Management of Appendicitis During Pregnancy

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Abstract

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Introduction

Nonoperative management of appendicitis is increasingly common, however its role in pregnancy is unclear. Appendectomy and appendicitis treated with antibiotics can both increase the risk of adverse pregnancy outcomes (APO). We aim to characterize trends in the use of nonoperative management and the incidence of APO with either treatment.

Methods

A retrospective cohort study of patients with appendicitis during singleton pregnancies (14-55y) using the IBM MarketScan Research Databases (2007-2019), applying a unique algorithm to determine gestational age from administrative claims. Appendicitis, appendectomy within 2 days of diagnosis, and APO (pregnancy loss and preterm birth) were defined using claims, and multivariable logistic regression was used to account for differences in patient characteristics and disease severity.

Results

3,735 patients were diagnosed with appendicitis during pregnancy, of whom 7.1% were initially managed without surgery. This proportion increased significantly over the study period, from 4.5% in 2007 to 12% in 2019 ($p<0.001$). APO were similar between those managed with and without surgery in the first and third trimesters, however nonoperative management in the second

trimester was associated with a significantly higher incidence of APO (28% vs. 18%, p = 0.014). This association remained statistically significant after adjusting for pregnancy risk factors and appendicitis severity (adjusted odds ratio 1.75, 95% CI 1.09-2.81).

Conclusions

Nonoperative management is increasingly used for appendicitis in pregnancy. While this strategy appears to have similar outcomes to surgery for first and third trimester cases, nonoperative management in the second trimester may be associated with greater risk of APO.

Introduction

Up to 2% of pregnant people will undergo a nonobstetric operation during their pregnancy[1], and 25% of these will undergo appendectomy for acute appendicitis[2], accounting for an estimated 2800 cases per year in the United States[3]. Compared to other operations, appendectomy has been associated with higher incidence of adverse pregnancy outcomes (APO) such as pregnancy loss and preterm birth [4]. Pregnancy loss refers to both miscarriage (before 20 weeks gestation) and intrauterine fetal demise or stillbirth (during and after 20 weeks gestation). Preterm birth is defined as delivery before 37 weeks gestational age, and is a leading cause of neonatal mortality and long-term morbidity[5]. Preventing both of these outcomes is of high interest to pregnant patients and the clinicians who treat them, however it is unknown whether appendicitis itself, the appendectomy procedure, or the effect of anesthesia poses the greatest risk of APO.

Acute appendicitis is an infectious process that can cause both intra-abdominal inflammation near the uterus as well as sepsis, which has been linked to APO[6]. Pregnancy loss and preterm birth may be associated with the appendectomy procedure as well, due to either the mechanical manipulation of the gravid uterus[7] or the pro-inflammatory state that occurs in response to surgery[8]. Finally, the hemodynamic changes associated with undergoing anesthesia may play a role in precipitating APO[9]. All of these mechanisms may result in APO soon after appendicitis, however delayed adverse outcomes are also plausible, as appendicitis and surgery have been linked to intrauterine growth restriction[10], which is a risk factor for both stillbirth and preterm birth[11].

Understanding the relationship between APO, appendicitis, anesthesia, and surgery is key to guiding management decisions, however this remains poorly understood, as all studies of appendicitis in pregnancy have had significant limitations. The most common study designs have used birth registries, claims databases, and single-institution series with small sample sizes, all of which have important limitations that we seek to address in the present study.

Birth registry studies

The highest-quality study evaluating the impact of appendicitis on adverse pregnancy outcomes was performed by Ibiebele et al, who conducted a population-based study linking a regional birth registry and inpatient clinical registry in Australia[12]. The advantage of using birth

registry data is the ability to estimate population-based estimates of disease incidence, and the precise estimation of gestational age at the time of appendicitis. The authors compared preterm birth among patients who underwent appendectomy vs. pregnant controls without appendicitis. Among 1,024 patients undergoing appendectomy, they report a significantly increased preterm birth rate of 10.6% compared to 5.9% among controls. However, while 79% of appendectomies were performed before 24 weeks gestational age, the birth registry only contained information on deliveries after 20 weeks, therefore pregnancies ending in pregnancy loss before 20 weeks were not included. Not only is pregnancy loss an important pregnancy outcome of interest to patients and clinicians, it is a competing risk with preterm birth, therefore excluding these cases may lead to biased estimates of preterm birth among patients undergoing appendectomy[13]. Additionally, patients were included if they underwent appendectomy; it is unknown how many "negative appendectomies" were performed for patients without appendicitis (in pregnancy, this has been reported in up to 23% of cases, even in the era of advanced ultrasound, computed tomography, and magnetic resonance imaging[14]). Finally, this study was not able to evaluate cases of appendicitis that were treated with nonoperative management.

Mazze and Kallen conducted a similar birth registry study in Sweden, also finding an increased risk of preterm birth after appendectomy[15]. While the greatest proportion of appendectomies in their sample were performed in the first trimester, they were also unable to include pregnancies ending before 28 weeks gestation, and were therefore unable to evaluate the risk of pregnancy loss and may have had biased preterm birth estimates as well. Of additional concern is the finding that 36% of cases were negative appendectomies. Wei et al also conducted a birth registry study in Taiwan with similar findings and limitations[10]; in this study cases were included based on diagnosis codes for acute appendicitis rather than appendectomy, however it is unknown which of these patients underwent surgery and which did not.

Claims database studies

Several additional large observational studies have evaluated the impact of appendicitis on APO using inpatient claims data. Compared to using birth registries, this approach has the advantage of being able to capture pregnancy loss as an outcome of interest, yet information on gestational age is not directly available. Because up to 15% of all clinically recognized pregnancies end in pregnancy loss before week 20 of gestation, with most of these occurring in

the first trimester[16 17 18], estimates of pregnancy loss incidence are strongly influenced by the gestational age at which appendicitis occurs. Consequently, if gestational age is unknown yet exposures occur at different points in pregnancy, unmeasured confounding will be present in any associations between exposure and outcome.

Sachs et al assessed obstetric outcomes after appendectomy and cholecystectomy in pregnancy using the Nationwide Inpatient Sample, which is a claims database derived from a representative sample of inpatient hospitalizations in the United States[3]. In this study, pregnancy loss occurred in 1.3% of cases and preterm birth in 1.8%, which is much lower than other estimates, and likely a substantial underestimate due to lack of follow-up after index hospitalization.

Abbasi et al also used the Nationwide Inpatient Sample to evaluate cases of appendicitis in pregnancy[19]. While these authors do not report adverse pregnancy outcomes, they do report 413 cases of appendicitis in pregnancy that were managed without surgery, the largest cohort of such cases to date. The authors report higher proportion of diagnosis codes for peritonitis and sepsis among these patients compared to those who underwent surgery. While both peritonitis and sepsis in appendicitis have been linked to APO[3], claims data do not specify whether these conditions are complications of treatment or identified at the time of presentation. Some forms of perforated appendicitis with abscess or phlegmon are preferentially treated nonoperatively in nonpregnant patients due to the increased morbidity of surgery[20 21], raising the possibility of reverse causality, i.e. the presence of severe appendicitis may have resulted in nonoperative management, rather than the other way around.

McGory et al used the California Inpatient File, a discharge database containing inpatient claims from all hospitals in the state, to evaluate pregnancy loss and preterm birth after appendectomy in 3,133 pregnant patients, among whom 4% experienced pregnancy loss and 7% preterm birth, however they were also unable to estimate gestational age or identify outcomes occurring after hospital discharge[14]. Cheng et al identified 859 cases of appendicitis during pregnancy in the Taiwanese National Health Insurance Research Database, including 78 that were managed without surgery[22]. This database does allow longitudinal follow up of APO, and the authors report a preterm birth rate of 10.4% and a pregnancy loss rate of 6.2%, compared to 4.4% and 0.4% respectively in pregnant controls without appendicitis. They were similarly unable to estimate gestational age at the time of appendicitis, and do not report their process for

sampling pregnant controls, therefore it is unknown whether they are appropriately matched in terms of baseline risk of APO.

Single-institution studies

Numerous single-institution retrospective clinical studies have reported pregnancy outcomes after appendectomy during pregnancy[23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42], however none have been able to assess the difference between observed APO and expected rates by gestational age, all have had small sample sizes (<100), and none report trimester-specific estimates of APO risk. In all of these studies, only patients undergoing appendectomy were included, and to date there is only one prospective study that has evaluated APO after nonoperative management[43]. In these highly selected patients (only 20 out of 81 screened patients were enrolled; appendiceal diameter >11mm and radiologic signs of complicated appendicitis were exclusion criteria), there was one case of pregnancy loss and three cases of preterm labor that did not result in preterm birth. Baseline risk of adverse pregnancy outcomes on the basis of gestational age was not assessed in this study, and it is difficult to assess whether these outcomes are unfavorable compared to patients undergoing surgery.

