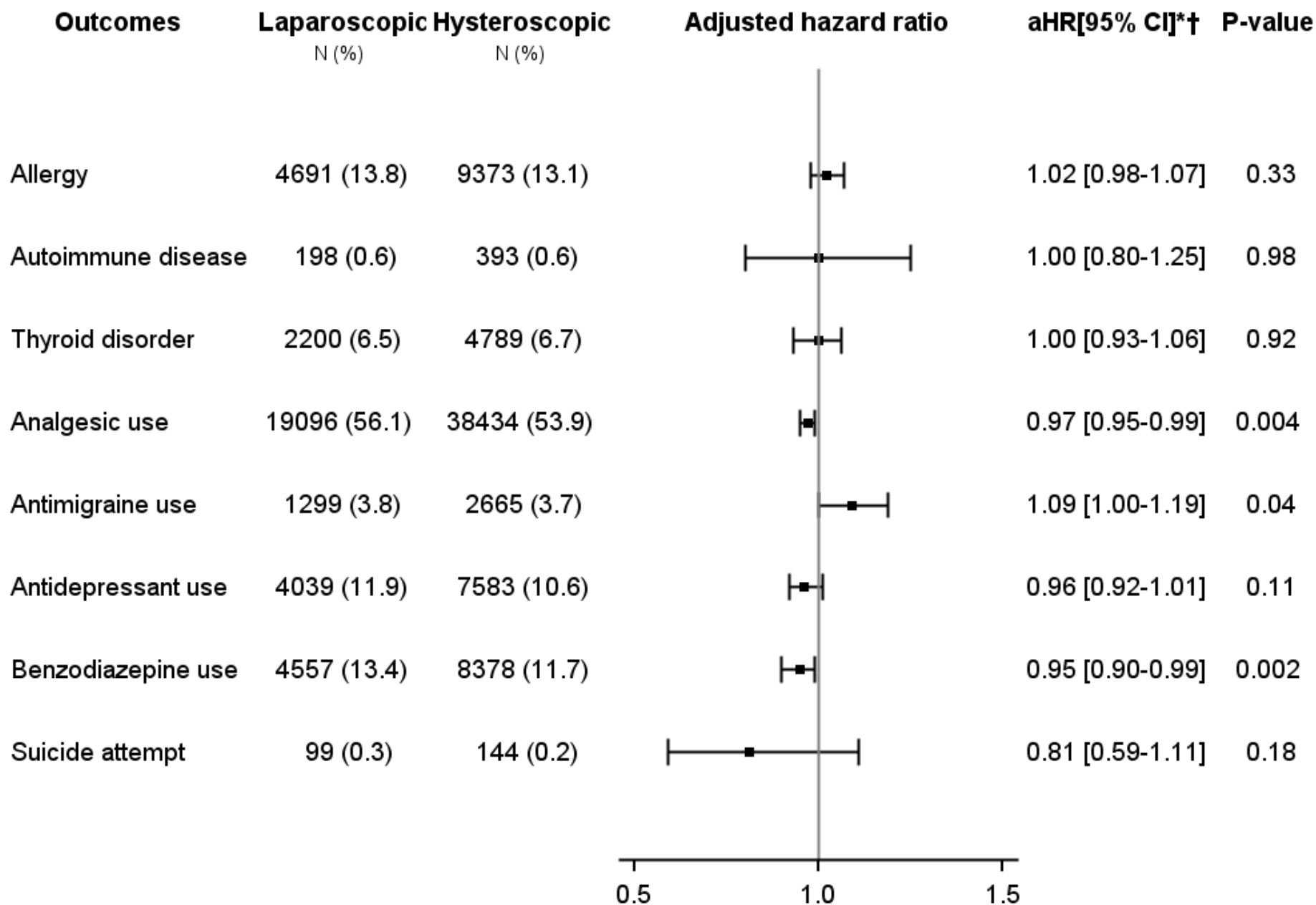
‡**Fallopian tubal disorder** includes complications of genitourinary prosthetic devices/implants and salpingectomy.

§ **Uterine disorder** includes hysterectomy, abnormal vaginal bleeding, endometrectomy/curettage, myomectomy (not concomitant to salpingectomy or second sterilization procedure).

