



Appendicitis in the Pregnant Patient: Risk, Diagnosis, Management, and Outcomes

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Abstract

Purpose of Review To evaluate outcomes related to operative and non-operative management of appendicitis during pregnancy

Recent Findings Several studies have evaluated preoperative laboratory values to improve the accuracy of diagnosis of appendicitis in the pregnant patient. Further, the Alvarado score appears to be accurate in the pregnant patient. Operative management continues to prevail in comparison to non-operative management consisting of antibiotics alone. Risks of preterm labor, fetal loss, and appendiceal perforation appear to be higher. Despite this, several recent studies have utilized MRI imaging to better stratify which patients may be better candidates for non-operative management. Additional future studies are still needed.

Summary Appendicitis remains a common non-obstetric reason for abdominal pain during pregnancy. Perforation can result in poor outcomes. Operative management appears to be safe and is commonly utilized. Laparoscopy is a safe approach for surgeons who can perform laparoscopic appendectomy. Additional study is required to determine the role of non-operative management in the pregnant patient.

Keywords Appendicitis · Pregnancy · Incidence · Complications · Diagnosis · Outcomes

Introduction

Appendicitis in the pregnant patient can be a disease with a wide range of severity. A recent estimation demonstrated that the incidence of appendicitis is increasing, especially in women [1]. Since appendicitis occurs throughout all age ranges, this disease can impact pregnant women and can be one of the most common non-obstetric emergencies occurring at a rate of 0.2–1% [2, 3]. Due to the broad spectrum of appendicitis severity, management can be diverse. For patients with uncomplicated appendicitis, antibiotics alone has been shown to be effective [4]. Appendicitis can also be conventionally managed via surgical resection of the appendix. This can be performed using a minimally invasive laparoscopic approach which has been shown to be equitable to open surgery for several important patient centered outcomes including reduction in pain, duration of hospital stay, and reduced wound related complications [5].

Because the diagnosis of appendicitis can often clinically mimic a variety of other disorders [6], it is important to understand the physiologic and anatomic alterations of pregnancy in order to accurately diagnose the condition. Quick, decisive, and accurate management of appendicitis in the pregnant patient is necessary in order to prevent perinatal and maternal complications [7–9]. Further, any delay in diagnosis can potentially result in perforation of the appendix and increase the risk of premature delivery and potential fetal mortality [10•, 11].

Improving the recognition and accurate diagnosis of appendicitis for pregnant patients can potentially augment

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maternal and fetal outcomes. By defining the severity of the appendicitis using through physical exam, laboratory evaluation, and focused cross-sectional imaging, the decision to provide non-operative or operative management can be better informed despite limited data in pregnant patients. Understanding the advantages and limitations of each modality and the impact on both mother and fetus will help better define the optimal treatment dependent on a variety of clinical factors including gestational age, comorbidity profile of the mother, and acute physiologic changes.

Incidence and Risk of Appendicitis during Pregnancy

Several studies have utilized population-based cohort data to estimate the incidence of appendicitis in pregnant women. In England, among women aged 15–44 years of age, the absolute rate of appendicitis was 35% lower in pregnant women compared to those who were not pregnant [12]. The risk of appendicitis was highest during the first and second trimesters decreasing during the third trimester [12]. In the post-partum period, however, the rates equalized to non-pregnant women after adjusting for age and time [12]. Interestingly, among those who underwent an operation, the negative appendectomy rates were greatest in pregnant women during their second and third trimesters [12]. Similarly, Moltubak et al. demonstrated decreased rates of appendicitis in pregnant women compared to non-pregnant women and that the rates of appendicitis after pregnancy increased to similar rates compared to non-pregnant women [13••]. Further, the authors found that the rates of negative appendectomy decreased during the study period [13••]. Data from the United States during 2003–2010 utilizing the Healthcare Cost and Utilization Project, Nationwide Inpatient Sample, found that there was a 0.1% incidence of developing appendicitis during pregnancy [14]. The authors also found that the rates of appendicitis were highest among pregnant Hispanic and Black women compared to matched non-pregnant females [14]. Overall, the rates of peritonitis and healthcare utilization were increased in comparison to the non-pregnant population [14].