Evidence Gaps and Aims

Multiple randomized trials have established a role for nonoperative management of appendicitis in some nonpregnant adults [44 45 46 47 48 49], however it remains unknown whether this strategy is also being implemented for pregnant patients. There are currently no guidelines to inform decisions for nonoperative management during pregnancy, and due to the limitations in the literature discussed above, the risk of adverse pregnancy outcomes associated with this approach in each trimester remains unknown. The IBM MarketScan Commercial Claims and Encounters Database provides a unique opportunity for addressing these evidence gaps. Unlike other claims databases referenced above, MarketScan links data from inpatient and outpatient encounters, allowing for longitudinal follow-up. In recent years, methods have been developed to estimate pregnancy intervals using codes for pregnancy outcomes and prenatal care that occur in claims data. These methods have been validated in linked clinical data[50]. This allows researchers to identify pregnancy outcomes, estimate the beginning of the pregnancy episode as dated from the last menstrual period (LMP), and then identify exposures that occur within the pregnancy

episode. Acute appendicitis and its operative treatment are also identifiable using diagnosis and procedure codes, allowing for the assessment of cases that do not undergo surgery[51].

Using the MarketScan database, in this study we aim to 1) describe trends in the use of nonoperative management for appendicitis during pregnancy, and 2) evaluate the trimester-specific incidence of adverse pregnancy outcomes compared to patients undergoing appendectomy.

Methods

Data Source

We performed a retrospective cohort study using the IBM® MarketScan Research Database, which includes administrative claims data for commercially insured individuals, using records from 2007-2019. The University of Washington Institutional Review Board determined this study to be exempt from review (STUDY00011093).

Identifying Pregnancy Intervals

We adapted a previously-validated algorithm by Matcho et al[50] for estimating pregnancy intervals from claims data. This algorithm uses International Classification of Diseases, 9th Revision (ICD-9) diagnosis codes and Current Procedural Terminology (CPT) procedure codes mapped to pregnancy concepts and outcomes, to which we added ICD-10 codes identified by Sarayani et al[52]. First, pregnancy outcomes were identified based on the presence of a diagnosis and/or procedure code for a birth outcome (see Appendix A). An estimated pregnancy start date (estimated last menstrual period or LMP date) was then determined. In ICD-10, the Z3A diagnosis code subgroup assigns the clinician's estimate of gestational age for all pregnancies greater than 8 weeks; if these codes were present, they were used to assign gestational age at the time of the pregnancy outcome, and the LMP date was calculated by subtracting this gestational age from the date of the outcome. These codes are not present in ICD-9, so the algorithm produces an estimate of gestational age and LMP date based on the average gestational age at which that outcome is observed to occur (i.e. 40 weeks gestation for a term delivery, 10 weeks gestation for spontaneous abortion, etc.). These are summarized in Appendix A. Earlier pregnancy outcomes, such as spontaneous abortion, have more uncertainty in their estimate of gestational age. If diagnosis codes for early pregnancy care that occurs at predictable gestational

ages (such as first trimester nuchal translucency ultrasound) were present, these were used to more precisely estimate the last menstrual period, and if diagnosis codes for pregnancy related care were found to occur prior to the estimated LMP, these were used to increase the estimated gestational age to include these episodes of care within the pregnancy episode.

While previous validation of this algorithm using linked clinical data has found it to correctly identify the pregnancy start date within 7 days in 90-97% of cases overall[50], it is less reliable for pregnancies that end in pregnancy loss, as these may occur before the first prenatal visit and have fewer diagnosis codes from which information about gestational age can be gleaned. Similarly, early pregnancy loss may often be managed at home without a clinical encounter; these pregnancies would not be captured under our algorithm. Finally, because of delayed recognition, codes for early pregnancy loss may not occur on that date when the outcome actually occurred, and multiple diagnosis codes may be present on separate calendar dates that refer to the same outcome. This method requires that codes for pregnancy loss occur at least 42 days apart to be considered separate pregnancy episodes; even with this definition there is potential overlap in pregnancy episodes ending in pregnancy loss. These cases are a minority of the overall cohort, and we do not expect this potential misclassification of pregnancy episode and outcome to be related to cases of appendicitis or to be differentially distributed between treatment groups.

Cohort Identification

Having identified unique pregnancy episodes, we then identified all diagnosis codes of appendicitis (see Appendix B) occurring within a pregnancy interval (i.e. between estimated LMP and pregnancy outcome date). The index date of appendicitis was defined as the first date on which a diagnosis code for appendicitis occurred. We excluded multiple gestation pregnancies because the gestational age algorithm assigns a preterm birth outcome to all of these. We also excluded ectopic and molar pregnancies and those ending in elective termination of pregnancy (ETOP), neither of which are suspected to be associated with appendicitis diagnosis or management. Ectopic pregnancies were defined as diagnosis codes for ectopic pregnancy followed procedure codes for surgical or medical treatment; ectopic pregnancy codes followed by codes for pregnancy care or a different birth outcome were considered not to be true ectopic pregnancies and were included in the sample.

Exposure and Outcome Definitions

An "index case" of appendicitis was defined as the first date on which an appendicitis diagnosis code occurred during a pregnancy interval (between 4 weeks GA and the pregnancy outcome, see Appendix B for full list of codes). Treatment of appendicitis was categorized as operative according to CPT codes for laparoscopic appendectomy, open appendectomy, and partial colectomy associated with appendicitis diagnosis. Each of these treatment modalities was assigned as the "initial" treatment if they occurred within 2 days of the index diagnosis. Nonoperative management of appendicitis was defined as a case of appendicitis without surgical intervention within 2 days. Because erroneous diagnosis codes are common in claims data[53], a stricter case definition for nonoperative management of appendicitis was applied. To be included, a case was required to 1) have a subsequent appendectomy code or 2) have an appendicitis code occurring on two separate dates and an outpatient prescription for antibiotics upon discharge or an inpatient stay of at least 4 days (the shortest described antibiotic course for intraabdominal infections) (Figure 1).

Outcomes of interest were adverse pregnancy outcomes, which included preterm birth (indicated by diagnosis codes for preterm birth or a live birth with estimated gestational age <37 and >= 24 weeks) and pregnancy loss, a composite outcome describing both stillbirth and spontaneous abortion as indicated by diagnosis codes. Birth events occurring before 24 weeks were classified as pregnancy loss.

Statistical Analysis

All analyses were performed using Stata 17 (College Station, TX), parametric and nonparametric hypothesis tests were used where appropriate, and p-values less than 0.05 were considered statistically significant. Confidence intervals were calculated for unadjusted point estimates using the *proportion* and *cs* commands. We calculated the incidence of APO after appendicitis diagnosis and presented these unadjusted proportions with confidence intervals for cases of appendicitis managed with and without surgery.

The associations between nonoperative management and APO may vary by gestational age in a nonlinear fashion, and understanding trimester-specific outcomes is of clinical interest, therefore APO were stratified by trimester of appendicitis occurrence. The uncertainty in

gestational age estimates and small sample size in the nonoperative treatment group precluded using gestational age as a continuous variable. This approach may still mask important variation in APO risk within trimesters. Because pregnancy loss and preterm birth are widely different outcomes in terms of their impact on maternal and fetal well-being, we also reported these outcomes separately.

