

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 question¹ 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

¹ <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 USA¹ and 1 in France²) 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

¹Mao et al, BMJ 2015; Perkins et al, Gbstet & Gynecol 2016

²Fernandez 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[®] 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

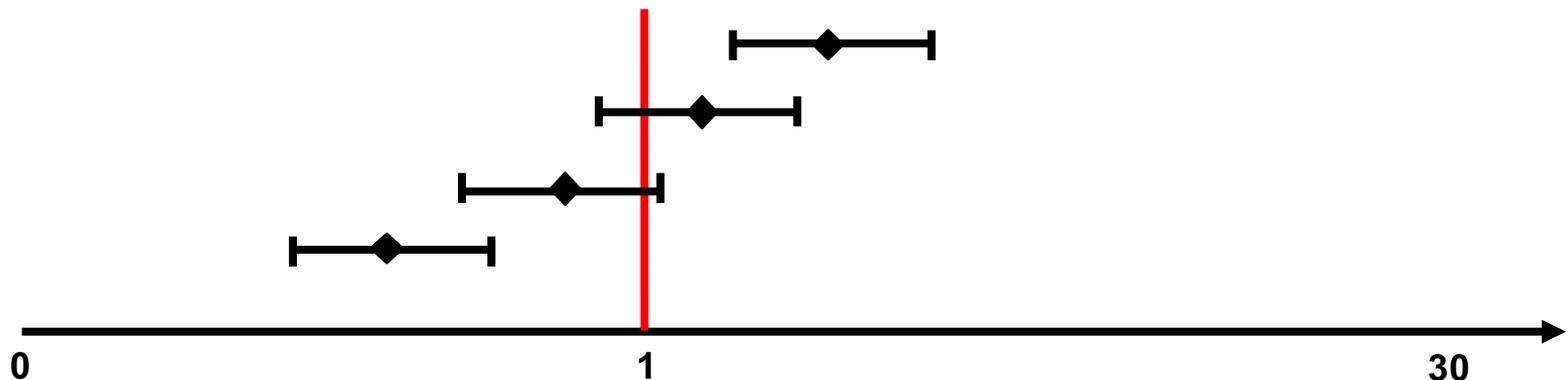
◆ Hazard ratio (HR)

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

◆ 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[®] 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] ¹ Essure® vs laparoscopic | P-value |
|---|------------------------|-------------------|---|-------------------|
| | Laparoscopic 34,054 | Essure® 71,303 | | |
| Surgical complications² | 265 (0.78) | 96 (0.13) | 0.18 (0.14-0.23) | <0.0001 |
| Medical complications³ | 39 (0.11) | 41 (0.06) | 0.51 (0.30-0.89) | 0.02 |

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

²**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.

³**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 | | |
| Gynecologic disorder | | | | |
| 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 |
| Second sterilization procedure | 56 (0.16) | 2955 (4.10) | 26.0 (17.8-37.9) | <0.0001 |
| Pregnancy¶ | 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.

