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Association of complicated appendicitis on the risk of later in vitro fertilization treatment requirement and ectopic pregnancy: a nationwide cohort study

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ABSTRACT

Introduction: A Population-based register study utilizing three Finnish National Registers was carried out to determine whether uncomplicated appendicitis, complicated appendicitis, and appendectomy without appendicitis are associated with a subsequent risk of requiring in vitro fertilization (IVF) treatment or a risk of ectopic pregnancy among reproductive-aged women.

Material and methods: A total of 23 997 women who underwent appendectomy for uncomplicated or complicated appendicitis or for nonspecific abdominal pain or had nonspecific abdominal pain without surgical procedures between 2000 and 2012 were included in the study. The later IVF treatment requirement and ectopic pregnancy risk were assessed after uncomplicated appendicitis, complicated appendicitis, and appendectomy without appendicitis. Women with nonspecific abdominal pain without surgical procedures served as a reference group.

Results: The rates of later IVF treatment after uncomplicated appendicitis, complicated appendicitis, and appendectomy without appendicitis were low (2.1%, 2.5%, and 2.3%, respectively; $P = 0.681$). Neither appendicitis nor appendectomy was associated with the risk of requiring IVF treatment. The rate of ectopic pregnancy after uncomplicated and complicated appendicitis was very low (0.8%). Women with uncomplicated appendicitis had a significantly lower risk of ectopic pregnancy than patients with nonspecific abdominal pain.

Conclusions: Appendicitis, whether complicated or uncomplicated, and appendectomy without appendicitis does not raise the risk of requiring later IVF treatment or the risk of ectopic pregnancy.

Key Words

Appendicitis, appendectomy, infertility, ectopic pregnancy, in vitro fertilization

Abbreviations:

IVF, in vitro fertilization;

NSAP, nonspecific abdominal pain;

UA, uncomplicated appendicitis;

CA, complicated appendicitis;

NSAP-A nonspecific abdominal pain with appendectomy.

Key Message:

Complicated appendicitis is not significantly associated with the risk of later requiring in vitro fertilization treatment or with the risk of ectopic pregnancy.

INTRODUCTION

Acute appendicitis is one of the most common indications for emergency surgery. Women face a 6.7% lifetime risk of acute appendicitis.[1] Despite advancements in preoperative diagnostics, 15–25% of patients with appendicitis suffer perforation of the appendix, thus experiencing a more severe disease with a greater risk of complications.[1,2] Perforation of the appendix with peritonitis or peritoneal abscess and the trauma caused by surgery can cause peritoneal adhesions followed by possible blockage of the fallopian tubes, potentially leading to infertility or ectopic pregnancy. Previous studies on the association of appendicitis and female infertility have reported conflicting results.[3–9]A meta-analysis found that appendectomy was not associated with decreased fertility in women but did increase the risk of ectopic pregnancy.[6]However, due to the heterogeneity of the included studies, the quality of the evidence was low. Furthermore, studies on appendicitis and fertility often lack information on complicated appendicitis.

Tubal factor infertility has been a primary cause of infertility. However, studies suggest that its incidence is decreasing. A large nationwide study found a decreasing incidence in the United States.[10] In Finland, its incidence dropped from 35% in 1992 to 10% in 2004.[11] Several known factors can cause tubal infertility, including pelvic inflammatory disease, endometriosis, and complications after abdominal surgery. In vitro fertilization (IVF) is commonly used in the treatment of tubal factor infertility and is the gold standard if both tubes are damaged.[12]

As suspected appendicitis is a common reason for surgical intervention on the population level, potential consequences on the later fertility of reproductive-aged women constitute a relevant research question. Moreover, the diagnosis of appendicitis is most challenging in reproductive-aged women, which increases the rate of unnecessary appendectomies in this patient group.[13]

Due to a lack of studies with sufficient information on the type of appendicitis, we aimed to study whether appendectomy and complicated appendicitis among reproductive aged women are associated with the risk of later requiring IVF treatment or with the risk of ectopic pregnancy using high-quality national registers.