We developed a multivariable logistic regression model to control for potential confounders of the association between treatment group and APO. The conceptual model describing these associations is presented in Figure 2. Because trimester-specific estimates of the association between nonoperative management and APO are of clinical interest, and because the association between nonoperative management and APO may vary by trimester, this was modeled with an interaction term between trimester of appendicitis occurrence and treatment group (Equation 1). Characteristics of appendicitis such as appendiceal abscess are likely related to both treatment assignment (cases with abscesses may be preferentially treated with antibiotics with or without percutaneous drainage)[21] and APO (appendicitis with abscess represents a more severe disease state than uncomplicated appendicitis). Additionally, the perceived risk of APO may influence decisions for surgery, therefore the presence of diagnosis codes indicating a high-risk pregnancy was included as a covariate. Similarly, we included diagnosis codes that have been previously associated with APO after surgery: pre-existing hypertension, history of C-section, history of preterm labor, cigarette smoking, alcohol use, illicit drug use, vaginitis and urinary tract infections during pregnancy, and cervical incompetence[54 3], including only those codes that occurred during the pregnancy interval. The full list of codes used to derive these variables is listed in Appendix B. The frequency of many of these codes was low (Table 1), likely because administrative claims data tend to only contain diagnoses directly relevant to the episode of care rather than a patient's full medical history. The low number of outcomes in each trimester limited the number of covariates that could be accommodated by the model without losing statistical power, therefore a binary variable was created to indicate the presence of any of these APO risk factors. This variable was not well correlated with the presence of high-risk pregnancy diagnosis codes (Spearman's correlation coefficient = 0.15), therefore both variables were used. Because exposures occurring later in pregnancy have greater potential to accumulate these codes, both the high-risk pregnancy variable and the pregnancy risk factor variable were modeled using interaction terms with trimester of exposure (Equation 1). The Charlson

comorbidity index [55] was used to identify the presence of additional comorbidities that may influence treatment decisions; this was also modeled as a binary variable indicating any score of 1 or greater. Trimester-specific odds ratios for nonoperative management were estimated using *lincom*, a Stata command that allows the linear combination of regression coefficients(Equation 2).

Equation 1: Logistic regression model for APO:

$$Logit(APO) = \beta_0 + \beta_1 nonoperative + \beta_2 trimester + \beta_3 nonoperative * trimester + \beta_4\ high\ risk\ pregnancy + \beta_5 high\ risk\ pregnancy * trimester + \beta_6 APO\ risk\ factor + \beta_7 APO\ risk\ factor * trimester + \beta_8 age + \beta_9 abscess + \beta_{10} peritonitis + \beta_{11} Charlson\ Index \geq 1$$

Equation 2: Trimester-specific effects:

$$\text{Odds ratio} = \exp(\beta_1 nonoperative + \beta_3 nonoperative * trimester)$$

Results

We identified 5,452 potential cases of appendicitis occurring during a pregnancy episode between 2007 and 2019 (Figure 2). Of these, 1,717 were excluded, 1,287 of these because they did not fulfill case definition criteria for appendicitis. In total, 3,735 cases of appendicitis during pregnancy were identified, 1,186 (32%) in the first trimester, 1,663 (45%) in the second, and 886 (24%) in the third. Patient characteristics are summarized in Table 1. Mean age at appendicitis diagnosis was 29 (SD 6.3), 555 (15%) had a Charlson Comorbidity Index of 1 or greater, 1,058 (28%) had diagnosis codes indicating a high-risk pregnancy, and 1,219 (33%) had at least one APO risk factor. On presentation, diagnosis codes for abscess and peritonitis were present in 6.8% and 18% of cases, respectively, with a greater proportion of codes for abscess in the nonoperative group (11% vs. 6.5%, $p = 0.002$).

Overall, 3,471 patients (93%) underwent appendectomy within 2 days of diagnosis, while 264 (7.1%) did not (Table 1). Nonoperative management was most common in the third trimester (11% of cases, compared to 6.0% in the first and 5.6% in the second, Table 2, $p<0.001$). Patients with appendicitis in the third trimester were also more likely to undergo open appendectomy, and were more likely to have diagnosis codes for abscess, peritonitis, and sepsis (Table 2).

The proportion of cases managed nonoperatively increased during the study period (Figure 4), from 4.5% in 2007 to 12% in 2019 ($p = 0.001$ for trend). Of those initially managed nonoperatively, 20% underwent surgery within 1 week, and 28% underwent surgery within 30 days. Of the patients who underwent surgery after initial nonoperative management, 58% underwent surgery during the same pregnancy, while 42% underwent surgery after conclusion of the pregnancy. Compared to those undergoing surgery, patients managed nonoperatively were slightly older, had greater gestational age at the time of appendicitis, were more likely to have diagnosis codes for abscess and sepsis (but not peritonitis), Charlson index >=1, and diagnosis codes for urinary tract infection during pregnancy.

Adverse Pregnancy Outcomes

Overall, the cumulative incidence of adverse pregnancy outcomes after diagnosis of appendicitis was 23%, with 8.3% of patients experiencing pregnancy loss and 15% preterm birth. APO occurred after 35% of appendicitis cases diagnosed in the first trimester, 18% of cases in the second, and 19% of cases in the third, although the type of APO varied significantly by

trimester. Pregnancy loss occurred in 21% of first trimester appendicitis cases, but only 3.4% of second trimester cases, and 0.2% of third trimester cases, while preterm birth occurred after 14% of first trimester cases, 15% of second trimester cases, and 19% of third trimester cases. The proportions of these outcomes by treatment group are summarized in Table 3 and Figures 4-6. In the unadjusted analysis, the incidence of all APO and pregnancy loss were both significantly higher for nonoperative management in the second trimester; in the first and third trimesters, there was no statistically significant difference between the surgical and nonoperative management groups. There was no significant difference in preterm birth incidence between surgery and nonoperative management in any trimester. Among patients initially managed nonoperatively who underwent surgery within 7 days of diagnosis (likely "failed" nonoperative management), APO were similar to the nonoperative cohort overall (Table 4).

The adjusted, trimester-specific estimates of APO risk associated with nonoperative management are summarized in Table 5 and Figure 7. Adjusted for maternal age, Charlson comorbidity index >1, codes for abscess, peritonitis, sepsis, high-risk pregnancy, and presence of APO risk factors, the odds of adverse pregnancy outcomes were significantly higher for nonoperative management in the second trimester, relative to surgery in the second trimester (OR 1.75, 95% CI 1.09-2.81, $p = 0.03$). There was no statistically significant difference in the odds of adverse pregnancy outcomes in the first and third trimesters between the surgical and nonoperative groups. All adjusted odds ratios and confidence intervals were similar to the unadjusted analysis (Figure 7).

Discussion

In this retrospective study of appendicitis in pregnancy using administrative claims, nearly one in four patients experienced an adverse pregnancy outcome after acute appendicitis, with the highest rates of APO occurring after appendicitis in the first trimester. Nonoperative management of appendicitis was associated with similar outcomes to surgery in the first and third trimesters, however we identified a significantly higher incidence of APO among those managed without surgery in the second trimester; this appeared to be influenced by a higher incidence of pregnancy loss among these patients.

This is the largest study to date that evaluates the risks of APO associated with nonoperative management of appendicitis in pregnancy. Historically, appendicitis was

considered a surgical emergency during all trimesters of pregnancy. Yet even in the 21st century, the rate of negative appendectomy in pregnancy remains high[14], and the success of nonoperative management in nonpregnant adults has led to significant patient interest in this option. Pregnant patients have been excluded from randomized trials of nonoperative management for appendicitis, and there are no guideline recommendations supporting the use of this strategy in pregnancy. Despite this, in this study we observe a significant rise in the incidence of nonoperative management of appendicitis in pregnancy over the past 12 years, highlighting the need for ongoing research to evaluate the outcomes of this strategy.

The limitations discussed below preclude any strong conclusions about the comparative effectiveness of nonoperative management vs. surgery. However, we do observe a statistically significant increased risk of APO after nonoperative management in the second trimester. The point estimates for APO risk also favored surgery in the first and third trimesters as well, however these associations were smaller, and confidence intervals were wide, because of the small sample sizes in the nonoperative cohort. Based on these findings, for patients with a strong preference to avoid surgery, this study supports the use of nonoperative management as an alternative to surgery in the first and third trimesters, recognizing that the possibility of an increased APO risk with this approach has not yet been ruled out.

There is significant potential confounding in the association between appendicitis treatment and APO by disease severity and patient characteristics (Figure 3). Nonpregnant adults with appendiceal abscess are often treated nonoperatively [20 21], and it is likely that pregnant individuals are treated similarly despite the lack of evidence-based guideline recommendations. Because appendicitis with abscess represents a more severe disease state, it can be expected to be associated with increased risk of APO as well. We therefore included appendiceal abscess as a potential confounder in our model, along with peritonitis and sepsis. Similarly, a patient's perceived baseline risk of APO, based on gestational age and underlying medical conditions, may also influence the decision to pursue nonoperative management vs. surgery. After controlling for these factors, the observed associations between nonoperative management and APO were unchanged, along with their confidence intervals. While this suggests that there was no significant confounding by these measured covariates, there remains potential for residual confounding by unmeasured confounders, as discussed below.

