The association between prior appendectomy and/or tonsillectomy in women and subsequent pregnancy rate

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The association between prior appendicectomy and/ or tonsillectomy in females and subsequent pregnancy rate: A cohort study

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Capsule

In a population-based study, previous appendicectomy and /or tonsillectomy were associated with an increase in subsequent pregnancy rates and shorter time to pregnancy after surgery.

ABSTRACT

Objective: To study pregnancy rates after appendicectomy and /or tonsillectomy.

Design: A population based cohort study using the UK primary health care based Clinical Practice Research Datalink (CPRD).

Setting: UK Primary Care

Patients: Female patients who underwent appendicectomy, tonsillectomy or both between 1987 and 2012 and appropriate comparators.

Intervention: Timed follow up until first pregnancy after surgery. The association between prior surgery and subsequent pregnancy was determined by Cox regression models.

Main Outcome Measures: Pregnancy rate and time to first pregnancy after surgery.

Results: The analyses included 54,675 appendicectomy only patients, 112,607 tonsillectomy only patients, 10,340 patients who had both appendicectomy and tonsillectomy with 355,244 comparators matched for exact age and practice from the rest of female patients in the database. There were 29,732 (54.4%), 60,078 (53.4%) and 6,169 (59.7%) pregnancies in the appendicectomy only, tonsillectomy only and both appendicectomy tonsillectomy cohorts respectively *vs* 155,079 (43.7%) in the comparator cohort during a mean follow up of 14.7 (SD, 9.7) years. Adjusted hazard ratios (HRs) for subsequent birth rates were 1.34 (95% CI 1.32 to 1.35), 1.49 (95%CI 1.48 to 1.51) and 1.43 (95%CI 1.39 to 1.47), respectively. Time to pregnancy was shortest after both appendicectomy and tonsillectomy followed by appendicctomy only and then tonsillectomy only in comparison to the rest of the population.

Conclusions: Appendicectomy and /or tonsillectomy were associated with increased subsequent pregnancy rates and shorter time to pregnancy. The effect of the surgical procedures on the pregnancy outcome was cumulative.

Key Words: Appendectomy; Tonsillectomy; Prgnancy rate; Time to pregnancy.

INTRODUCTION

Appendicectomy and tosillectomy are amongst the most common surgical procedures, particularly in children and young adults [1, 2]. The lifetime risk of appendicectomy is estimated to be 10 – 20% [3, 4] and this risk is nearly as high as for tonsillectomy before the age of 20 years [5]. The appendix and tonsils are secondary lymphoid organs and prominent constituents of the mucosa-associated lymphoid tissue (MALT) system. The lymphoid function of these tissues is particularly pronounced at young age [2, 6-9] but continues attenuated into adulthood.

We have previously shown that appendicectomy in females is associated with an increased subsequent pregnancy rate and shorter time to pregnancy (TTP) in two different populations [10, 11]. In these studies, two matched cohorts from different populations were followed up after appendicectomy. In one study, a local database included 2935 patients who had appendicectomy and 5870 comparators between 1980 and 2008[10]. The second study included 76,426 appendicectomy patients, with 152,852 comparators from the Clinical Practice Research Datalink (CPRD) database between 1986 and 2009[11]. The pregnancy rate was found to be increased by 20% and 54% respectively in the two cohorts of patients who had appendicectomy when compared with comparators[10, 11]. A Swedish study similarly found an association between removal of a normal appendix or a non-perforated appendix and a higher subsequent birth rate in women aged less than 25 years[12]. Although we were surprised by our findings, we postulated that the increased pregnancy rate following appendicectomy might be related to removal of the appendix, which if left can have episodes of subclinical, chronic or recurrent inflammation. The removal of the cause of local inflammation or inflammatory adhesions in the vicinity of the pelvic fallopian tubes protects their patency. In order to further explore the possible mechanisms of this association, we selected another cohort of females who had removal of a different lymphoid organ located at a remote site from the pelvis. We examined the subsequent pregnancy rate in a cohort of females who had previous tonsillectomy.

Our hypothesis was that prior tonsillectomy would not alter subsequent pregnancy rate if local pelvic inflammation or inflammatory adhesions formation, reduced by appendicectomy were significant factors in the observed increased pregnancy rate.

The aim of this study was thus to compare pregnancy rates in cohorts who had appendicectomy, tonsillectomy or both surgical procedures in comparison with an appropriate control cohort from the general population in the UK Clinical Practice Research Data-link.

