

Association between prior appendectomy and/or tonsillectomy in women and subsequent pregnancy rate: a cohort study

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

Design: Population-based cohort study using the United Kingdom (U.K.) primary health care-based Clinical Practice Research Datalink (CPRD).

Setting: Not applicable.

Patient(s): Female patients who underwent appendectomy, tonsillectomy, or both from 1987 to 2012 and appropriate comparators.

Intervention(s): Timed follow-up until first pregnancy after surgery. The association between prior surgery and subsequent pregnancy was determined with the use of Cox regression models.

Main Outcome Measure(s): Pregnancy rate and time to first pregnancy after surgery.

Result(s): The analyses included 54,675 appendectomy-only patients, 112,607 tonsillectomy-only patients, 10,340 patients who had both appendectomy and tonsillectomy, and 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 appendectomy-only, tonsillectomy-only, and both appendectomy tonsillectomy cohorts, respectively versus 155,079 (43.7%) in the comparator cohort during a mean follow-up of 14.7 ± 9.7 years. Adjusted hazard ratios (HRs) for subsequent birth rates were 1.34 (95% confidence interval [CI] 1.32–1.35), 1.49 (95% CI 1.48–1.51), and 1.43 (95% CI 1.39–1.47), respectively. Time to pregnancy was shortest after both appendectomy and tonsillectomy followed by appendectomy only and then tonsillectomy only compared with the rest of the population.

Conclusion(s): Appendectomy and/or tonsillectomy was associated with increased subsequent pregnancy rates and shorter time to pregnancy. The effect of the surgical procedures on the pregnancy outcome was cumulative. (Fertil Steril® 2016; ■:■–■. ©2016 by American Society for Reproductive Medicine.)

Key Words: Appendectomy, tonsillectomy, pregnancy rate, time to pregnancy

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Appendectomy and tonsillectomy are among the most common surgical procedures, particularly in children and young adults (1, 2). The lifetime risk of appendectomy 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 previously showed that appendectomy in women is associated with an increased subsequent pregnancy rate and shorter time to pregnancy (TTP) in two different populations (10, 11). In those studies, two matched cohorts from different populations were followed after appendectomy. In one study, a local database included 2,935 patients who had appendectomy and 5,870 comparators from 1980 to 2008 (10). The second study included 76,426 appendectomy patients and 152,852 comparators from the United Kingdom (U.K.) Clinical Practice Research Datalink (CPRD) database from 1986 to 2009 (11). The

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pregnancy rate was found to be increased by 20% and 54%, respectively, in the two cohorts of patients who had appendectomy compared with comparators (10, 11). A Swedish study similarly found an association between removal of a normal appendix or a nonperforated appendix and a higher subsequent birth rate in women aged <25 years (12). Although we were surprised by our findings, we postulated that the increased pregnancy rate following appendectomy 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. To further explore the possible mechanisms of this association, we selected another cohort of women who had undergone removal of a different lymphoid organ located at a remote site from the pelvis: We examined the subsequent pregnancy rate in a cohort of women who had prior tonsillectomy.

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

The aim of the present study was therefore to compare pregnancy rates in cohorts who had appendectomy, tonsillectomy, or both surgical procedures compared with an appropriate control cohort from the general population in the CPRD.

METHODS

Study Design

This was a population-based cohort study using the prospectively collected data from the CPRD (13). The CPRD is the world's largest computerized database of anonymized longitudinal medical records from primary care. It contains individual patients' primary care records from more than 500 primary care practices with 4.4 million active patients throughout the U.K. The data have been collected since 1987, covering ~9% of the U.K. population, and are generalizable to the whole U.K. population. The National Health Service in the U.K. is tax funded and free at the point of delivery and covers the entire population. Each patient has a unique health index number, and all health visits are recorded under this number. The CPRD captures data on diagnosis, prescriptions, primary care test results, hospital referral, and admissions. The dataset also contains information on lifestyle and anthropometric measurements. It also holds the Hospital Episode Statistics (HES) data for ~40% of the practices, which started from 1997. HES contains routinely collected administrative data, which covers hospital in-patient and day case care in the National Health Service. As such, HES data are more accurate and reliable and provide additional information. HES data were 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 with the use of the search terms "appendectomy," "tonsillectomy," and "appendectomy and tonsillectomy" and separated into the three respective cohorts. Selected subjects were women who had a record of the index surgical procedure(s) and who were younger than 45 years from 1987 to 2012. Subjects entered the study at the date of the surgical procedure (or the earlier surgical procedure if they had both) and were followed until December 2012. For HES data, the exposure cohort was extracted from the HES database with the use of the primary OPCS codes of H011, H012, H013, H018, and H019 for appendectomy, F34, F341, F342, F343, F344, F345, F346, F347, F348, and F349 for tonsillectomy, and both codes for the composite cohort.

Comparator Cohort

An exact age- and practice-matched cohort of two comparators for each study subject was generated from the rest of the CPRD female population who did not have an appendectomy or tonsillectomy during the same period. Control subjects 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 appendectomy or tonsillectomy.

Scientific Approval

Approval for this study was obtained from the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency Database Research.

Exclusions

Subjects were excluded from the study if they were younger than 12 years old at the end of follow-up or had fewer than 30 days of follow-up available. Subjects were censored after the first pregnancy or if they reached the age of 53 years, had a sterilization or 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 general practice records with the use of potential pregnancy codes and cross-checked against a previous publication (14), or the HES database with the use of the primary ICD9 codes (630–676) and ICD10 codes (O00–O99 and Z34–Z39).

Definition of Covariates

Age at entry to the study was a covariate, as was parity, use of oral contraceptives, the number of previous hospitalizations,

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