In observational studies of pregnancy outcomes, estimates of pregnancy loss incidence are strongly influenced by the gestational age at which exposure occurs or follow-up begins[56 57 58]. Because pregnancy loss most commonly occurs in the early 1st trimester and its incidence steadily decreases with gestational age, cohorts that are followed from earlier gestational ages have higher estimates of pregnancy loss than cohorts that are enrolled later[59]. This has been a major limitation of prior studies of appendicitis in pregnancy; for example, the strong association between laparoscopic surgery and pregnancy loss reported by McGory et al[14] is likely confounded by gestational age, since laparoscopic appendectomy tends to be performed earlier in pregnancy than open appendectomy[33 29]. As a result, it is problematic to compare "overall" rates of APO between cohorts, if the gestational age distribution is different or unknown.

While there are several observational studies with large sample sizes that have evaluated the association between appendicitis and preterm birth, this is only one of two important outcomes of a pregnancy. Because pregnancy loss is a competing risk with preterm birth, excluding these cases is likely to result in biased estimates of preterm birth. Furthermore, pregnancy loss is an important outcome of interest to patients, and a complete understanding of the risks of both outcomes is key to guiding treatment decisions and counseling patients.

Cases of appendicitis were not evenly distributed across pregnancy; the greatest proportion were diagnosed in the second trimester, followed by the first trimester, while the third trimester accounted for only half as many cases as the second. This pattern has been observed in several other studies[60 61], and a satisfying explanation has yet to be identified. Diagnosis of appendicitis in the third trimester is more challenging, and it is possible that mild cases are self-resolving without ever being diagnosed; the higher proportion of abscess, peritonitis, and sepsis we observed in third trimester cases is consistent with this possibility[62]. Alternatively, late pregnancy is associated with a state of immune tolerance[63], which may influence the pathogenesis of appendicitis.

Limitations

This study has several important limitations inherent to the data source and sample, the gestational age algorithm, and the ascertainment of exposures and outcomes.

Limitations related to the sampling frame

The MarketScan database only contains insurance claims data on patients with employer-provided commercial health insurance, yet 42% of pregnancies in the United States are covered by Medicaid[64]. This limits the generalizability of our findings describing patterns of care and outcomes, as these may be different among patients without commercial insurance. Similarly, while the experience of systemic racism is strongly associated with adverse pregnancy outcomes[65 66], with non-Hispanic Black patients experiencing a two-fold greater risk of preterm birth than non-Hispanic White patients[67], we were unable to evaluate this due to the lack of demographic data in MarketScan. Because successful treatment of appendicitis relies on proper evaluation, prompt initiation of therapy, and monitoring for treatment failure and complications, it is important to understand who has access to these elements of care and who does not.

Despite being derived from a data source containing 40 million patients per year[68], our study may be underpowered to detect significant differences in APO between operative and nonoperative groups, due to the low observed rate of nonoperative management, the uncommon occurrence of appendicitis in pregnancy overall, the mismatched alignment between the sampling frame and pregnancies as described above, and the need to control for the influence of gestational age. A post-hoc power calculation suggests that at least 1500 patients per group would be required for an unadjusted analysis to detect the differences of 4-5 percentage points in APO risk we observed in the first and third trimesters with 80% power.

Limitations associated with the gestational age algorithm

Many cases of pregnancy loss do not result in a healthcare encounter and are subsequently not captured in claims data- these patients would not be included in this study. While this may bias our estimates of pregnancy loss incidence after appendicitis, this bias is unlikely to be differential between the surgery and nonoperative management groups.

The uncertainty in the algorithm for estimating gestational age from diagnosis and procedure codes is another major limitation of our study. Accordingly, particularly for cases of appendicitis in early pregnancy (earlier than 8 weeks GA), there is uncertainty in whether that patient was in fact pregnant at the time of appendicitis. In a similar vein, the date on which a claim for pregnancy loss occurs may not be the true outcome date. This would lead to inaccurate estimation of the pregnancy interval as described above; if estimated LMP is later than true LMP, cases of appendicitis very early in the pregnancy could be excluded, which would lower estimates of the incidence of pregnancy loss. Similarly, we would not expect the magnitude of this misclassification to be differential between surgery and nonoperative management groups, although it could partially explain the differences in appendicitis incidence observed in the different trimesters.

Misclassification of exposure and outcome

The use of insurance claims data to identify clinical concepts is known to introduce misclassification of exposure and outcome[69 70]. In this study, misclassification may have introduced both conservative and anticonservative bias into comparisons of APO between exposure and treatment groups. There is uncertainty in the diagnosis of appendicitis as well as the timing and nature of adverse pregnancy outcomes. While procedure codes for appendectomy are more likely to be accurate, due to the financial incentive for providers to accurately code procedural care[71], the reliability of diagnosis codes in claims data is less certain. In particular, in a patient population with a high negative appendectomy rate [14], a considerable proportion of the operative cohort may not have truly had appendicitis, and the accuracy of claims data for identifying negative appendectomy is low [71]. However, given that this represents real world treatment patterns, and because APO associated with negative appendectomy may be one of the harms associated with a low threshold to operate for suspected appendicitis[72], it is helpful to know the outcomes associated with appendectomy.

There may be misclassification of appendicitis diagnosis in the nonoperative cohort as well. We used a conservative case definition based on appendicitis care patterns to minimize the bias introduced by false appendicitis diagnoses, resulting in a proportion of nonoperative management that is similar to that observed among nonpregnant adults[51]. As a result, the proportion of cases managed nonoperatively may be underestimated in this study, although this

would be unlikely to bias the observed increasing trend in nonoperative management over time. Sensitivity analysis demonstrates that without this case definition, the proportion of nonoperative management is implausibly high at 33% of cases (Supplementary Table 2), with higher incidence of APO in first trimester cases compared to the surgical cohort, but not in second or third trimester cases.

While we describe treatment groups as "operative" and "nonoperative" for simplicity's sake, claims data do not provide information about treatment intent, which is key to using these findings to inform treatment choice. For example, all cases that underwent surgery within 2 days were considered "operative management," and we are unable to distinguish those who underwent a trial of nonoperative management and failed. Because those who fail nonoperative management and require surgery may have more severe appendicitis than those managed successfully without surgery, this would bias outcomes in favor of the nonoperative management group. To investigate this possibility, we evaluated the risk of APO among those in the nonoperative cohort who underwent surgery within 7 days of diagnosis (consistent with "failed" nonoperative management); their outcomes were similar to the nonoperative cohort overall (Table 4).

While we attempted to control for measures of appendicitis severity and baseline APO risk, there remains significant potential for residual confounding in this study. We used diagnosis codes for appendiceal abscess, peritonitis, and sepsis as potential confounders, however it is unknown how accurate these codes are in administrative data. While some authors using claims data to evaluate nonoperative management of appendicitis have restricted their sample to "simple appendicitis" [51], we avoided this strategy, because of concerns about the reliability of appendicitis diagnosis codes, and because this would reduce the generalizability of the study, given the high rate of perforated appendicitis observed in pregnant patients compared to nonpregnant adults. The reliability of diagnosis codes for APO risk factors is similarly unknown. Misclassification of these covariates based on diagnosis codes may result in residual confounding that is not controlled for in our regression model, and also decrease this study's power to detect a significant difference between treatment groups. Finally, there is likely unmeasured confounding due to elements of disease severity that we could not ascertain via claims data, including imaging findings (appendicolith, appendiceal diameter, evidence of

perforation and phlegmon) and clinical characteristics (vital signs, pain scores) that may have been associated with both treatment choice and APO.

Misclassification of pregnancy outcomes is another important limitation of this study. We excluded pregnancies ending in elective termination of pregnancy (ETOP) as it is not likely to be related to appendicitis and its treatment, however there is uncertainty about the accuracy of using claims data to distinguish ETOP from miscarriage[50]. Sensitivity analysis with a more restrictive definition of ETOP (only cases with codes specific to ETOP, such as Z33.2 "Encounter for elective termination of pregnancy" were assigned this outcome, otherwise all were classified as miscarriage) demonstrated a slightly higher estimate of pregnancy loss, with no change in the primary outcome.

Conclusion

Despite these limitations, this study represents a significant advance in our understanding of APO after appendicitis and its management. While a causal relationship cannot be inferred between non-operative management and APO compared to operative management given the potential for unmeasured confounding, we demonstrate that the observed incidence of APO was similar in both groups in the first and third trimesters, and higher in the nonoperative group in the second trimester. The adjusted analysis suggests that this difference is not attributable to measured confounders, however further research is necessary to clarify this relationship.

This study also highlights the challenges inherent in assessing pregnancy outcomes in observational data, and demonstrates the importance of accounting for gestational age at the time of exposure.