MATERIAL AND METHODS

The study utilized the Finnish National Hospital Care Register maintained by the National Institute for Health and Welfare [14] and the Drug Reimbursement Register and Procedure Register maintained by the Social Insurance Institution.[15] Information on all inpatient and outpatient care in public hospitals, including data on diagnosis and procedures, is recorded in the Hospital Care Register. In Finland, IVF treatments are provided in specialized public and private clinics. The medications used during IVF treatment and treatments provided in private clinics are reimbursed by Social Insurance Institution. These reimbursements are registered in the Drug Reimbursement Register and the Procedure Register.

Data on all hospital visits of female patients aged 18–35 with a discharge diagnosis of appendicitis or nonspecific abdominal pain or with appendectomy procedure codes registered between 2000 and 2012 were obtained from the Hospital Care Register. International Classification of Diseases, Tenth Revision (ICD-10) and Nordic Classification of Surgical Procedures (NCSP) codes were used for patient identification. The data included age, primary diagnosis, secondary diagnoses, admission dates, and codes of performed interventions. The information on following admissions with a diagnosis of infertility or codes of infertility-related procedures or medications or diagnosis of ectopic pregnancy until 2013 was obtained from the Hospital Care Register and the Social Insurance Institution registers.

The study population with appendicitis, appendectomy, or nonspecific abdominal pain during the observation period was divided into four groups: women who had undergone appendectomy for uncomplicated appendicitis (UA), women who had appendectomy for complicated appendicitis (CA), women who had appendectomy due to nonspecific abdominal pain (NSAP-A), and women with nonspecific abdominal pain who underwent no surgical procedures (NSAP). NSAP patients with nonoperative management were identified from the database after the exclusion of patients with appendicitis or appendectomy; thus, any visits due to NSAP before or after appendicitis or surgery were ignored. In cases of multiple admissions with NSAP, the first admission was considered as the index admission. Women who underwent additional surgical procedures or appendectomy upon a later admission, patients with a secondary diagnosis of endometriosis, pelvic inflammatory disease, or infertility, and patients with secondary pregnancy-related diagnoses were excluded. Details on the identification of the study groups are shown in Figure 1.

Women with a diagnosis of acute appendicitis with perforation and acute peritonitis (ICD-10 code K35.0) or acute appendicitis with perforation and appendiceal abscess (ICD-10 code K35.1) were defined as women with complicated appendicitis. Women with a diagnosis of acute

appendicitis (ICD-10 code K35.9) were defined as women with simple appendicitis. Appendectomies included open (NCSP code JEA00 and JEA10) and laparoscopic appendectomies (NCSP code JEA01). NSAP was identified as indeterminate abdominal pain (ICD-10 code R10.4) or indeterminate lower abdominal pain (ICD-10 code R10.3) and no other diagnoses were allowed at the admission.

Women were considered IVF-treated if they received medication including both gonadotropins (Anatomical Therapeutic Chemical [ATC] Classification System codes G03GA02, G03GA04, G03GA05, G03GA06, and G03GA09) and gonadotropin-releasing hormone antagonists (ATC codes H01CC01 and H01CC02) or gonadotropin-releasing hormone or analogue (ATC codes L02AE01 and H01CA02), as gonadotropins alone can be used also in intrauterine inseminations. Additionally, a woman was defined as IVF-treated if she had a diagnosis of infertility of tubal origin (ICD-10 code N97.1) or unspecified infertility (ICD-10 code N97.9) or complications associated with artificial fertilization (ICD-10 code N98) or IVF (ICD-10 code Z31.2) and procedure codes of fresh embryo transfer (NCSP code TLW10), frozen embryo insertion (NCSP code TLW12), intracytoplasmic sperm injection (NCSP code TLW14), or ovarian puncture (NCSP code LAA10) in the registers. Based on the World Health Organization's definition of infertility as inability to conceive after one year of trying,[9] new-onset tubal factor infertility was considered when the first episode of IVF treatment occurred at least 365 days after appendicitis or NSAP diagnosis (index admission). Information on ectopic pregnancies was based on the ICD-10 codes for ectopic pregnancy (O00).