Diagnosis of Appendicitis in the Pregnant Patient

The classic diagnosis of appendicitis relies on several relevant clinical data points including nausea, emesis, fever, loss of appetite, and right lower quadrant pain [15, 16]. This classic presentation is less common in pregnant women, however, and becomes even more common in later term pregnancies. While right lower quadrant pain remains

the most common presenting symptom, the site of the pain moves cephalad as the uterus enlarges. Third trimester women may have pain as high as the level of the umbilicus or even in the lower portion of the right upper quadrant. (House JB, Bourne CL, Seymour HM, Brewer KL. Location of the appendix in the gravid patient. *J Emerg Med.* 2014 May;46[5]:741–4.) These symptoms can occur in conjunction with physiologic elevation in white blood cell count and C-reactive protein during pregnancy. All of this can obfuscate the accurate and timely diagnosis of appendicitis [17] which can have considerable impact on the mother and fetus [9, 10].

Despite the limitations of diagnosis of acute appendicitis in pregnant patients, clinical laboratory tests can still be utilized to assist in accurate diagnosis throughout gestation. Several authors have proposed ratios of neutrophils to lymphocytes (NLR) and platelets to lymphocytes (PLR) to assist in laboratory diagnosis of acute appendicitis. Authors from Turkey evaluated 25 patients with pathologically confirmed appendicitis to retrospectively determine whether changes in NLR and PLR were efficacious to diagnose acute appendicitis. In patients who were in their second and third trimesters, the NLR and PLR were increased and may be utilized to indicate acute inflammation [18]. Yazar et al. retrospectively evaluated 78 pregnant who were suspected to have acute appendicitis. The authors determined that the patients with elevated CRP, white blood cell count, NLR, and PLR were higher among those with pathologically confirmed appendicitis in comparison to pregnant women without appendicitis and healthy pregnant and non-pregnant control groups [19]. Using receiver operating characteristic analysis, the authors found that the combination of WBC count, NLR, PLR, CRP level, and lymphocyte count, establishing a diagnosis of appendicitis, was possible with a > 90% accuracy [19]. Gentles et al. evaluated 164 patients suspected to have acute appendicitis during pregnancy. The authors determined that the presence of an elevated neutrophil count (> 70%) along with presence of a left shift demonstrated a sensitivity and negative predictive value of 100% [20]. Even though pregnancy causes alterations in normal laboratory values, considerable changes reflective of acute inflammation can aid providers in recognizing acute appendicitis.

Utilizing both clinical and laboratory data, the Alvarado score has been incorporated as a severity score to ascertain the likelihood of appendicitis in pediatric and adult populations globally. Tatli et al. retrospectively assigned scores to both pregnant and non-pregnant women with appendicitis confirmed after appendectomy using pathology. The Alvarado score was found to be similar in both pregnant and non-pregnant patients, demonstrating its ability to accurately predict the presence of appendicitis in pregnant patients [21]. These results demonstrated that several

clinical and laboratory values were associated with the diagnosis of appendicitis and can be used to better classify and diagnose patients early.

Since there is a considerable need to rapidly diagnosis pregnant patients with suspected appendicitis and the physiologic and anatomic changes inherent in pregnancy impedes diagnosis, imaging that is safe and accurate is required. Ultrasonography is a preferred modality because of the lack of ionizing radiation. Ultrasonography in the first and second trimesters is useful; however, in the third trimester, the accuracy diminishes due to increased size of the uterus [22]. This can be further complicated by appendix location (retrocecal or pelvic) [23]. Because of this, a variety of studies have demonstrated indeterminate results (ranging 88–96%); the clinical utility of ultrasonography (US) can be used for other causes of pain (gynecologic) [24]. While the US may not provide accurate diagnosis, especially in the third trimester, the safety of this technique is well established [25, 26].

In non-obstetric patients, non-contrast computed tomography (CT) can provide high quality images that can be used to rapidly and accurately assess anatomy and make a diagnosis of acute appendicitis [27]. While CT is available for pregnant patients suspected to have acute appendicitis, there are considerable risks to both the mother and fetus (radiation-induced teratogenesis and carcinogenesis) [28, 29]. Receipt of fewer than 5 Gy is perceived as the limit wherein no harm; yet, the perceived risk of radiation is still present [30]. Despite potential changes in protocols to ameliorate perceived and real risk of carcinogenesis, CT should be cautiously utilized in pregnant patients to diagnose appendicitis.

Magnetic resonance imaging has been evaluated in several pregnant patient cohorts and has been found to be both sensitive and specific. In a systematic review, Kave et al. assessed several high quality studies to determine the clinical efficacy of MRI in the pregnant patient with appendicitis. The authors determined that sensitivity was 92% and specificity 98% [31]. In patient with the suspected diagnosis of appendicitis, the utilizing of MRI for diagnosis was a clinically useful tool and minimized risk to the mother, fetus [32]. Burns et al. confirmed this finding retrospective review of MRI scans in pregnant women with appendicitis. Tsai et al. evaluated interrater specificity of MRI for appendicitis and found that there was substantial agreement [33]. These findings suggest that MRI be utilized as a first-line tool for pregnant patients who require imaging to diagnosis a suspected diagnosis of appendicitis [34]. Further, in a retrospective analysis of pregnant patients who received MRI compared to those who did not with a suspicion for appendicitis, there was an association of fewer non-therapeutic interventions, increased utilizing

on non-operative management, and a decreased duration of hospital stay [35••].