METHODS

Study Design:

This was a population based cohort study using the prospectively collected data from the UK Clinical Practice Research Data-link (CPRD)[13]. CPRD is the world's largest computerised database of anonymised longitudinal medical records from primary care. It contains individual patient's primary care records from over 500 primary care practices with 4.4 million active patients throughout the UK. The data has been collected since 1987, it covers about 9% of the UK population and it is generalisable to the whole UK population. The National Health Service in the UK is tax-funded, free at the point of delivery, and it covers the entire population. Each patient has a unique health index number and all health visits are recorded under this number. CPRD captures data on diagnosis, prescriptions, primary care test results, hospital referral and admissions. The dataset also contains information on lifestyle and anthropometric measurements. CPRD also holds the Hospital Episode Statistics (HES) data for about 40% of the practices, which started from 1997 onwards. HES contains routinely collected administrative data, which covers hospital in-patient and day case care in the National Health Service. As such, HES data is more accurate, reliable and provides additional information. HES data was linked for each person showing successive admissions, operations, morbidities and mortality derived from death registration. Morbidity data were coded according to the *International Classification of Diseases (ICD)* 9th or 10th editions. Surgical operations data were coded according to the 4th revision of the Office of Population Censuses and Surveys' (OPCS) classification of surgical operations.

Exposure cohorts*:* Data were extracted from the CPRD database using the search terms for 'appendicectomy', 'tonsillectomy' or 'appendicectomy and tonsillectomy' and separated into the three respective cohorts. Selected subjects were females who had a record of the index surgical procedure(s) and who were below the age of 45 between 1987 and 2012. Subjects entered the study at the date of the surgical procedure (or the earlier surgical procedure if they had both) and were followed up until December 2012. For HES data, the exposure cohort was extracted from the

HES database with the primary OPCS codes of (H011, H012, H013, H018 and H019) for appendicectomy, (F34, F341, F342, F343, F344, F345, F346, F347, F348 and F349) for tonsillectomy or both codes for the composite cohort.

Comparator cohort*:* An exact age and practice-matched cohort of 2 comparators for each study subject was generated from the rest of the CPRD female population who did not have an appendicectomy or tonsillectomy during the same period. Controls entered the study on the same date as the relevant exposure cohort. For HES data, the comparator cohort was extracted from the HES database excluding patients who had appendicectomy or tonsillectomy.

Scientific Approval: Approval for this study was obtained from the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency (MHRA) database research.

Exclusions: Subjects were excluded from the study if they were under 12 years old at the end of follow up or had less than 30 days of follow-up available. Subjects were censored after the first pregnancy, if they reached the age of 53 years, had a sterilisation, hysterectomy, died or reached the end of the study follow up.

Study outcome: The study outcome was the first recorded delivery of a live birth, miscarriage or termination during the follow up period and we used the date of the first of these events. Outcome ascertainment was obtained from the GP records with potential pregnancy codes and cross checked against a previous publication[14], or the HES database with the primary ICD9 codes (630-676) and ICD10 codes (O00-O99 and Z34-Z39).

Definition of co-variates: Age at entry to the study was a covariate as was parity, use of oral contraceptives, the number of previous hospitalisations, inflammatory bowel disease (ICD10 codes K50, K51, K52), pelvic inflammatory disease (ICD10 codes N70, N71, N73, N74), recorded chlamydial infection (ICD 10 codes A55-56, A70-74), other abdominal surgery (defined by OPCS4 codes), smoking history, Body Mass Index (BMI) and Index of Multiple deprivation Score (a measure of socioeconomic status available in CPRD data set). The covariates were selected on the basis of their availability in the database and biological plausibility to influence sexual activity and / or fecundity.

Statistical analysis: For the exposure and comparator cohorts, data were presented as mean (SD) for continuous variables and as numbers (%) for categorical variables. The distribution of categorical variables were compared and examined using the Chi-squared test between the exposure groups and appropriate comparators. Cox proportional-hazards regression models with a time dependent variable of oral contraceptives use, were used to determine the association between the study and comparator groups. Uni-variate and multi-variate analyses were carried out. In the multi-variate models the hazards ratios were adjusted for all covariates between the study and control groups. The results were expressed as hazards ratios (95% confidence intervals). A ratio larger than 1, implied a greater probability of a pregnancy in the exposure group earlier than in the comparator group. Pregnancy events were plotted by Kaplan-Meier curves.