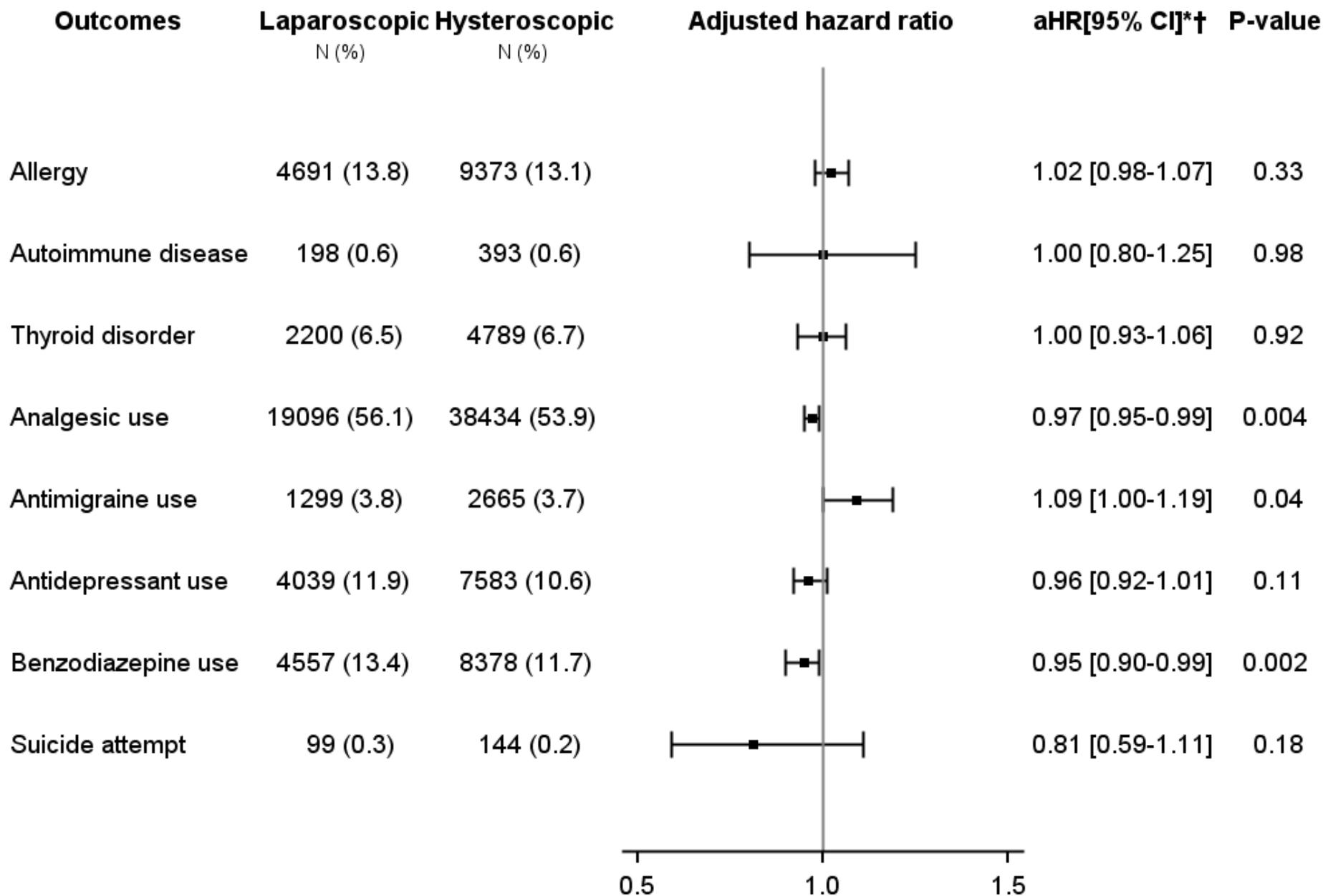
‡**Fallopian tubal disorder** includes complications of genitourinary prosthetic devices/implants and salpingectomy.

§ **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.