Management of Appendicitis During Pregnancy

In most adult and pediatric patients, appendicitis can be managed using either non-operative or operative management [36, 37]. Evidence for the management of appendicitis healthy children and adults using antibiotics alone is increasing [38]. Operative management has been frequently utilized in pregnant patients diagnosed with appendicitis at all trimesters of gestation. Both laparoscopic and open appendectomy can be used to access the abdomen and surgically resect the appendix. Management that is focused on successful treatment of the appendicitis will benefit the mother and ultimately the fetus. Determining the type of management, however, remains controversial.

Appendectomy, either open or laparoscopic, has been utilized extensively to treat pregnant patients with appendicitis. In a population-based study, Cheng et al. evaluated maternal outcome in patients who underwent appendectomy (either laparoscopic or open) or non-operative management for appendicitis during pregnancy [39]. The 859 patients, who did not undergo an operation, there was an increased risk of preterm labor (10.4 vs 4.4%, $p < 0.0001$), abortion (6.2 vs 0.4%, $p < 0.0001$), and rate of cesarean section (38.9 vs 34%, $p = 0.0072$) [39]. Compared to healthy controls, patients managed with antibiotics alone demonstrated increased risks of preterm labor (OR 10.9) and abortion (OR 31.37 CI 13.12–75.01) in pregnant patients with appendicitis. The risk of abortion was highest in the non-operative management followed by open and laparoscopic appendectomy. However, risk of abortion, preterm labor, and cesarean section were similar between open and laparoscopic appendectomy. In comparison, those who underwent laparoscopic appendectomy demonstrated a short duration of hospital stay compared to those who underwent open appendectomy [39].

In a retrospective study by Yoo et al., pregnant patients with appendicitis were compared by open versus laparoscopic appendectomy. The most striking difference between groups was the duration of hospital stay, 5 versus 8 days [40]. In the small cohort, there were no considerable differences between management type with regard to preterm delivery or fetal loss [40]. Cox et al. utilized the NSQIP database to assess both laparoscopic and open appendectomy/cholecystectomy in pregnant patients [41]. Among those undergoing appendectomy, similar findings of reduced maternal hospital duration of stay and wound complications were found. The study was limited by lack of data regarding the fetus. In an Australian population-

linked dataset, Ibiebele et al. used multivariable analysis assessing risk factors in pregnant patients with appendicitis and pregnant patients without appendicitis. The authors determined that appendectomy was associated with increased preterm labor, maternal, and fetal comorbidity but no fetal loss [42]. Finally, in a large population-based study in the United States, management of pregnant patients with appendicitis varied. In comparison to non-pregnant patients with appendicitis, utilization of laparoscopy was less frequent (OR 0.5 CI 0.5–0.5), and non-operative management was also administered more frequently (OR 1.3 CI 1.2–1.5) [14]. Each study highlights that appendectomy, regardless of approach, is associated with risk to the pregnancy and possible maternal/fetal comorbidity but that fetal loss was infrequent. While these large datasets provide some insight, to safety and utility of laparoscopic appendectomy in comparison to open appendectomy, several systematic reviews and analyses have conflicting data.

In a study in 2012 by Wilasrusmee et al., the authors evaluated laparoscopic versus open appendectomy in pregnant patients with appendicitis. Alarming, the authors found a statistically significant association of fetal loss in women who underwent laparoscopic compared to open appendectomy (relative risk 1.91 CI 1.31–2.77) [43]. The remaining pooled data were not able to discern differences with regard to preterm delivery, hospital duration of stay, and maternal or immediate fetal outcomes other than loss [43]. In 2018, another meta-analysis of observational cohort data comparing open and laparoscopic appendectomy demonstrated an increased risk of fetal loss among women who underwent laparoscopic management compared to open appendectomy (OR 1.82 CI 1.3–2.57, $p = 0.0006$) [44]. Two additional systematic reviews and meta-analyses were published in 2019. The first by Frountzas et al. demonstrated a 2.1 odds ratio for fetal loss in pregnant women who underwent laparoscopic appendectomy for appendicitis [45]. Conversely, in pregnant patients undergoing open appendectomy for appendicitis, the first 5 min Apgar score was lower in comparison to patient undergoing laparoscopic appendectomy [45]. There were no considerable differences in the remainder of outcomes. The second analysis contradicted the first analysis with regard to fetal loss and management type. Among the included studies, the authors accounted for sensitivity of fetal loss based on operative technique (laparoscopic vs open). Ultimately, there was no difference in fetal loss between laparoscopic and open appendectomy after removal of a single study, which contributed considerably to the finding that fetal loss was associated with laparoscopic approach [46]. To verify this, the authors used meta-regressions to assess procedure type with complicated appendicitis, publication year, gestational age, and