To assess the risk of later requiring IVF treatment, women who had UA, CA, and NSAP-A were compared to women with NSAP. Women who were diagnosed with infertility prior to or within 365 days of index admission (n = 455) were excluded from the analyses. Also in the assessment of the risk of ectopic pregnancy after UA, CA, and NSAP-A, the NSAP group served as a reference group. Patients with ectopic pregnancies prior to or within 30 days of index admission for appendicitis or NSAP (n = 325) were excluded from the analysis.

Statistical Analyses

Stata/SE 13.1 (StatCorp, Texas, USA) for Mac and IBM SPSS Statistics 26 (IBM, Armonk, NY, USA) for Windows were used for the data analysis. To assess differences between the study groups, the chi-squared test was used for categorical variables, and the Kruskal-Wallis test was used for continuous variables. Data on continuous variables are presented as mean with standard

deviation and median with interquartile range. The level of statistical significance was set to $P < 0.05$. The risks of later infertility treatment requirement and ectopic pregnancy were determined by Cox regression and expressed as hazard ratios with 95% confidence intervals. Both crude and adjusted analyses were performed. The demographic factors that showed statistical significance in the univariate analysis were used as confounding variables. Kaplan-Meier analysis was performed to demonstrate the risk of later requiring IVF treatment in the entire study population.

Ethical Approval

The study protocol was approved by the Ethics Committee for gynecology and obstetrics, pediatrics, and psychiatry of the Hospital District of Helsinki and Uusimaa on 11 of June 2014 (310/13/03/03/2013).

RESULTS

The study population comprised 23 997 women (Figure 1). The mean follow-up time was 7.4 ± 3.5 years in the entire population, 7.1 ± 3.5 years in the UA group, 6.8 ± 3.5 years in the CA group, 7.5 ± 3.5 years in the NSAP-A group, and 7.7 ± 3.5 years in the NSAP group. The differences between the follow-up times of the study groups were statistically significant ($P < 0.001$). Of those women who were operated 70.7% underwent appendectomy in laparotomy and 29.3% in laparoscopy and the proportion of laparoscopic appendectomy rose during the study period.

A total of 23 542 women were included in the analysis of the risk of requiring IVF treatment after appendicitis or appendectomy. 40.2% of the women underwent appendectomy for UA, 4.5% underwent appendectomy for CA, 10.9% underwent NSAP-A, and 44.5% had NSAP (Table 1). The mean age upon index admission was 25.6 ± 5.13 years in the entire population and differed significantly between the study groups (Table 1).

The rate of IVF treatments after index admission was low (2.2%; n = 523). All the women with IVF had received medication including both gonadotropins and gonadotropin-releasing hormone antagonists or gonadotropin-releasing hormone or analogue. The assessment of IVF diagnosis and procedure codes did not add more IVF cases. There were no statistically significant differences in IVF treatment rates between the groups (Table 1). The mean time between index admission and

IVF treatment in the entire study population was 5.0 ± 2.7 years. The NSAP group had the shortest mean time. However, the differences between the study groups were not statistically significant (Table 1).

The crude analysis showed that UA, CA, and NSAP-A did not increase the risk of later requiring IVF treatment compared to NSAP (Table 2). The age at the time of index admission showed statistical significance in the crude analysis and was thus selected as a confounding variable (Table 2). However, after adjustment for age, the differences in the risk of requiring IVF treatment between the groups remained insignificant (Table 2). The cumulative Kaplan-Meier risk estimates of IVF treatment requirement in the study groups after index admission are shown in Figure 2.