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Table 1: Patient Characteristics	**Surgery (n = 3471)**	**Nonoperative Management (n = 264)**	**p**
Maternal age (mean, SD)	29 (6.2)	30 (7.1)	0.03
Trimester of appendicitis (n, %)			
1	1115 (94%)	71 (6.0%)	<0.001
2	1570 (94%)	93 (5.6%)	-
3	786 (89%)	100 (11%)	-
Abscess	224 (6.5%)	30 (11%)	0.002
Peritonitis	642 (19%)	39 (15%)	0.13
Sepsis	35 (1.0%)	7 (2.7%)	0.015
Charlson Index >=1	504 (15%)	51 (19%)	0.04
High-risk Pregnancy Code	972 (28%)	86 (33%)	0.11
Any Pregnancy Risk Factor	1122 (32%)	97 (37%)	0.14
Obesity	338 (9.7%)	24 (9.1%)	0.73
Pre-existing hypertension	233 (6.7%)	18 (6.8%)	0.95
Tobacco abuse during pregnancy	179 (5.2%)	10 (3.8%)	0.33

Alcohol abuse during pregnancy	10 (0.3%)	2 (0.8%)	0.19
Drug abuse during pregnancy	35 (1.0%)	3 (1.1%)	0.84
Previous fetal loss	53 (1.5%)	3 (1.1%)	0.61
Previous C-section	57 (1.6%)	4 (1.5%)	0.88
Previous preterm labor	16 (0.5%)	2 (0.8%)	0.50
Urinary tract infection during pregnancy	427 (12%)	47 (18%)	0.010
Vaginitis during pregnancy	36 (1.0%)	5 (1.9%)	0.20
Sickle cell anemia	3 (0.1%)	0 (0%)	0.63

Table 2: Appendicitis Management and Severity by Trimester	**Trimester 1**	**Trimester 2**	**Trimester 3**	**p**
Management Type				
Nonoperative	71 (6.0%)	93 (5.6%)	99 (11%)	<0.001
Laparoscopic appendectomy	954 (80%)	1208 (73%)	318 (36%)	
Open appendectomy	161 (14%)	362 (22%)	469 (53%)	
Abscess	80 (6.7%)	92 (5.5%)	82 (9.3%)	0.002
Peritonitis	199 (17%)	294 (18%)	188 (21%)	0.026
Sepsis	7 (0.6%)	19 (1.1%)	16 (1.8%)	0.034

Table 3
Pregnancy Outcomes by Treatment Group, Unadjusted

Adverse Pregnancy Outcomes	**Surgery** n (%)	**Nonoperative Management** n (%)	**Relative Risk** (95% CI)	**Risk Difference** (95% CI)
Trimester 1 Appendicitis (n = 1,186)	381 (34%)	28 (39%)	1.15 (0.86-1.56)	5% (-6-17%)
Trimester 2 Appendicitis (n = 1,663)	279 (18%)	26 (28%)	**1.57 (1.12-2.22)***	**10% (1-20%)***
Trimester 3 Appendicitis (n = 886)	146 (19%)	23 (23%)	1.24 (0.84-1.82)	4% (-4-13%)
Pregnancy Loss				
Trimester 1 Appendicitis (n = 1,186)	228 (20%)	21 (30%)	1.45 (0.99-2.11)	9% (-2-20%)
Trimester 2 Appendicitis (n = 1,663)	49 (3%)	8 (9%)	**2.76 (1.34-5.65)***	**5% (0-11%)***
Trimester 3 Appendicitis (n = 886)	1 (0.1%)	1 (1.0%)	7.86 (0.5-124)	1% (-0.1-28%)

Preterm Birth				
Trimester 1 Appendicitis (n = 1,186)	153 (14%)	7 (10%)	0.72 (0.35-1.47)	-4% (-11-3%)
Trimester 2 Appendicitis (n = 1,663)	230 (15%)	18 (19%)	1.32 (0.86-2.03)	5% (-4-13%)
Trimester 3 Appendicitis (n = 886)	145 (18%)	22 (22%)	1.19 (0.80-1.77)	4% (-5-12%)

***p < 0.05**

Table 4
Pregnancy Outcomes Associated With Failed Nonoperative Management

	Adverse Pregnancy Outcomes (n, %)		
	Surgery within 7 days n = 53	**No surgery within 7 days n = 211**	**p**
Trimester 1 Appendicitis (n = 71)	5 (45%)	23 (38%)	0.66
Trimester 2 Appendicitis (n = 83)	5 (33%)	21 (27%)	0.61
Trimester 3 Appendicitis (n = 100)	7 (26%)	16 (22%)	0.67

Table 5 Adjusted Odds of APO After Nonoperative Management Compared to Surgery

	Adjusted OR (95% CI)
Trimester 1 Appendicitis (n = 1,186)	1.27 (0.77-2.08)
Trimester 2 Appendicitis (n = 1,663)	**1.75 (1.09-2.81)***
Trimester 3 Appendicitis (n = 886)	1.32 (0.80-2.18)