Sensitivity analysis: Several sensitivity analyses were performed to test the robustness of the results. We repeated the analysis by using only the practices that had the HES dataset record-linked. In this case, appendicectomy, tonsillectomy, pregnancy and the co-variates (except oral contraceptives) were extracted from the HES dataset. All covariates were adjusted for 5 years prior to cohort study entry (baseline). A sensitivity analysis was carried out to exclude patients who may have been pregnant before and during the appendicectomy episode. Another sensitivity analysis was done which included covariates that occurred both prior to and after study entry in the matched cohort. Due to the time span of the study with evolution in surgical practice, a further sensitivity analysis was carried out to assess the calendar year as a covariate. An additional sensitivity analysis was carried out to establish whether there was an additive effect to the two surgical procedures on the pregnancy outcome. An exploratory analysis was carried out to examine the effect of having the exposure (operative procedure) in childhood (<16 years of age) or adulthood (>16 years of age).

All Statistical analyses were carried out using SAS (version 9.2).

RESULTS

Cohorts characteristics: The study contained 54,675 subjects in the appendicectomy only cohort, 112,607 in the tonsillectomy only cohort, 10,340 in the appendicectomy and tonsillectomy cohort and 355,244 age and practice matched subjects in the comparator cohort (Table 1). More subjects in the surgical cohorts (appendicectomy, tonsillectomy or both) in comparison to the appropriate comparators used oral contraceptives previously and had a diagnosis of inflammatory bowel disease, pelvic inflammatory disease and chlamydial infections. In addition, more of them had previous surgical operations and a previous pregnancy. The average age at tonsillectomy was 10.8 years (± 7.2) and was lower than that for appendicectomy; 16.2 years (± 7.8).

Pregnancy rates: During a mean follow up of 14.7 (SD, 9.7) years, 29,732 (54.4%), 60,078 (53.4%) and 6,169 (59.7%) first pregnancies were recorded in the appendicectomy only, tonsillectomy only and the appendicectomy and tonsillectomy cohorts respectively in comparison to 155,079 (43.7%) in the comparator cohort. The first pregnancy events were more frequent in the appendicectomy and tonsillectomy cohorts than in the respective comparator cohorts, adjusted HRs for subsequent pregnancy rates in the appendicectomy only, tonsillectomy only and the appendicectomy and tonsillectomy cohorts respectively were 1.34 (95% CI 1.32 to 1.35), 1.49 (95%CI 1.48 to 1.51) and 1.43 (95%CI 1.39 to 1.47), respectively (Table 2). The Time to Pregnancy (TTP) after the index surgical procedure(s) was progressively shorter after tonsillectomy, appendicectomy and after both tonsillectomy and appendicectomy in comparison to the comparator cohort (Figure 1).

Sensitivity analyses: In order to establish whether the effects of previous appendicectomy and tonsillectomy were additive, we carried out several sensitivity analyses. The HR (95% CI) results changed slightly across different analyses (Tables 2).

Another analysis was carried out on only the proportion of the population within the HES database. From the total cohort, there were 67,613 patients from practices which had data that could be linked to Hospital Episodes Statistics (HES) database (6,757 patients in the appendicectomy only cohort, 15,544 in the tonsillectomy only cohort, 355 in the appendicectomy and tonsillectomy cohort and 45,312 patients in the comparator cohort). The adjusted HRs (95% CI) for subsequent pregnancy rates in the appendicectomy only, tonsillectomy only and the appendicectomy and tonsillectomy cohorts respectively were changed slightly to 1.54 (95%: CI 1.46 - 1.63), 1.40 (95% CI: 1.34 - 1.46) and 1.62 (95% CI: 1.31 – 2.00) (Table 3). Further sensitivity analysis adjusting for BMI, smoking and previous pregnancies (including pregnancies during the surgical episode) made minor changes to the HR (95% CI), (Table 3).