A total of 23 672 women were included in the analysis of the risk of ectopic pregnancy after appendicitis/appendectomy. 40.1% of the women underwent appendectomy for UA, 4.5% underwent appendectomy for CA, 10.9% underwent NSAP-A, and 44.5% had NSAP (Table 3).

The incidence of ectopic pregnancy after index admission in the entire study population was 1.1% (n = 254). The mean time between index admission and ectopic pregnancy was 4.2 ± 2.8 years in the entire study population, and the shortest time was after CA (Table 3). The ectopic pregnancy rate after UA and CA was very low (Table 3). The UA group had a significantly lower risk of ectopic pregnancy than the reference group even after adjustment for age upon index admission (Table 4).

DISCUSSION

This is the first nationwide registry-based cohort study to assess the association between CA and the risk of later requiring IVF treatment or ectopic pregnancy. We found that UA, CA, and NSAP-A among reproductive aged women did not increase the risk of a later need for IVF treatment compared to patients with abdominal pain who did not receive surgical treatment. The rate of ectopic pregnancies after UA and CA was very low. Patients with UA had a significantly lower risk of ectopic pregnancy than NSAP patients.

Earlier cohort studies reported conflicting results regarding pregnancy rates after appendectomy and CA.[4,7] These studies used pregnancy rates as a measure of fertility and thus investigated infertility indirectly. Some studies found that perforated appendicitis increases the risk of

tuboperitoneal pathology and subfertility and other studies associated appendectomy for UA with higher pregnancy rates later in life compared to general population.[3–5,7,8,16–18] A meta-analysis found no association between infertility and appendectomy.[6] Information on the association between perforated appendicitis and infertility is mainly based on case-control studies with small numbers of patients with a history of appendicitis.[6,8,16] Many of them were conducted in earlier times, when the capabilities of preoperative diagnostics and laparoscopic surgery were limited. Our results are encouraging for patients with CA. Although CA increases the risk of complications in the short term, our findings suggest that patients should not be overly concerned about the risk of later requiring IVF treatment.

Our study also shows that in Finland, the rate of appendectomies without appendicitis (NSAP-A) remains high among reproductive-aged women. A liberal attitude to appendectomy resulting in a high rate of removal of normal appendix has traditionally been justified by the high risk of perforation and a risk of later infertility[7]. However, even before this study, the evidence justifying this practice was of low quality.[6,16]

In contrast to meta-analysis by Elraiyah et al,[6] we did not find an association between appendicitis and a higher risk of ectopic pregnancy. The result of the previous meta-analysis was based on small number of moderate quality observational studies with potentially high risk of bias,[6] as our study used data on a large number of patients retrieved from a national database. In our study the rate of ectopic pregnancy was significantly lower in UA than in NSAP patients. This may indicate different etiologies of NSAP diagnosed after the index admission, such as *C. trachomatis* infection and endometriosis, which may increase the risk of adhesions and ectopic pregnancy.

The strengths of this study include the use of data on a large number of patients retrieved from a comprehensive national database and the use of actual IVF treatment as a measure of infertility. The cohorts were based on nationwide hospital admission data of all women aged 18–35 years who had appendicitis or underwent appendectomy during the study period. Three large national registers were used for the screening of women who received IVF treatments. Despite a wide variety of health registers in Finland, a cycle-based register of IVF treatments is lacking. However, a previous study has showed that the identification of IVF treatments through medication reimbursements is accurate.[19] Furthermore, we used diagnosis and procedure codes to ensure that we could identify all IVF treatments.

The rate of IVF treated women in the study was 2.2% which seems low compared to the rate of IVF treatments in population level.[14] However, the mean age of the women at the index admission were 25 years and the mean time of follow up was 7 years. The women included in the study might not have tried to conceive yet at the end of the study period. However, instead of complete estimate of the lifetime risk of IVF, the aim of the study was to compare the risks of the study groups during an equal follow up time.