¶Pregnancy occurring subsequent to a second sterilization procedure or to a marker of post-sterilization regret (fertility treatment or surgical reanastomosis of the fallopian tubes) was not considered.

# Various general and non-specific symptoms at 1 year of follow-up (forest plot)

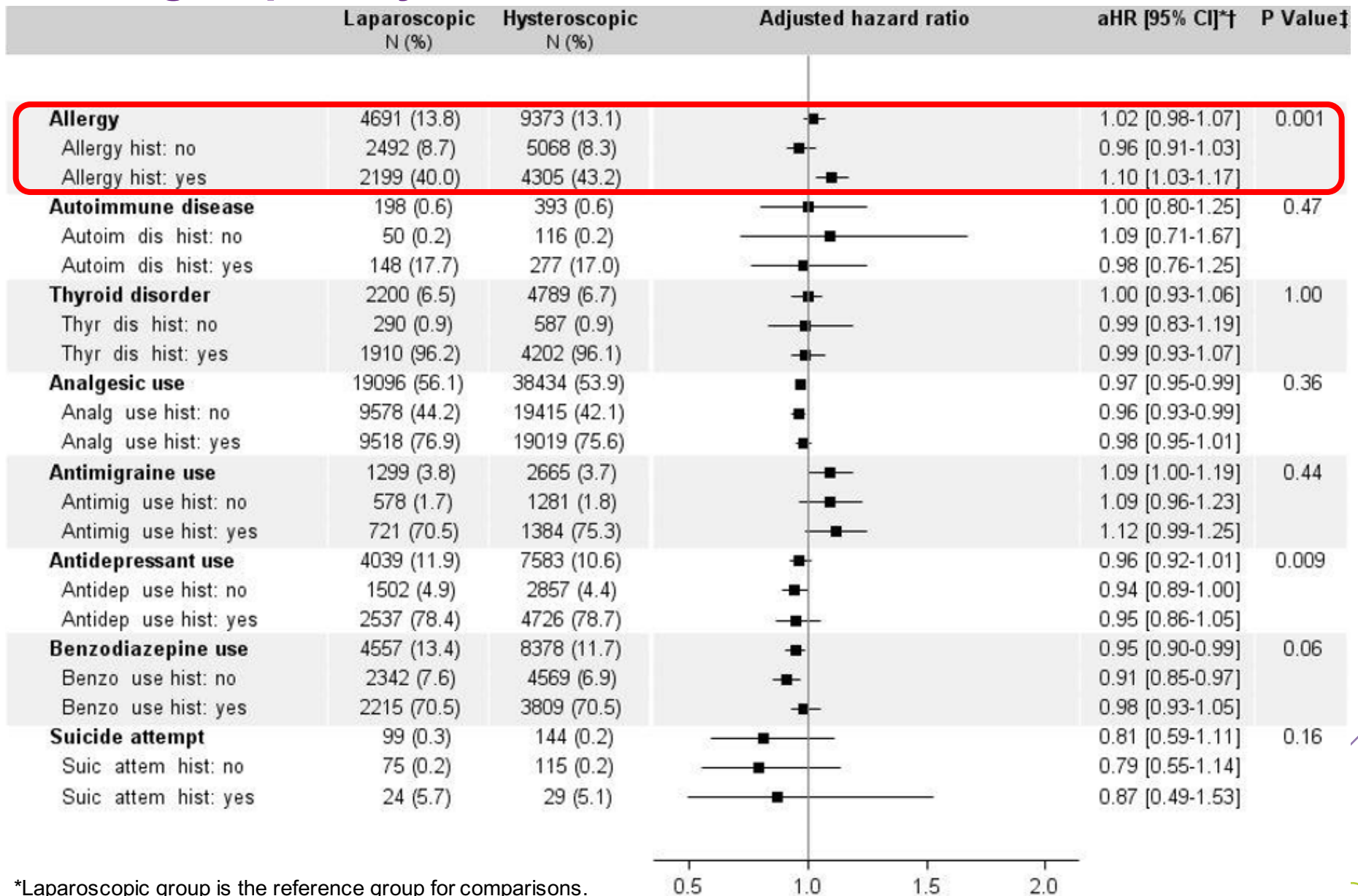




\*Laparoscopic group is the reference group for comparisons.