Further exploratory analysis showed a very strong association between appendicectomy/tonsillectomy and miscarriage (number of events=19,498) with adjusted HRs of 1.61 (95% CI 1.53 - 1.68) for the appendicectomy only cohort, 1.60 (95% CI 1.54 - 1.66) for the tonsillectomy only cohort and 1.74 (95% CI 1.59 - 1.91) for the appendicectomy and tonsillectomy cohort compared with the comparator cohorts. A similar association was observed between the surgical procedures and live births with adjusted HRs of 1.38 (95% CI 1.35 – 1.42), 1.50 (1.48 – 1.60) and 1.47 (95% CI 1.42 – 1.53) for the appendicectomy only, the tonsillectomy only and for the appendicectomy and tonsillectomy cohorts respectively, (Table 2).

Another exploratory analysis showed that the effect sizes were similar in patients who had the operative procedures in childhood (≤16 years old) (n= 351,988) or in adulthood (>16 years old) (n= 180,878). The adjusted HRs for patients who had the operative procedures in childhood were 1.35 (95% CI 1.33 - 1.38), 1.51 (95% CI 1.49 - 1.53) and 1.46 (95% CI 1.41 - 1.52) for the appendicectomy only cohort, the tonsillectomy only cohort and the appendicectomy and tonsillectomy cohort respectively, when compared with the comparator cohorts. The corresponding figures for patients who had the operative procedures in adulthood were 1.31 (95% CI 1.28 - 1.33), 1.45 (95% CI 1.42 - 1.48) and 1.39 (95% CI 1.34 - 1.45) respectively, (Table 2).

DISCUSSION

The results from this population-based study confirmed the previously reported observation of a higher pregnancy rate and shorter time to pregnancy (TTP) following appendicectomy [10, 11]. The adjusted HR for the pregnancy outcome in females who had a previous appendicectomy was 1.34 (95% CI 1.32 to 1.35). Having selected a positive control group who had tonsillectomy (removal of another lymphoid organ at a remote site from the pelvis), we were further surprised to find that removal of the tonsils also increased the subsequent pregnancy rate with an adjusted HR 1.49 (95%CI 1.48 to 1.51) with a shorter TTP after surgery and removal of both the appendix and tonsils resulted in an adjusted HR 1.43 (95%CI 1.39 to 1.47) and the shortest TTP after surgery. The association was strong between the surgical procedures and both subsequent miscarriages and live birth pregnancies. Given that the groups with previous appendicectomy, tonsillectomy or both procedures also had a higher rate of inflammatory bowel disease, pelvic inflammatory disease and previous surgery than the control population, which may reduce sexual activity [15] and pregnancy rate, the effect size of a higher subsequent pregnancy rate and shorter TTP after surgery in the index groups is counter intuitive. The results suggest that the increased subsequent pregnancy rate and shorter TTP after surgery may not be due to pelvic local mechanisms as we had hypothesised. One possible explanation is that by selecting for cohorts who had appendicectomy or tonsillectomy this study has inadvertently selected a female phenotype that had more frequent sexual intercourse (higher libido, a more liberal attitude towards sex or unknown factors). Our data shows that the groups with previous appendicectomy and tonsillectomy had a higher rate of chlamydial infections, pelvic inflammatory disease and previous pregnancies; all surrogate markers of increased sexual activity. The tonsillectomy cohort had a higher rate of oral contraceptive use than the appendicectomy cohorts but lower than the comparator group. The surgery cohort also had a higher rate of inflammatory bowel disease. It is possible that episodes of pelvic inflammatory disease resulting from liberal sexual activity or inflammatory bowel disease, necessitated hospital admission with lower abdominal pain which eventually lead to removal of the appendix. Indeed prior to the widespread adoption of laparoscopy for young women with right iliac fossa pain, approximately a third of appendices removed were histologically normal[16]. By the same rationale a similar group of females developed recurrent throat infections as a result of intimate contact with males, which led to recurrent episodes of tonsillitis necessitating surgery.

Another intriguing and biologically plausible explanation for the increased subsequent pregnancy rate and shorter time to pregnancy (TTP) after appendicectomy and tonsillectomy or both is due to reduced systemic inflammation emanating from these organs. A degree of systemic or uterine inflammation is essential for normal implantation and pregnancy[13, 17, 18]. However, when inflammation becomes too excessive, chronic or consists of specific mediators in high concentration, it might cause degeneration of the embryo and impaired implantation [19]. In general, patients with inflammatory bowel disease have fewer children than the general population [20]. An active disease decreases fertility significantly via inflammation, surgical sequel, secondary amenorrhoea or sexual dysfunction [20]. Similarly, untreated asthma significantly prolongs time to pregnancy and reduce fertility mainly because of systemic inflammation [21]. The same applies to untreated rheumatoid arthritis [22]. It is likely that the increased time to pregnancy in these disorders is biological rather than behavioural [15]. The appendix and tonsils are lymphoid organs which may be susceptible to episodic, chronic and or recurrent inflammation either de novo[23, 24] or after previous acute attacks[24, 25]. Surgical removal may reduce the risk of attacks of inflammation related to these organs, which could result in improved wellbeing of young females including a more permissible utero-tubo-ovarian environment for a pregnancy [15].