One of the limitations of this study is that information was based solely on registered data, and patient files were not accessed. Discharge diagnoses of UA can be false-positive or false-negative because histopathological analysis is required for confirmation. However, perforated appendicitis is reliably recognized during surgery.[20]Furthermore, there is a small chance that registers overestimate the rate of ectopic pregnancies in the situations when the location of early pregnancy is unclear. However, in this relatively large data it is unlikely to cause a bias and the validation data from Finnish Hospital Care register has shown very good clinical relevance in diagnoses of early pregnancy events .[21] There is a possibility that few women in NSAP group could have a history of appendectomy in childhood. However, the appendicitis in the childhood is rare and considering the large number of women in the NSAP group we believe that it does not have an effect on the outcome. Also, data on other factors that might have been associated with the use of IVF treatment or on the risk of ectopic pregnancy, such as pelvic inflammatory diseases or endometriosis diagnosed after index admission, smoking and contraceptive use, were not assessed. Moreover, the potential effect of *Chlamydia trachomatis* infection on future infertility or ectopic pregnancy could not be evaluated, as register data on *C. trachomatis* infections were not available for the entire study period. However, a Danish population-based study showed that after a single treated *Chlamydia* infection, the risk of tubal factor infertility is only 0.6%.[22] Another Danish study estimated a 0.7% risk of ectopic pregnancy among women with previously treated *C. trachomatis* infections.[23]

Based on our study we cannot rule out the possibility of mild or severe unilateral tubal adhesions after appendicitis leading to subfertility. However, in the case of unilateral tubal adhesions the normal conception or insemination is still an option not leading necessarily to IVF. Another limitation of our study is that demographic characteristics were limited to woman's age, which is, however, the most important factor in fertility assessments.

As CA does not seem to cause long-term harm in terms of fertility, it is essential to improve preoperative diagnostics using algorithms incorporating diagnostic scoring and selective imaging

instead of prompt operative approach. Recent studies have evaluated the treatment of uncomplicated appendicitis with antibiotics instead of appendectomy.[24] Future studies are needed to determine the effect of this treatment modality on later fertility.

CONCLUSION

Complicated and uncomplicated appendicitis and appendectomy in reproductive-aged women does not raise the subsequent risk of requiring IVF treatment or the risk of ectopic pregnancy. Therefore, reproductive-aged women with appendicitis can be treated according to the same principles as other appendicitis patients and should not be overly concerned about the risk of infertility.

Author contributions:

HS, MN, MM, PM participated in the design of the study. JM and PM carried out the data analysis. The manuscript was written and revised by all authors.

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Figure and table captions

Figure 1. Flowchart of the study. Dg: diagnosis; NSAP: nonspecific abdominal pain.

Figure 2. Cumulative risk estimates of later IVF treatment in the study groups after index admission. NSAP: nonspecific abdominal pain.

Table 1. Demographics of the women included in the analysis of the risk of later requiring IVF treatment (n = 23 542).

Table 2. Results of unadjusted and adjusted Cox regression analyses of the risk of later requiring IVF treatment.

384 **Table 3.** Demographics of the women included in the analysis of the later risk of ectopic
385 pregnancy (n = 23 672).
386
387 **Table 4.** Results of unadjusted and adjusted Cox regression analyses of the later risk of ectopic
388 pregnancy.
389

TABLE 1

Demographics of the women included in the analysis of the risk of later requiring IVF treatment (n = 23 542).