Full model parameters are displayed in Supplementary Table 1

Figures

Figure 1: Appendicitis Case Definition

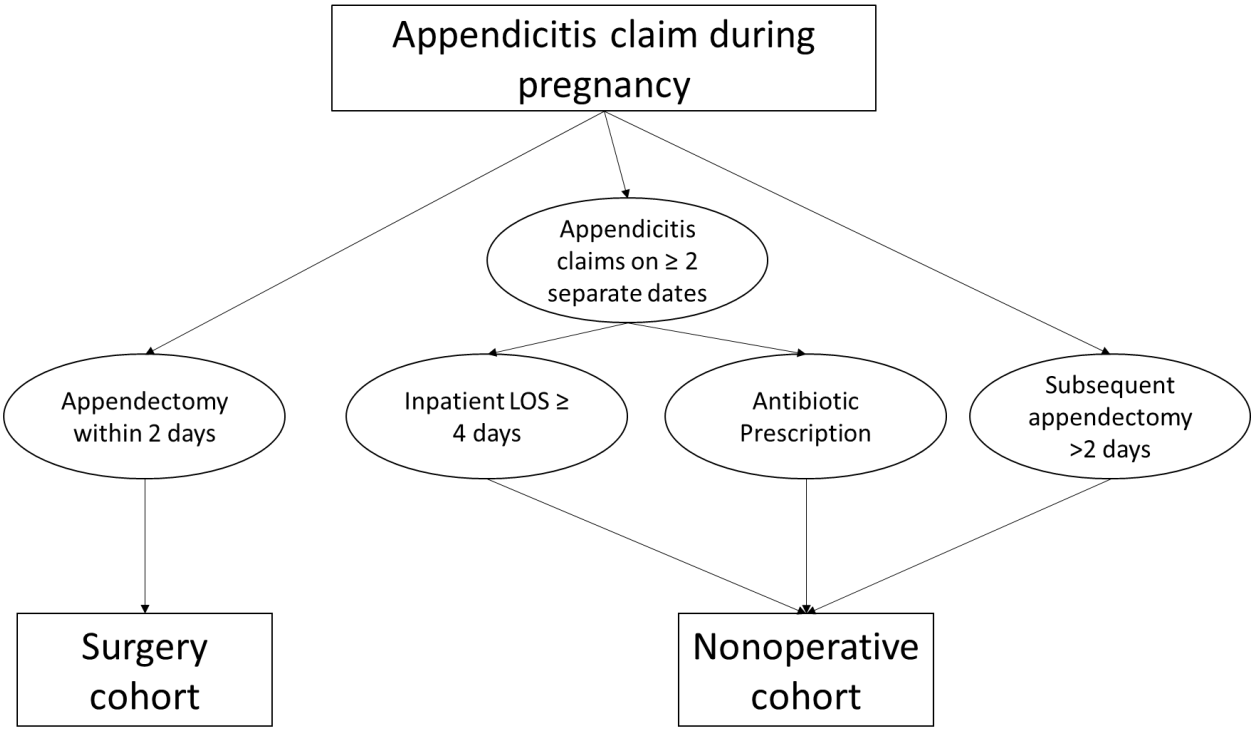


Figure 2: Study Inclusion/Exclusion Criteria

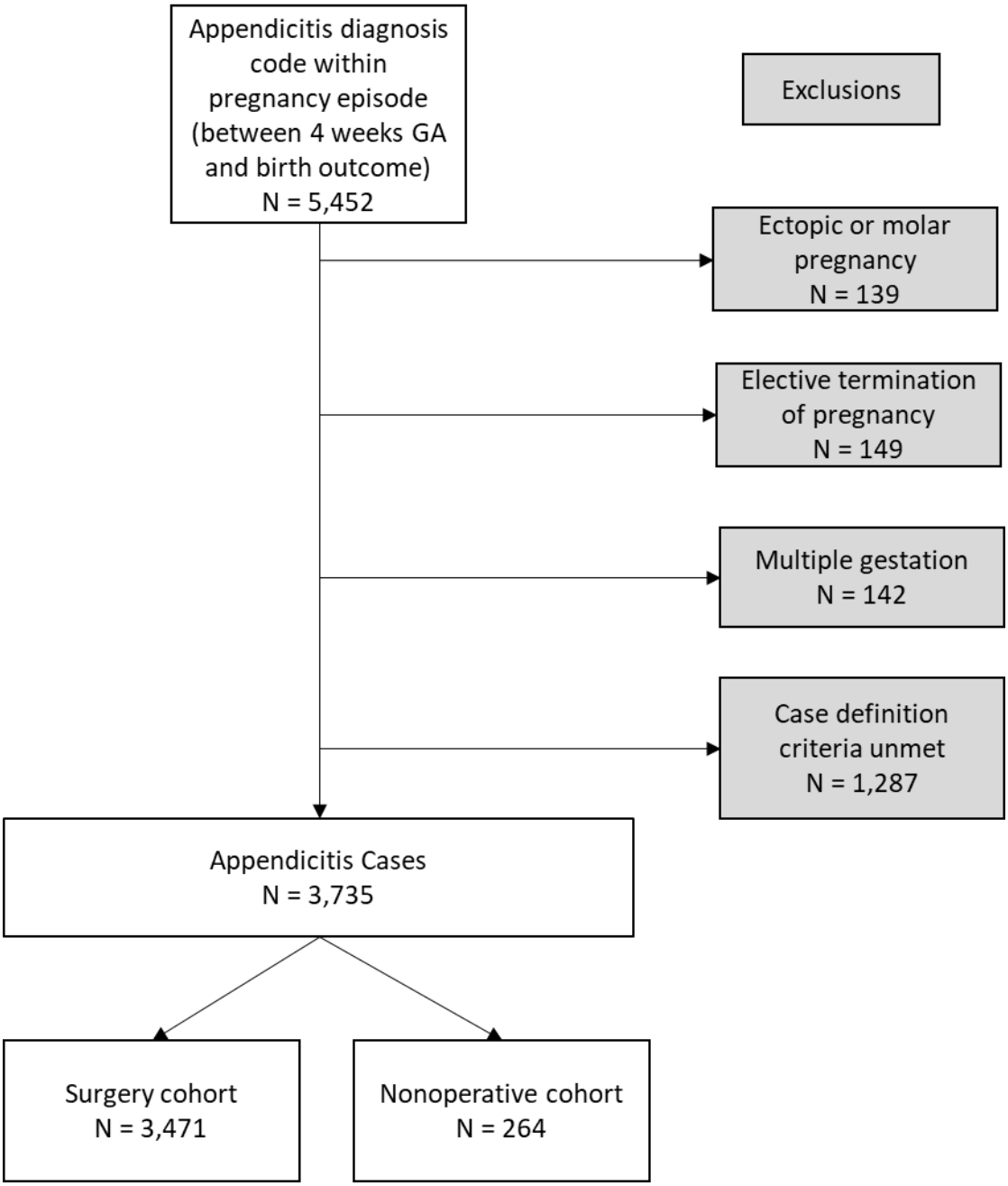
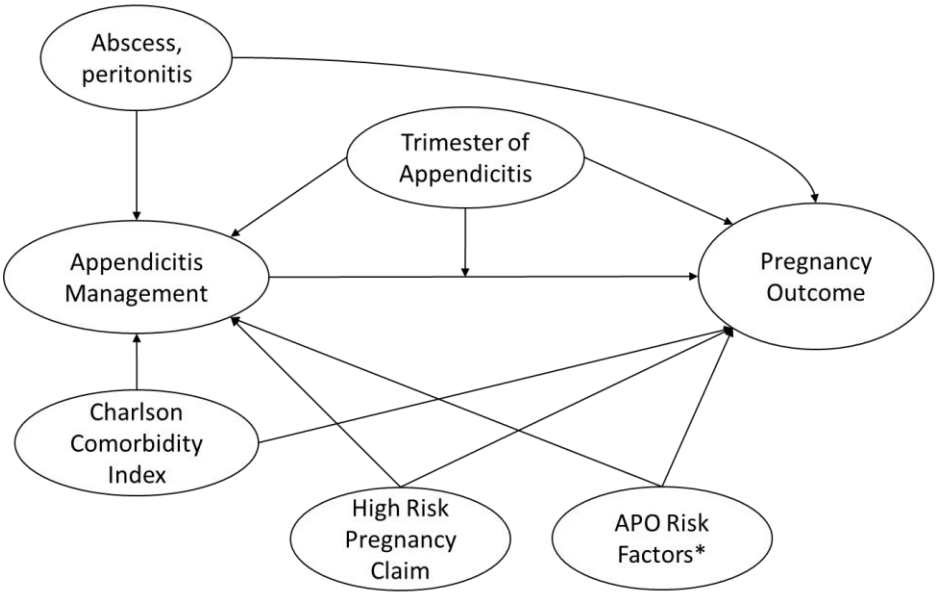


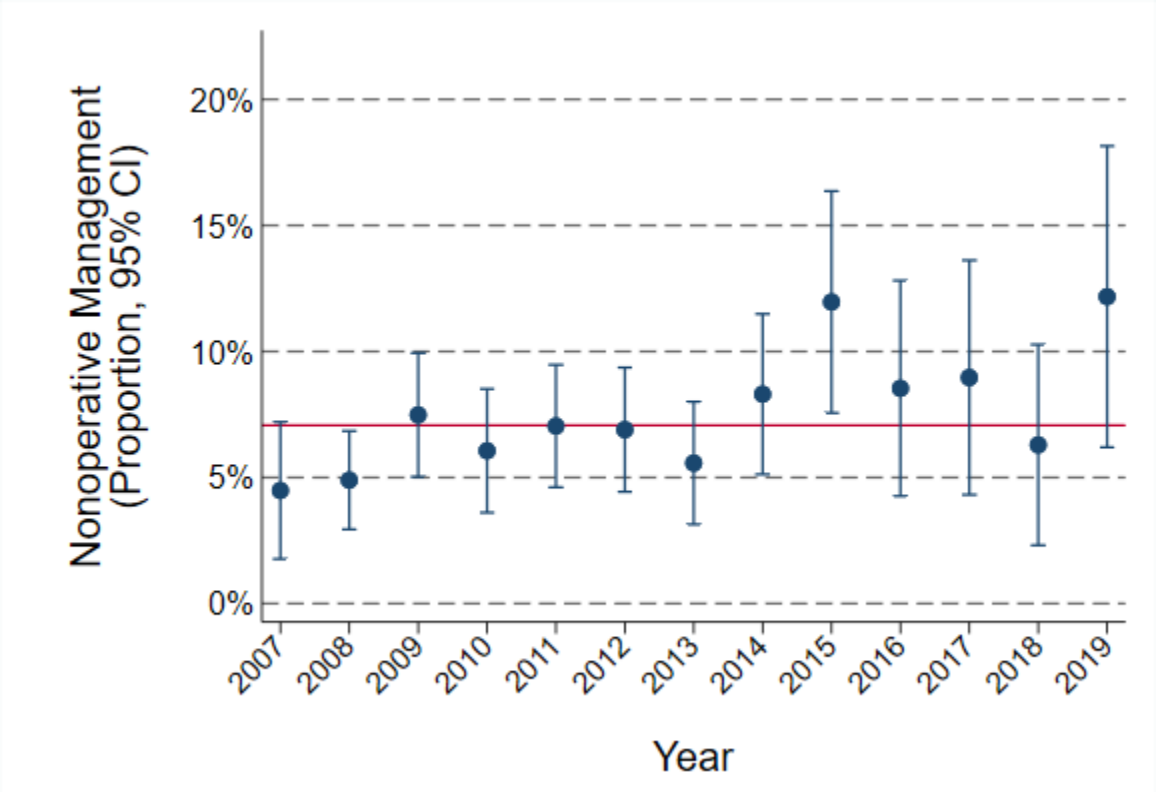
Figure 3: Conceptual model describing the association between appendicitis management and adverse pregnancy outcomes



Unmeasured Confounders
- Clinical Severity
- Systemic racism
- Healthcare access
- Wealth
- Family support
- Environmental exposures
- Education level
- Inter-pregnancy interval

APO Risk Factors
- Obesity
- Pregnancy complicated by alcohol, tobacco, or drug abuse
- Urinary tract infection
- Previous fetal loss
- Pre-existing hypertension
- Sickle-cell anemia
- Prior C-section
- Cervical incompetence
- Previous preterm labor
- Vaginitis

Figure 4: Trend in nonoperative management over time



Overall proportion of nonoperative management during the study period was 7.1% (red line). Nonparametric test of trend p = 0.001.