†Adjusted for age, propensity score for sociodemographic characteristics, medicines use, and medical, surgical, gynecologic history.

# Subgroup analyses



\*Laparoscopic group is the reference group for comparisons.

†Adjusted for age, propensity score for sociodemographic characteristics, medicines use, and medical, surgical, gynecologic history.

‡P-value for interaction.

# Conclusion

- ◆ Our study confirms that Essure® was associated with
  - a lower risk for
    - ❖ immediate surgical and medical complications
    - ❖ hysterectomy
  - similar risk for unintended pregnancy
  - higher risk for undergoing a second sterilization procedure and salpingectomy.
- ◆ Regarding studied general health outcomes, our study did not show an increased risk of Essure® compared with laparoscopic sterilisation.
- ◆ Our study did suggest a small increased risk of allergy in case of pre-existing allergy.

### **Avertissement**

- Lien d'intérêt : personnel salarié de l'ANSM (opérateur de l'Etat).
- La présente intervention s'inscrit dans un strict respect d'indépendance et d'impartialité de l'ANSM vis-à-vis des autres intervenants.
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### **Warning**

- Link of interest: employee of ANSM (State operator).
- This speech is made under strict compliance with the independence and impartiality of ANSM as regards other speakers.
- Any further use of this material must be submitted to ANSM prior approval.

# Results: characteristics of sterilization

	Laparoscopic N=34,054	Essure® N=71,303	P-value
<b>Number of hospitals</b>	814	654	
<b>Type of hospitals, %</b>			<0.0001
Public	55.9	58.2	
Private	44.1	41.8	
<b>Anesthetic procedure, %</b>	99.5	73.2	<0.0001
<b>Duration of hospitalisation (days), %</b>			
0	51.7	98.7	<0.0001
1	41.6	1.3	
>1	6.7	0.0	
<b>Level of experience in Essure® placements (median number)</b>	10	24	

# Essure<sup>®</sup> confirmation test

	<b>N=71,303</b>
Simple abdominal X-ray	44,333 (62.2%)
Pelvic ultrasound	15,314 (21.5%)
Hysterosalpingography	11,419 (16.0%)
Pelvic CT scan	718 (1.0%)
<b>At least one of the tests listed above</b>	<b>57,258 (80.3%)</b>

Median delay after sterilization: 3 months

# Essure® group: gynaecologic outcomes at 1 year according to sterilization practice

## ◆ According to Essure confirmation test

	N (%)		aHR [95% CI] No/Yes
	Test = no	Test = yes	
	14,045	57,258	
<b>Pregnancy</b>	<b>37 (0.28%)</b>	<b>93 (0.16%)</b>	<b>1.49 (1.01-2.19)</b>

## ◆ According to level of physicians' experience in Essure® placements (private hospitals)

	N (%)		aHR [95% CI] <12 / ≥12
	< 12/year	≥ 12/year	
	6,065	23,132	
<b>Failure of sterilization</b>	<b>277 (4.6%)</b>	<b>933 (4.0%)</b>	<b>1.14 (1.00-1.31)</b>
Reoperation	322 (5.3%)	1147 (5.0%)	1.08 (0.95-1.22)

Failure of sterilization includes salpingectomy, second sterilization procedure, or pregnancy.

Reoperation includes salpingectomy, hysterectomy, endometrectomy/curettage, myomectomy, or second sterilization procedure.