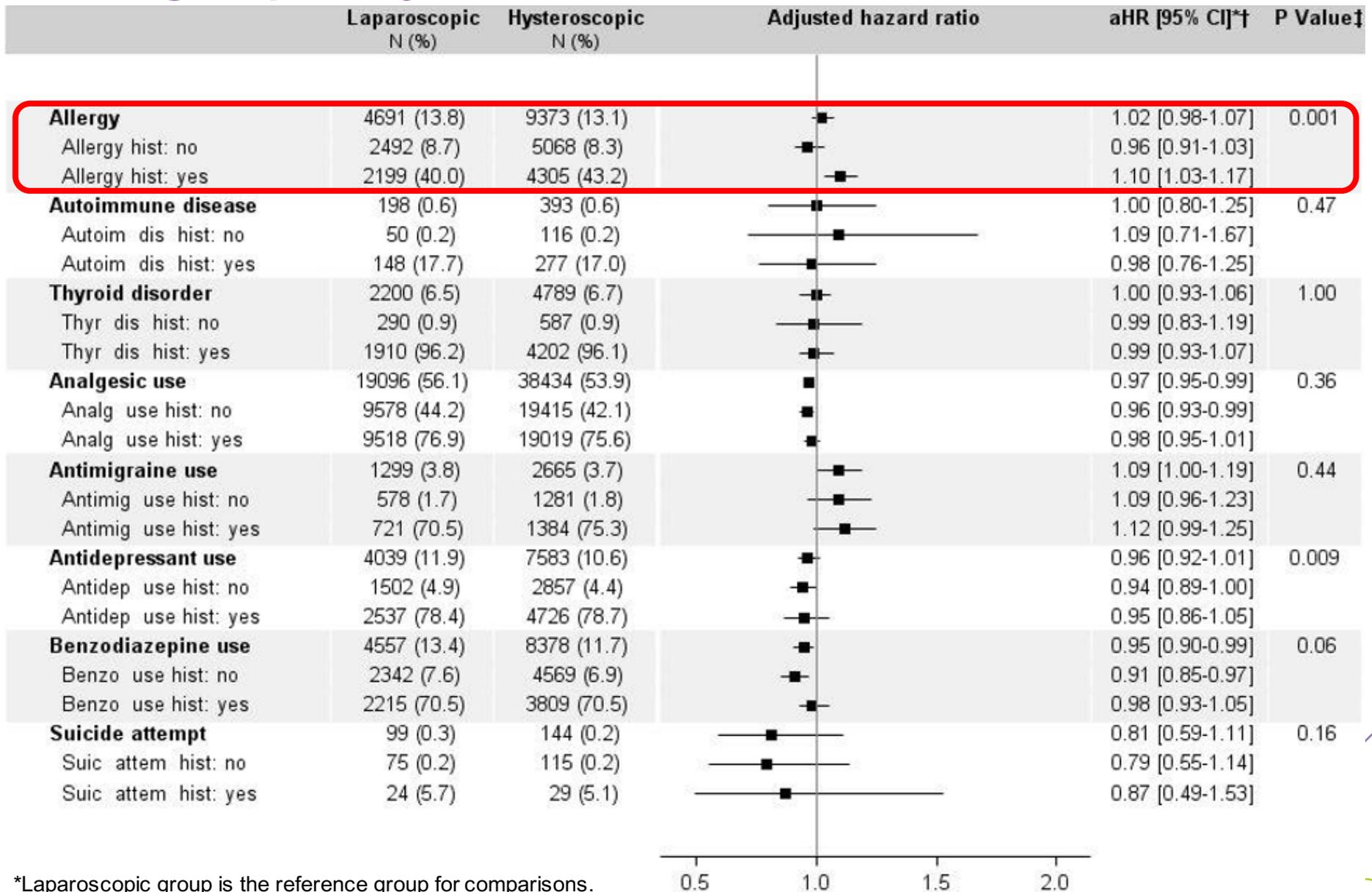
Various general and non-specific symptoms at 1 year of follow-up (forest plot)



*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.
- Toute utilisation du matériel présenté, doit être soumise à l'approbation préalable de l'ANSM.

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 |
|--|--------------------------|---------------------|---------|
| Number of hospitals | 814 | 654 | |
| Type of hospitals, % | | | <0.0001 |
| Public | 55.9 | 58.2 | |
| Private | 44.1 | 41.8 | |
| Anesthetic procedure, % | 99.5 | 73.2 | <0.0001 |
| Duration of hospitalisation (days), % | | | |
| 0 | 51.7 | 98.7 | <0.0001 |
| 1 | 41.6 | 1.3 | |
| >1 | 6.7 | 0.0 | |
| Level of experience in Essure® placements (median number) | 10 | 24 | |

Essure[®] confirmation test

| | N=71,303 |
|---|-----------------------|
| 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%) |
| At least one of the tests listed above | 57,258 (80.3%) |