Parameter	Uncomplicated appendicitis n = 9453	Complicated appendicitis n = 1052	NSAP with appendectomy n = 2565	NSAP n = 10 472	*P* value
Age upon index admission, mean/median (IQR)	25.4/25 (21–30)	25.8/26 (21–30)	25.1/25 (21–29)	26.0/26 (21–30)	<0.001
Age upon index admission, n (%)					<0.001
18–23 years	3915 (41.4)	417 (39.6)	1115 (43.5)	3904 (37.3)	
24–29 years	3132 (33.1)	332 (31.6)	867 (33.8)	3504 (33.5)	
30–35 years	2406 (25.5)	303 (28.8)	583 (22.7)	3064 (29.3)	
IVF treatments, n (%)	197 (2.1)	26 (2.5)	59 (2.3)	241 (2.3)	0.681
Years from index admission to IVF, mean (SD)	5.2 (2.6)	5.0 (2.6)	5.0 (2.4)	4.7 (2.8)	0.134

Note: NSAP = nonspecific abdominal pain; IQR = interquartile range; SD = standard deviation.

TABLE 2

Results of unadjusted and adjusted Cox regression analyses of the risk of later requiring IVF treatment.

	Unadjusted		Adjusted[a]	
Parameter	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Index admission group				
Uncomplicated appendicitis	0.99 (0.82–1.19)	0.909	1.00 (0.83–1.21)	0.989
Complicated appendicitis	1.24 (0.83–1.86)	0.301	1.26 (0.84–1.88)	0.268
NSAP with appendectomy	1.03 (0.78–1.37)	0.821	1.05 (0.79–1.39)	0.760
NSAP (reference)	1.00	NA	1.00	NA
Age upon index admission				
18–23 years	1.0	NA	NA	NA
24–29 years	1.91 (1.56–2.33)	<0.001	NA	NA
30–35 years	1.16 (0.92–1.47)	0.214	NA	NA

HR = hazard ratio; CI = confidence interval; NSAP = nonspecific abdominal pain; NA = not applicable.

[a] Adjusted for woman age at the time of index admission.

TABLE 3

Demographics of the women included in the analysis of the later risk of ectopic pregnancy (n = 23 672).

	Uncomplicated appendicitis	Complicated appendicitis	NSAP with appendectomy	NSAP	*P* value
Parameter	n = 9496	n = 1061	n = 2572	n = 10 543	
Age upon index admission, mean/median (IQR)	25.5/25 (21–30)	25.9/26 (21–30)	25.1/25 (21–29)	26.0/26 (21–30)	<0.001
Age upon index admission, n (%)					<0.001
18–23 years	3908 (41.2)	419 (39.5)	1112 (43.2)	3872 (36.7)	
24–29 years	3160 (33.3)	332 (31.3)	872 (33.9)	3545 (33.6)	
30–35 years	2428 (25.6)	310 (29.2)	588 (22.9)	3126 (29.7)	
Ectopic pregnancies, n (%)	76 (0.8)	8 (0.8)	36 (1.4)	134 (1.3)	0.003
Years from index admission to ectopic pregnancy, mean (SD)	4.3 (2.8)	4.0 (2.1)	4.2 (2.6)	4.2 (3.0)	0.996

NSAP = nonspecific abdominal pain; IQR = interquartile range; SD = standard deviation.