# Results: intraoperative/postprocedural surgical and medical complications

At 1 year	N (%)		P-value
	Laparoscopic 34,054	Essure® 71,303	
<b>Surgical complication</b>	<b>265 (0.78%)</b>	<b>96 (0.13%)</b>	<b>&lt;0.0001</b>
Acute hemorrhage	56 (0.16%)	5 (0.01%)	<0.0001
Abdominal injury	117 (0.34%)	30 (0.04%)	<0.0001
Complications due to the placement of a prosthesis/ implant	20 (0.06%)	35 (0.05%)	0.52
Debridement, evacuation, ablation of a foreign body	37 (0.11%)	7 (0.01%)	<0.0001
Other surgical complications	62 (0.18%)	19 (0.03%)	<0.0001
<b>Medical complication</b>	<b>39 (0.11%)</b>	<b>41 (0.06%)</b>	<b>0.002</b>
Acute myocardial infarction and cardiac arrest	2 (0.01%)	11 (0.02%)	0.19
Stroke	2 (0.01%)	1 (0.00%)	0.20
Peripheral arterial thromboembolism	2 (0.01%)	1 (0.00%)	0.20
Deep vein thrombosis/pulmonary embolism	14 (0.04%)	18 (0.03%)	0.17
Anesthetic/anaphylactic shock	5 (0.01%)	1 (0.00%)	0.008
Respiratory complications	8 (0.02%)	2 (0.00%)	0.001
Infection	9 (0.03%)	8 (0.01%)	0.07
<b>Death</b>	<b>0 (0.00%)</b>	<b>0 (0.00%)</b>	<b>--</b>



# Results: gynaecologic outcomes at 1 year of follow-up

At 1 year	N (%)		P-value
	Laparoscopic 34,054	Essure® 71,303	
<b>Gynecologic disorder</b>			
<b>Fallopian tubal disorder</b>	<b>80 (0.23%)</b>	<b>500 (0.70%)</b>	<b>&lt;0.0001</b>
Complications of genitourinary devices	(0.00%)	(0.11%)	<0.0001
Salpingectomy	(0.23%)	(0.62%)	<0.0001
<b>Uterine disorder</b>	<b>510 (1.50%)</b>	<b>914 (1.30%)</b>	<b>0.005</b>
Hysterectomy	(0.81%)	(0.43%)	<0.0001
Abnormal vaginal bleeding	(0.33%)	(0.23%)	0.003
Endometrectomy/curettage	(0.63%)	(0.71%)	0.14
Myomectomy	(0.09%)	(0.22%)	<0.0001
<b>Second sterilization procedure</b>	<b>56 (0.16%)</b>	<b>2955 (4.10%)</b>	<b>&lt;0.0001</b>
<b>Pregnancy</b>	<b>138 (0.41%)</b>	<b>168 (0.24%)</b>	<b>&lt;0.0001</b>



# Various general and non-specific symptoms at 1 and 3 years of follow-up

# Autoimmune diseases

At 1 year	N (%)		P-value
	Laparoscopic 34,054 (32,3)	Essure® 71,303 (67,7)	
<b>Auto-immune diseases</b>	198 (0.58)	393 (0.55)	0.54
Demyelinating diseases of the CNS	47 (0.14)	92 (0.13)	0.71
Guillain-Barré syndrome	0 (0.00)	1 (0.00)	0.49
Cutaneous or systemic lupus	8 (0.02)	15 (0.02)	0.80
Localized or systemic scleroderma	4 (0.01)	7 (0.01)	0.77
Vasculitis	4 (0.01)	12 (0.02)	0.53
Rheumatoid arthritis or juvenile arthritis	29 (0.09)	38 (0.05)	0.06
Myositis, polymyositis, or dermatomyositis	1 (0.00)	3 (0.00)	0.75
Gougerot-Sjögren syndrome	9 (0.03)	9 (0.01)	0.11
Idiopathic thrombocytopenic purpura	1 (0.00)	1 (0.00)	0.59
Chronic inflammatory bowel disease	43 (0.13)	107 (0.15)	0.34
Coeliac disease	1 (0.00)	2 (0.00)	0.97
Type 1 diabetes	19 (0.06)	57 (0.08)	0.17
Pancreatitis	6 (0.02)	10 (0.01)	0.66

# Autoimmune diseases and thyroid disorders

At 1 year	N (%)		P-value
	Laparoscopic 34,054 (32.3)	Essure <sup>®</sup> 71303 (67.7)	
Autoimmune diseases	198 (0.58)	393 (0.55)	0.54
Thyroid disorders	2200 (6.50)	4789 (6.70)	0.12

## ◆ Essure<sup>®</sup> vs laparoscopic group

	At 1 year		At 3 years	
	aHR [95% CI] Essure <sup>®</sup> vs laparosc.	P-value	aHR [95% CI] Essure <sup>®</sup> vs laparosc.	P-value
Autoimmune diseases	1.00 (0.80-1.25)	0.98	0.94 (0.80-1.11)	0.48
Thyroid disorders	1.00 (0.93-1.06)	0.92	0.98 (0.92-1.04)	0.56