Figure 5

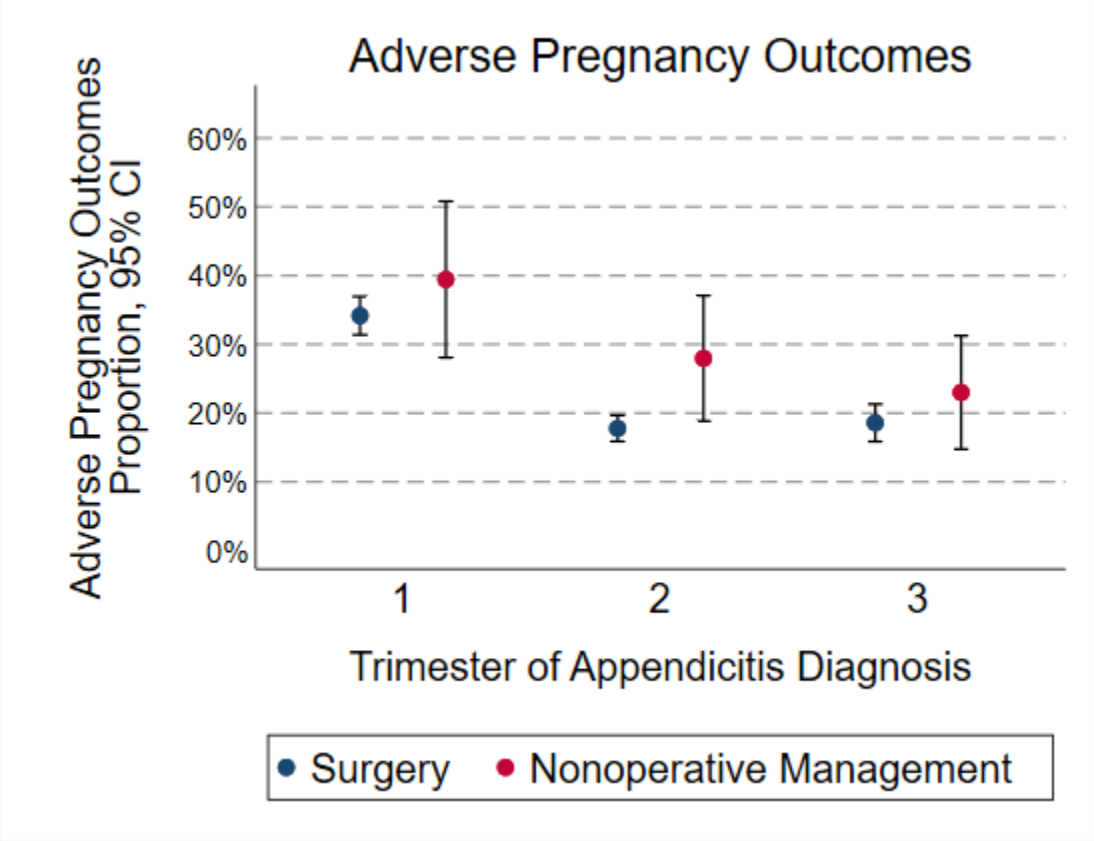

Adverse Pregnancy Outcomes
Adverse Pregnancy Outcomes
Proportion, 95% CI
60%
50%
40%
30%
20%
10%
0%
1
2
3
Trimester of Appendicitis Diagnosis
Surgery
Nonoperative Management

Figure 6

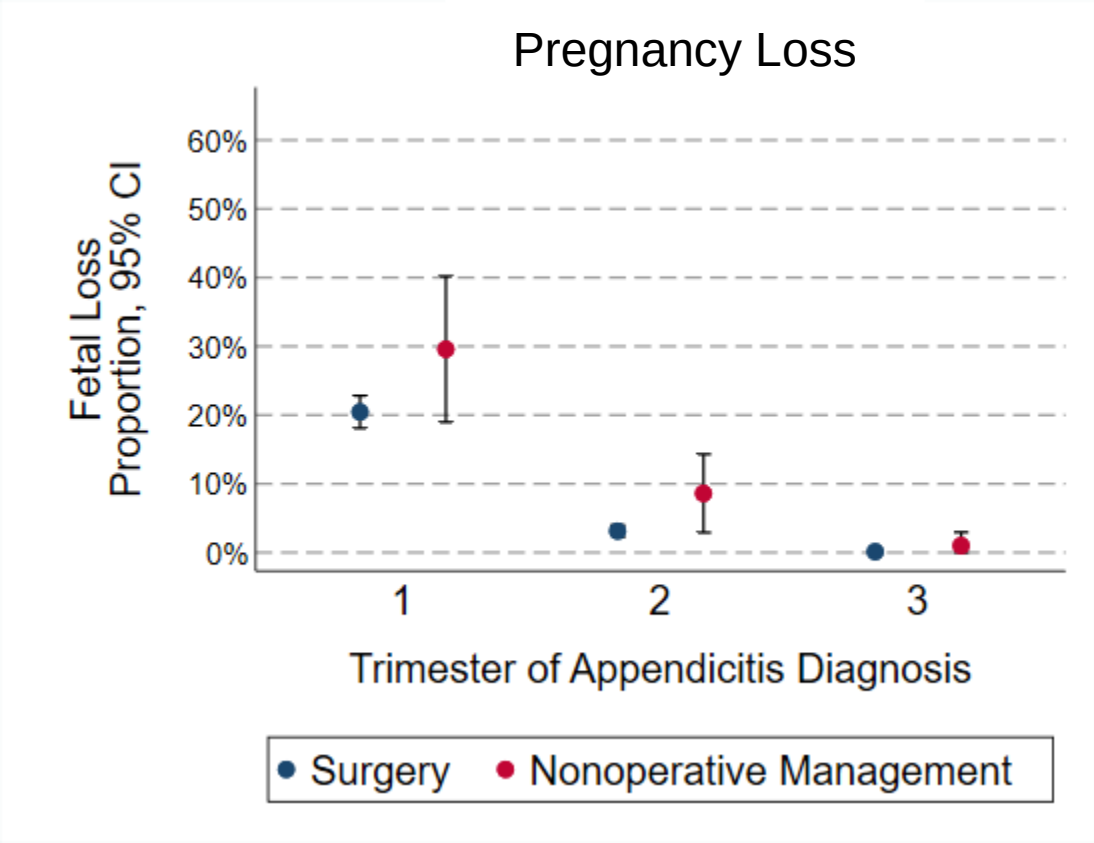

Pregnancy Loss
Fetal Loss Proportion, 95% CI
60%
50%
40%
30%
20%
10%
0%
1
2
3
Trimester of Appendicitis Diagnosis
Surgery
Nonoperative Management