For a successful pregnancy, active maternal tolerance to foreign fetal alloantigens is a prerequisite for successful trophoblast implantation and fetal development. The appendix and tonsils are secondary lymphoid organs. Removal of the appendix and/ or tonsils can alter several aspects of immune reactivity [8, 26]. The effect seems to be more pronounced when both the appendix and tonsils are removed [8]. These lymphoid organs are generally thought of as ‘gut associated’ with primary effects on gut immunity. Indeed, appendicectomy and tonsillectomy are risk factors for Crohn’s disease [27, 28] and appedicectomy appears to protect against ulcerative colitis [29, 30]. The systemic affects can also manifest out with the gut. Appendicectomy and tonsillectomy are risk factors for rheumatoid arthritis [31], premature acute myocardial infarction [32] and are associated with Hodgkin's lymphoma [33, 34]. It is conceivable that the systemic modulation of the immune response consequent on appendicectomy and or tonsillectomy at the feto-maternal interface is favourable towards the pregnancy outcome. It must be noted that where effect modification by age was considered in these studies, the associations seem to be restricted mainly or exclusively to individuals in whom the appendicectomy and/or tonsillectomy occurred before adulthood [29, 30, 34]. Although the production of auto-antibodies by lymphoid tissue (via molecular mimicry, bystander cell activation, epitope spreading, etc.) during any infection, can induce reproductive pathology in the short term, removal of the appendix and tonsils, still leaves an abundance of lymphoid tissue to counteract infection (and auto-antibody production). However, the exposure and response of the remaining lymphoid tissue are possibly different or attenuated. Indeed, if autoimmune mechanisms were implicated in the apparent increase in fecundity in this study, we should observe a reduction in miscarriages. Although the recorded data in CPRD is not sufficiently reliable to include all miscarriages, an exploratory analysis has shown an increased number of miscarriages in the groups, which had appendicectomy and or tonsillectomy in comparison with comparators. Not withstanding the limitation of the data, an autoimmune modification explanation for the increased fecundity after lymphoid organ removal is less likely. Further, the effect sizes in this study were similar in patients who had the operative procedures in childhood (≤16 years old) and adulthood (>16 years old).

Regardless of the explanation for the association between appendicectomy and/or tonsillectomy with increased pregnancy rate, there is sufficient evidence in this study for an association. The results reflect the practice of appendicectomy and or tonsillectomy over at least the last 30 years (the period of the current study). Recently, clinical practice has changed. Previously, the majority of young females with suspected acute appendicitis were referred for surgery and a third of appendices removed were normal[35]. Over the past 15 years, the majority of surgeons recommend a diagnostic laparoscopy to confirm the diagnosis[16]. If appendicitis was confirmed, appendicectomy was usually carried out laparoscopically at the same time. More recently, there has been a trend towards antibiotic treatment for appendicitis particularly in children with or without interval appendicectomy[35, 36]. For tonsillitis, the indications for tonsillectomy have become even more controversial. A recent update on a Cochrane review concluded that tonsillectomy in children leads to a reduction in the number of episodes of sore throat and days with sore throat in comparison to non-surgical treatment [37]. In practice, the rate of tonsillectomy in the general population has decreased markedly[38]. These changes to the management of relatively common conditions may impact on health consequences including the conception rates in the female population.

This study was done using the whole of the CPRD data with subsequent sensitivity analyses on subgroups to adjust for confounders. This methodology is less likely to produce a positive correlation between the exposure and outcome. The tonsillectomy group served as a positive control in this study. Despite its large size, long follow-up duration and population-based design, this study is subject to limitations. We relied on CPRD database, which provides good quality and reliable data, collected since 1987. HES data were collected from 1997 onwards and only for 40 % of practices. It is unlikely that the database missed a large number of females who had live birth pregnancies but it is likely that a number of females who had appendicectomy and/or tonsillectomy were missed. In addition, it is very likely that the database has not recorded all episodes of spontaneous abortions or terminations. However, the effect is unlikely to be differential or influence the results appreciably. To address this, we have age matched for the exposure and carried out sensitivity analysis on calendar time and inclusion in HES data, which recorded admissions for abortion/ termination.