# Allergy according to allergy history

At 1 year	Allergy history = yes			Allergy history = no		
	Laparoscopic 5,493	Essure <sup>®</sup> 9,970	P-value	Laparoscopic 28,561	Essure <sup>®</sup> 61,333	P-value
Allergie	2199 (40.0)	4305 (43.2)	0.0001	2492 (8.7)	5068 (8.3)	0.02

## ◆ Essure<sup>®</sup> vs laparoscopic group

	Allergy history = yes		Allergy history = no	
	aHR [95% CI] Essure <sup>®</sup> vs laparosc.	P-value	aHR [95% CI] Essure <sup>®</sup> vs laparosc.	P-value
Allergy at 1 year	1.10 (1.03-1.17)	0.004	0.96 (0.91-1.03)	0.26
Allergy at 3 years	1.10 (1.03-1.18)	0.006	0.99 (0.91-1.06)	0.70

# Medication consumption

At 1 year of follow-up	%		P-value
	Laparoscopic 34,054	Essure® 71,303	
<b>Analgesics</b>	56.1 %	53.9 %	<0.0001
Opioids	9.9 %	8.8 %	<0.0001
Non-steroidal anti-inflammatory drugs	31.8 %	29.9 %	<0.0001
Other	37.8 %	36.4 %	<0.0001
<b>Antimigraines</b>	3.8 %	3.7 %	0.54
<b>Antidepressants</b>	11.9 %	10.6 %	<0.0001
<b>Benzodiazepines</b>	13.4 %	11.7 %	<0.0001

## ◆ Essure® vs laparoscopic group

	At 1 year		At 3 years	
	aHR [95% CI]	P-value	aHR [95% CI]	P-value
<b>Analgesics</b>	<b>0.97 (0.95-0.99)</b>	<b>0.004</b>	<b>0.91 (0.89-0.93)</b>	<b>&lt;.0001</b>
<b>Antimigraines</b>	<b>1.09 (1.00-1.19)</b>	<b>0.04</b>	1.00 (0.93-1.07)	0.97
<b>Antidepressants</b>	<b>0.96 (0.92-1.01)</b>	<b>0.11</b>	<b>0.92 (0.88-0.96)</b>	<b>&lt;.0001</b>
<b>Benzodiazepines</b>	<b>0.95 (0.91-0.98)</b>	<b>0.002</b>	<b>0.90 (0.87-0.93)</b>	<b>&lt;.0001</b>

# Suicide attempts, death

At 1 year	N (%)		P-value
	Laparoscopic 34,054	Essure® 71,303	
<b>Suicide attempts</b>	99 (0.29)	144 (0.20)	0.005
<b>Death</b>	10 (0.03)	24 (0.03)	0.72

## ◆ Essure® vs ligature

	At 1 year		At 3 years	
	aHR [95% CI]	P-value	aHR [95% CI]	P-value
<b>Suicide attempts</b>	0.81 (0.59-1.11)	0.18	0.80 (0.66-0.97)	0.03
<b>Death</b>	1.28 (0.48-3.41)	0.62	1.12 (0.66-1.90)	0.67

# Healthcare use / sickness absence at 1 year

	Laparoscopic 34,054	Essure® 71,303	P-value
<b>N of office/outpatient visits (mean)</b>	<b>9.11</b>	<b>8.63</b>	<b>&lt;0.0001</b>
<b>Office visits</b>			
General practitioner	5.49	4.97	<0.0001
Gynecologist	0.61	0.65	<0.0001
Dermatologist	0.20	0.21	0.03
Endocrinologist	0.00	0.00	--
Neurologist	0.04	0.03	0.02
Otolaryngologist	0.05	0.04	0.02
Pneumologist	0.01	0.01	0.96
Other	1.59	1.45	<0.0001
<b>Outpatient visits</b>	<b>1.12</b>	<b>1.26</b>	<b>&lt;0.0001</b>
<b>N of sickness absence days (mean)</b>	<b>6.50 (26.0)</b>	<b>5.90 (24.6)</b>	<b>0.0004</b>