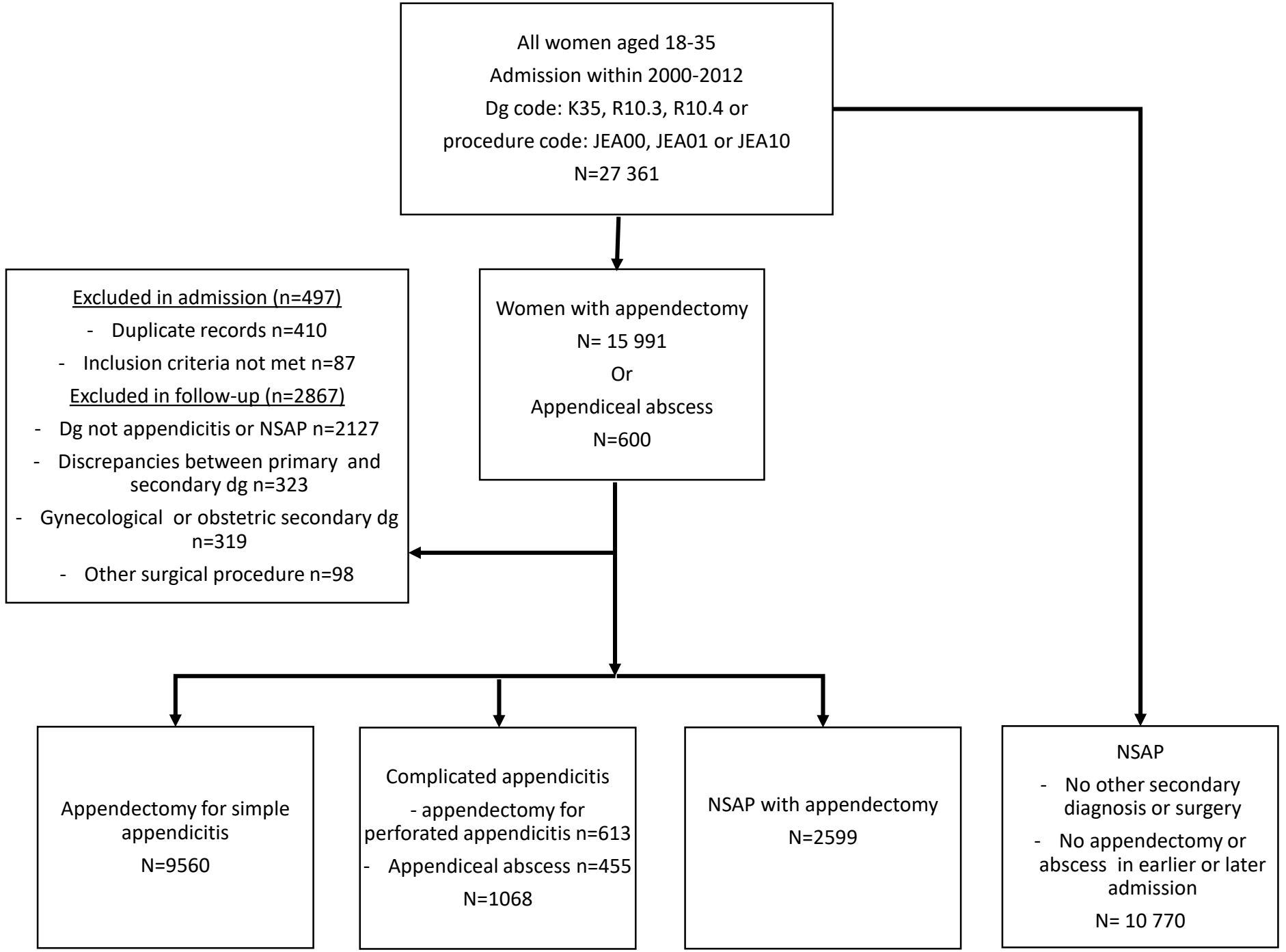
TABLE 4

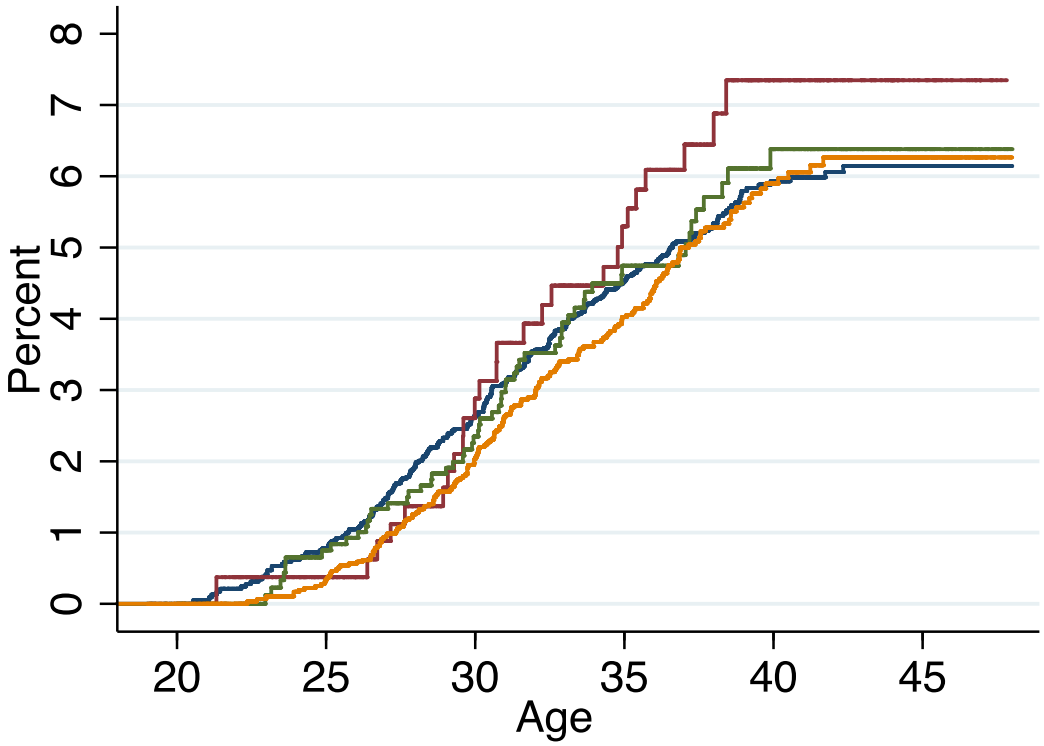
Results of unadjusted and adjusted Cox regression analyses of the later risk of ectopic pregnancy.

	Unadjusted		Adjusted[a]	
Parameter	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Index admission group				
Uncomplicated appendicitis	0.74 (0.56–0.98)	0.033	0.73 (0.55–0.96)	0.026
Complicated appendicitis	0.79 (0.39–1.60)	0.506	0.79 (0.39–1.61)	0.516
NSAP with appendectomy	1.19 (0.82–1.71)	0.362	1.17 (0.81–1.69)	0.410
NSAP (reference)	1.00	NA	1.00	NA
Age upon index admission				
18–23 years	1.0	NA	NA	NA
24–29 years	1.10 (0.83–1.45)	0.509	NA	NA
30–35 years	0.70 (0.51–0.98)	0.036	NA	NA

HR = hazard ratio; CI = confidence interval; NSAP = nonspecific abdominal pain; NA = not applicable.

[a] Adjusted for patient age at the time of index admission.


All women aged 18-35
Admission within 2000-2012
Dg code: K35, R10.3, R10.4 or
procedure code: JEA00, JEA01 or JEA10
N=27 361
Excluded in admission (n=497)
- Duplicate records n=410
- Inclusion criteria not met n=87
Excluded in follow-up (n=2867)
- Dg not appendicitis or NSAP n=2127
- Discrepancies between primary and secondary dg n=323
- Gynecological or obstetric secondary dg n=319
- Other surgical procedure n=98
Women with appendectomy
N= 15 991
Or
Appendiceal abscess
N=600
Appendectomy for simple appendicitis
N=9560
Complicated appendicitis
- appendectomy for perforated appendicitis n=613
- Appendiceal abscess n=455
N=1068
NSAP with appendectomy
N=2599
NSAP
- No other secondary diagnosis or surgery
- No appendectomy or abscess in earlier or later admission
N= 10 770



Number at risk					
Group = NSAP	1299	3600	4276	3893	1903
Group = Complicated appendicitis	144	346	351	325	143
Group = NSAP with appendectomy	397	990	1067	754	336
Group = Simple appendicitis	1338	3448	3621	2834	1259

aogs_14165_f2.eps