Figure 7

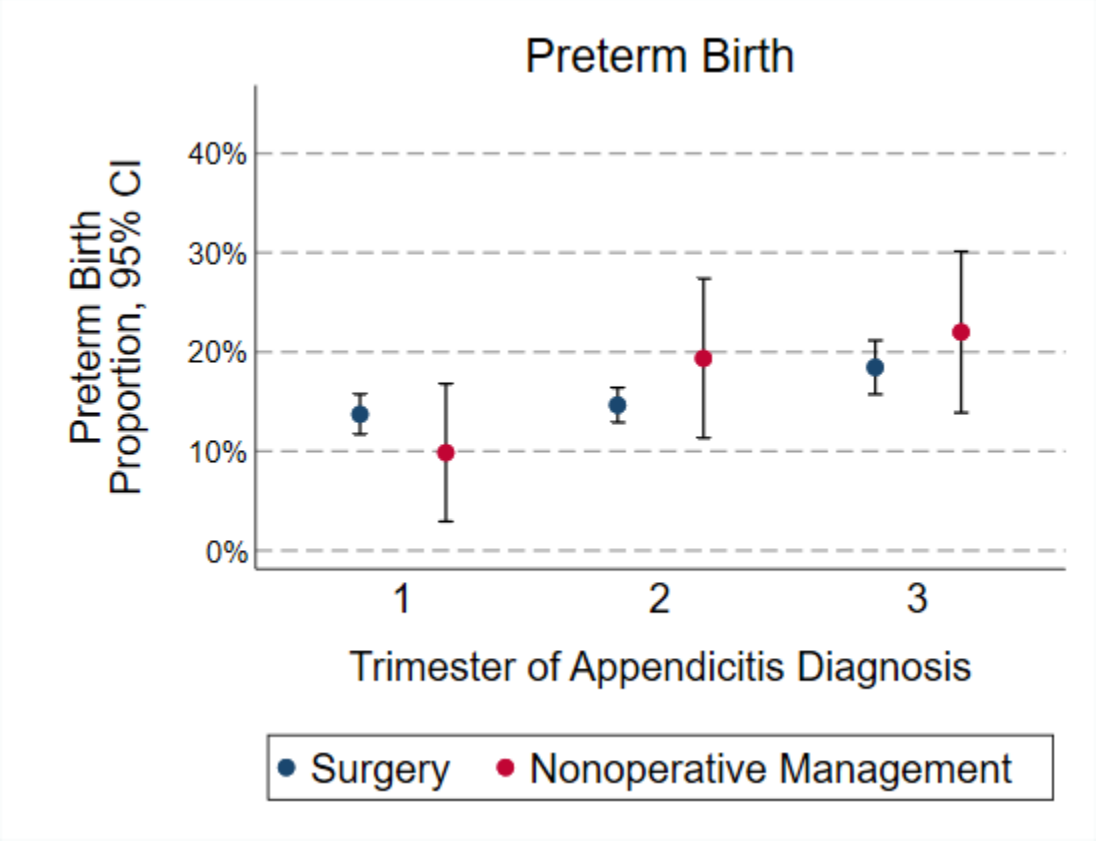
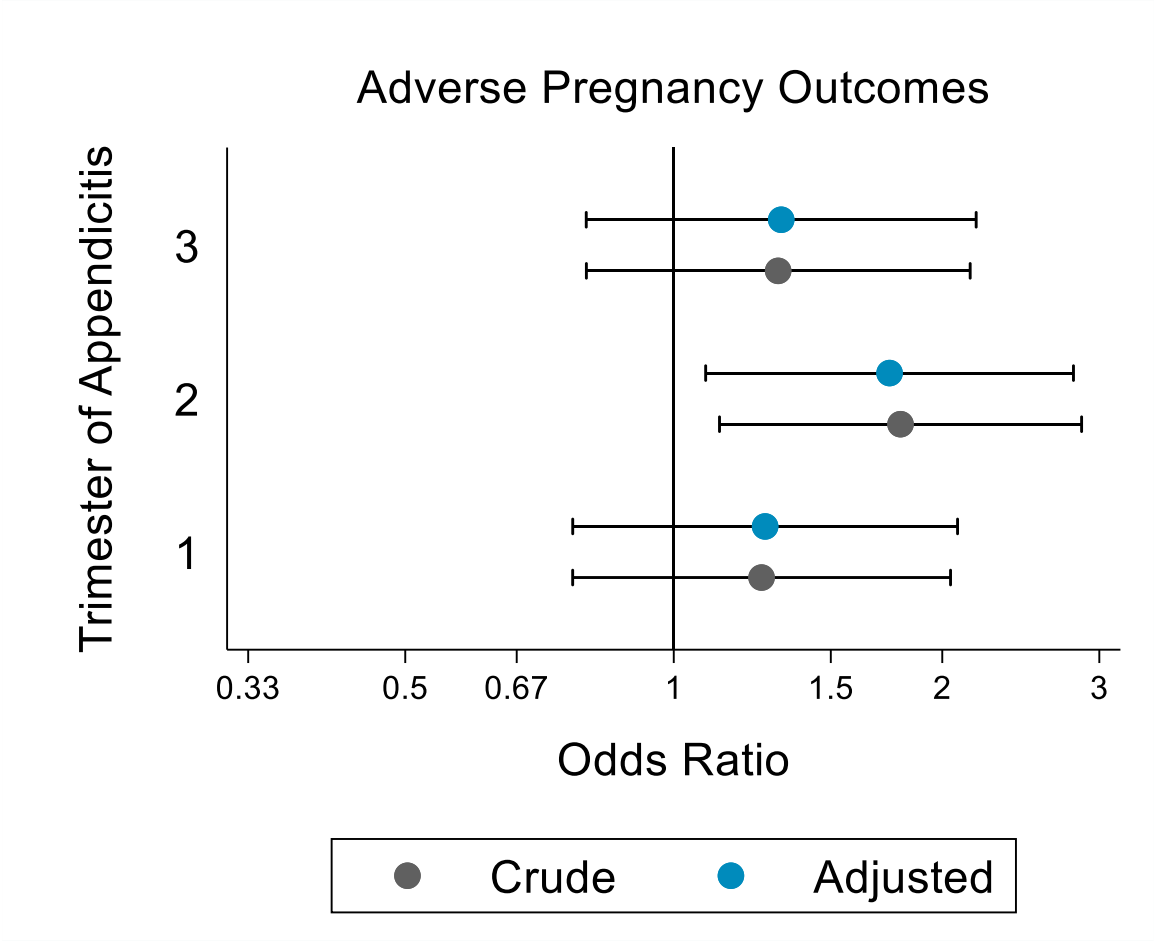

Preterm Birth
Preterm Birth
Proportion, 95% CI
40%
30%
20%
10%
0%
1
2
3
Trimester of Appendicitis Diagnosis
Surgery
Nonoperative Management

Figure 8



Full model parameters are listed in Supplementary Table 1.

Supplementary Table 1
Multivariable Logistic Regression Model for APO

	OR	95% CI	p
Nonoperative Management	1.26	0.77-2.09	0.35
Trimester 2 Appendicitis	0.29	0.23-0.37	<0.0005
Trimester 3 Appendicitis	0.33	0.25-0.45	<0.0005
Nonoperative Management x Trimester 2	1.33	0.68-2.71	0.38
Nonoperative Management x Trimester 3	1.03	0.50-2.07	0.50
Age	0.99	0.98-1.01	0.45
Abscess	1.19	0.90-1.64	0.20
Peritonitis	1.54	1.27-1.88	<0.0005
Sepsis	2.79	1.48-5.26	<0.001
Charlson Index >=1	1.10	0.90-1.38	0.33
High-risk Pregnancy code	0.66	0.49-0.88	0.005
High-risk x Trimester 2	2.05	1.38-3.04	<0.0005
High-risk x Trimester 3	1.80	1.13-2.90	0.014
Pregnancy Risk Factor	0.98	0.75-1.27	0.88
Risk Factor x Trimester 2	1.48	1.04-2.17	0.03
Risk Factor x Trimester 3	1.32	0.84-2.07	0.22
Constant	0.60	0.41-0.89	-

Supplementary Table 2
Sensitivity Analysis: Nonoperative Management Case Definition

Estimate	Primary Analysis (No Surgery Within 2 Days)	No Surgery Within 4 Days	No Case Definition Requirements
Nonoperative Management (%, 95% CI)	7.1% (6.3-7.9%)	6.1% (5.4-6.9%)	31% (30-32%)
APO After Nonoperative Management (Unadjusted OR, 95% CI)			
Trimester 1 Appendicitis	1.25 (0.77-2.04)	1.27 (0.76-2.12)	**1.35 (1.08-1.70)***
Trimester 2 Appendicitis	**1.80 (1.13-2.87)***	**1.73 (1.06-2.84)***	1.17 (0.92-1.49)
Trimester 3 Appendicitis	1.31 (0.80-2.15)	1.07 (0.60-1.89)	1.02 (0.77-1.35)

Supplementary Table 3
Sensitivity Analysis: Elective Termination of Pregnancy Case Definition

Estimate	Primary Analysis (Inclusive ETOP definition)	Restrictive ETOP definition
Nonoperative Management (%, 95% CI)	7.1% (6.3-7.9%)	7.1% (6.4-8.0%)
Pregnancy Loss, all trimesters (%, 95% CI)	8.2% (7.4-9.2%)	9.7% (8.8-11%)
APO After Nonoperative Management (Unadjusted OR, 95% CI)		
Trimester 1 Appendicitis	1.25 (0.77-2.04)	1.14 (0.71-1.83)
Trimester 2 Appendicitis	**1.80 (1.13-2.87)***	**1.73 (1.08-2.78)***
Trimester 3 Appendicitis	1.31 (0.80-2.15)	1.31 (0.80-2.15)

Appendix A: See attached Excel file of all pregnancy-related codes used to determine pregnancy outcome and gestational age

Appendix B: See attached Excel file of all codes used to derive all exposure, treatment, and risk factor variables