As with all observational studies, confounding factors, which we did not adjust for could explain our findings. For example, marital status, frequency of intercourse, use of other methods of contraception and wish to conceive may in theory explain our results. We could not adjust for these factors. We have however adjusted for socio-economic status, smoking history, BMI and previous pregnancies. Similarly, we did not have access to reliable pathology data on the removed appendix and tonsils. However, a previous study has shown that irrespective of pathology of the removed appendix subsequent pregnancy rates were increased after appendicectomy[11].

In conclusion, we have found an increased pregnancy rate and reduced time to pregnancy after appendicectomy and tonsillectomy. The explanation and mechanism of pregnancy facilitation after removal of these lymphoid organs remains speculative. However it is possible that young females with recurrent attacks or chronic symptoms of appendicitis or tonsillitis will stand a better chance of conception after removal of these lymphoid organs. Based on the results of this study, management algorithms and guidelines should stipulate a lower threshold for appendectomy and tonsillectomy in young females with acute, recurrent or chronic inflammation in these organs. Surgeons can reassure young females that there is no increased risk of infertility after appendicectomy and/ or tonsillectomy.

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Figure legends

Figure 1. Kaplan-Meier plot of pregnancy outcome between the four cohorts in the GPRD analysis.

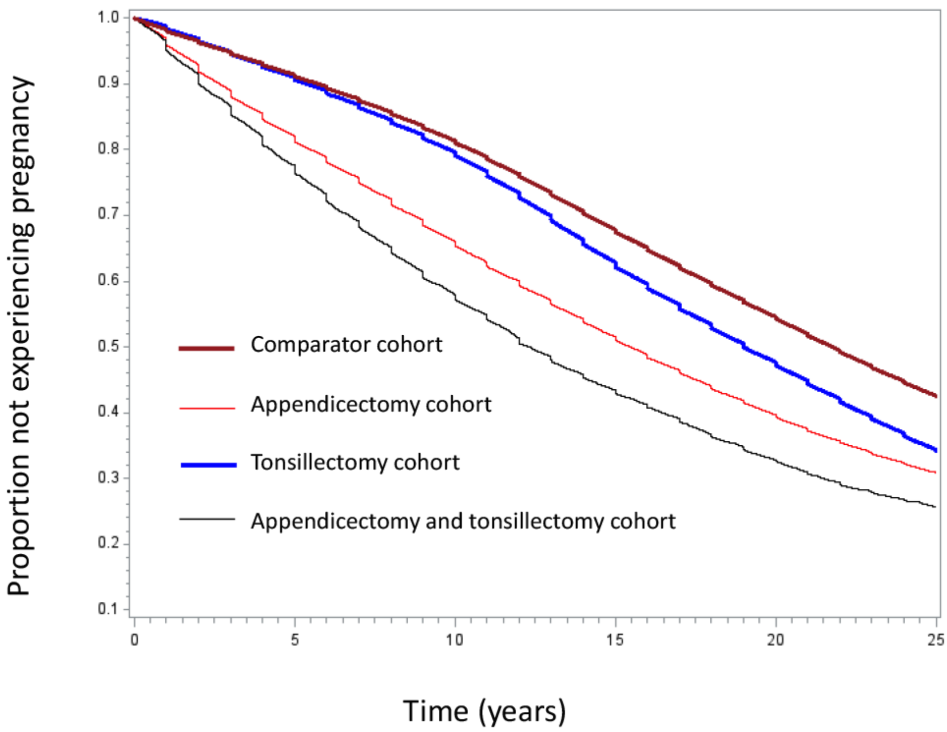

Table 1. Baseline characteristics

	Comparator cohort N=355244	**Appendicectomy only N=54675**	**Tonsillectomy only N=112607**	**App and ton cohort N=10340**	**Heterogeneity test**
Age at surgery in years (SD)	12.9 (7.9)	16.2 (7.8)	10.8 (7.2)	17.7 (7.2)	--
Follow up time in years (SD)	15.0 (9.8)	12.4 (9.4)	15.0 (9.6)	11.2 (9.0)	--
Age at first birth after surgical procedure in years (SD)	25.8 (6.2)	25.3 (6.1)	24.5 (6.0)	25.3 (5.9)	*
Current use of oral contraceptive n (%)	103368 (29.1%)	15115 (27.7%)	36914 (32.8%)	2836 (27.4%)	*
Inflammatory bowel disease n (%)	146 (0.04%)	44 (0.08%)	53 (0.05%)	11 (0.11%)	*
Pelvic inflammatory disease n (%)	331 (0.09%)	326 (0.6%)	113 (0.10%)	90 (0.87%)	*
Chlamydial infection n (%)	127 (0.04%)	41 (0.07%)	48 (0.04%)	10 (0.10%)	*
Other operations n (%)	1904 (0.54%)	459 (0.84%)	1094 (0.97%)	138 (1.33%)	*
Previous pregnancy n (%)	26378 (7.4%)	7103 (13.0%)	7799 (6.9%)	1669 (16.1%)	*