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 | |
| Pregnancy | 37 (0.28%) | 93 (0.16%) | 1.49 (1.01-2.19) |

◆ 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 | |
| Failure of sterilization | 277 (4.6%) | 933 (4.0%) | 1.14 (1.00-1.31) |
| 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 | |
| Surgical complication | 265 (0.78%) | 96 (0.13%) | <0.0001 |
| 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 |
| Medical complication | 39 (0.11%) | 41 (0.06%) | 0.002 |
| 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 |
| Death | 0 (0.00%) | 0 (0.00%) | -- |

Results: gynaecologic outcomes at 1 year of follow-up

| At 1 year | N (%) | | P-value |
|--|------------------------|---------------------|-------------------|
| | Laparoscopic 34,054 | Essure® 71,303 | |
| Gynecologic disorder | | | |
| Fallopian tubal disorder | 80 (0.23%) | 500 (0.70%) | <0.0001 |
| Complications of genitourinary devices | (0.00%) | (0.11%) | <0.0001 |
| Salpingectomy | (0.23%) | (0.62%) | <0.0001 |
| Uterine disorder | 510 (1.50%) | 914 (1.30%) | 0.005 |
| 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 |
| Second sterilization procedure | 56 (0.16%) | 2955 (4.10%) | <0.0001 |
| Pregnancy | 138 (0.41%) | 168 (0.24%) | <0.0001 |



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) | |
| Auto-immune diseases | 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 [®] 71303 (67.7) | |
| Autoimmune diseases | 198 (0.58) | 393 (0.55) | 0.54 |
| Thyroid disorders | 2200 (6.50) | 4789 (6.70) | 0.12 |

◆ Essure[®] vs laparoscopic group

| | At 1 year | | At 3 years | |
|---------------------|--|---------|--|---------|
| | aHR [95% CI] Essure [®] vs laparosc. | P-value | aHR [95% CI] Essure [®] 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 [®] 9,970 | P-value | Laparoscopic 28,561 | Essure [®] 61,333 | P-value |
| Allergie | 2199 (40.0) | 4305 (43.2) | 0.0001 | 2492 (8.7) | 5068 (8.3) | 0.02 |

◆ Essure[®] vs laparoscopic group

| | Allergy history = yes | | Allergy history = no | |
|--------------------|--|---------|--|---------|
| | aHR [95% CI] Essure [®] vs laparosc. | P-value | aHR [95% CI] Essure [®] 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 | |
| Analgesics | 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 |
| Antimigraines | 3.8 % | 3.7 % | 0.54 |
| Antidepressants | 11.9 % | 10.6 % | <0.0001 |
| Benzodiazepines | 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 |
| Analgesics | 0.97 (0.95-0.99) | 0.004 | 0.91 (0.89-0.93) | <.0001 |
| Antimigraines | 1.09 (1.00-1.19) | 0.04 | 1.00 (0.93-1.07) | 0.97 |
| Antidepressants | 0.96 (0.92-1.01) | 0.11 | 0.92 (0.88-0.96) | <.0001 |
| Benzodiazepines | 0.95 (0.91-0.98) | 0.002 | 0.90 (0.87-0.93) | <.0001 |

Suicide attempts, death

| At 1 year | N (%) | | P-value |
|-------------------------|------------------------|-------------------|---------|
| | Laparoscopic 34,054 | Essure® 71,303 | |
| Suicide attempts | 99 (0.29) | 144 (0.20) | 0.005 |
| Death | 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 |
| Suicide attempts | 0.81 (0.59-1.11) | 0.18 | 0.80 (0.66-0.97) | 0.03 |
| Death | 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 |
|---|------------------------|--------------------|-------------------|
| N of office/outpatient visits (mean) | 9.11 | 8.63 | <0.0001 |
| Office visits | | | |
| 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 |
| Outpatient visits | 1.12 | 1.26 | <0.0001 |
| N of sickness absence days (mean) | 6.50 (26.0) | 5.90 (24.6) | 0.0004 |