* : Heterogeneity test of difference between each of the study cohorts and the comparator cohort is statistically significant at < 0.01

Table 2. Hazard ratios and 95% CIs for the pregnancy outcome in different analysis.

		Comparator cohort	Appendicectomy only cohort	Tonsillectomy only cohort	App and Tons cohort
Main analysis	**Unadjusted HR (95% CI)**	1.00	1.36 (1.34 - 1.38)	1.42 (1.40 - 1.43)	1.48 (1.44 - 1.52)
	Adjusted HR (95% CI)	1.00	1.34 (1.32 - 1.35)	1.49 (1.48 - 1.51)	1.43 (1.39 - 1.47)
Sensitivity analysis	**Within HES practices**	1.00	1.06 (1.03 - 1.08)	1.25 (1.23 - 1.27)	1.12 (1.07 - 1.17)
	Including smoking and BMI	1.00	1.34 (1.32 - 1.36)	1.48 (1.46 - 1.49)	1.43 (1.39 - 1.47)
	Excluding previous pregnancy	1.00	1.38 (1.36 - 1.39)	1.47 (1.46 - 1.49)	1.53 (1.48 - 1.57)
Exploratory analysis	**Live births**	1.00	1.38 (1.35 – 1.42)	1.50 (1.48 – 1.60)	1.47 (1.42 – 1.53)
	Miscarriages	1.00	1.61 (1.53 – 1.68)	1.60 (1.54 – 1.66)	1.74 (1.59 – 1.91)
	Childhood surgery	1.00	1.35 (1.33 – 1.38)	1.51 (1.49 – 1.53)	1.46 (1.41 – 1.52)
	Adult surgery	1.00	1.31 (1.28 – 1.33)	1.45 (1.42 – 1.48)	1.39 (1.34 – 1.45)

Heterogeneity test of difference between each of the study cohorts and the comparator cohort is statistically significant at < 0.01

Table 3. Results from HES database

<u>Main analysis</u>	
Adjusted HR*	
Comparator cohort (n=45312)	1.00
Appendectomy alone (n=6757)	1.54, 1.46-1.63
Tonsillectomy alone (n=15544)	1.40, 1.34-1.46
Appendectomy alone and Tonsillectomy alone (n=355)	1.62, 1.31-2.00
<u>Including smoking and BMI in the model</u>	
Adjusted HR*	
Comparator cohort (n=45312)	1.00
Appendectomy alone (n=6757)	1.52, 1.43-1.60
Tonsillectomy alone (n=15544)	1.43, 1.37-1.49
Appendectomy alone and Tonsillectomy alone (n=355)	1.71, 1.37-2.14
<u>Excluding previous pregnancy from the model</u>	
Adjusted HR*	
Comparator cohort (n=39259)	1.00
Appendectomy alone (n=5632)	1.68, 1.58-1.79
Tonsillectomy alone (n=13058)	1.49, 1.43-1.57
Appendectomy alone and Tonsillectomy alone (n=317)	1.87, 1.48-2.36

* trend test for the HR, p<0.01

Contributors: The study was conceived by SMS, LW and TMM. All authors took part in the design of the initial study protocol. LW took part in the design of the protocol for the CPRD database and performed the data analysis. SMS and LW prepared the initial manuscript. All authors were involved in revisions of the manuscript. All authors commented and agreed on the final manuscript before submission.

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All authors, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis

Data sharing: no additional data available

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