trimester. No conclusive differences were found between open and laparoscopic appendectomy suggesting that the previously reported differences in fetal loss were due to a single study [46]. Furthermore, laparoscopic appendectomy is recommended as the preferred approach for pregnant patients by the Society of Gastroenterologic and Endoscopic Surgeons if the surgeon is proficient with the technique [47]. Management via open or laparoscopic appendectomy in a pregnant patient should take into consideration the risk of fetal loss, preterm delivery, and cesarean section. Laparoscopic approaches offer reductions in hospital duration but a potential risk of fetal loss in comparison to open techniques. Overall, there are no considerable differences regarding surgical site infection and maternal comorbidity. Therefore, surgeons should be capable of offering both techniques and use clinical judgment to rapidly remove the appendix, if indicated.

Trocar placement for laparoscopic approaches will be affected by the gravid uterus. We recommend a sloppy left lateral position to move the uterus to the left side of the abdomen during and after the 2nd trimester. Entry into the abdomen should be performed using an open techniques; Veress needle entry is relatively contraindicated. Ultrasound guidance should be used to determine the most superior aspect of the uterus to ensure its avoidance. The insufflation pressure should be reduced to 8–12 mm Hg but also must ensure adequate visualization to safely perform the operation. Intraabdominal pressure of 15 mm Hg or greater must be avoided as it can precipitate fetal hypotension, bradycardia, and hypoxia. (Pearl JP, Price RR, Tonkin AE, Richardson WS, Stefanidis D SO Surg Endosc. SAGES guidelines for the use of laparoscopy during pregnancy. 2017;31(10):3767.) The remainder of the trocars should be placed under direct camera visualization; their placement should be guided by the size and location of the uterus ensuring that the instruments will be able to easily avoid the uterus.

Appendectomy and the Risk to the Fetus

The impact of appendicitis on the fetus after surgical management can be considerable. Ibiebele et al. utilized population data to assess outcomes of the fetus after appendectomy in pregnant women compared to pregnant women without appendicitis. The majority of women underwent a laparoscopic procedure (55%) demonstrating that appendectomy at the third trimester was associated with preterm delivery [42]. Appendectomy (either open or laparoscopic) increased the risk of preterm birth (OR 1.73 CI 1.42–2.09), maternal morbidity (OR 2.68 CI 1.88–3.83), fetal morbidity (OR 1.42 CI 1.03–1.94), but no difference in fetal mortality [42]. The authors stressed that fetal

resources were available for those pregnant women who undergo appendectomy for appendicitis after twenty weeks of gestational age. Buitrago et al. also demonstrated that in 2507 women who underwent appendectomy for appendicitis during pregnancy in the 3rd trimester, there was the highest risk of preterm delivery [48]. Mourad et al. utilizing a large retrospective review of nearly 67,000 pregnancy deliveries to better quantify the risk of appendicitis and appendectomy on fetal outcomes. Many patients in the third trimester did undergo preterm labor; however, there preterm delivery was rare and fetal morbidity/mortality was infrequent [49]. In order to assess the risk of appendectomy on of the fetus, Choi et al. developed a prospective study that followed the outcomes of the newborn. The authors reported on 29 of 52 participants and found that appendectomy had no impact on the development of the child at three years of age [50]. Further, the trimester at which the appendectomy was performed had no impact on developmental outcomes [50]. While the overall impact of appendectomy appears low on the fetus, there is a need for multidisciplinary resources in order to minimize fetal loss and maternal complications. Some of these resources include urgent obstetric evaluation the need for operative intervention, and an anesthetic plan in conjunction with pre- and post-operative monitoring of the fetus. This includes fetal heart monitoring, serial biophysical profiles, and subsequent close follow-up with obstetric/maternal-fetal medicine provider for the remainder of the pregnancy. All of these together can minimize risk and poor outcome.

Non-operative Management of Appendicitis in Pregnant Patient

Few studies have evaluated the efficacy and safety of non-operative management of appendicitis in the pregnant patient. Among the recent available data, a post hoc analysis of multi-institutional prospectively collected data on appendicitis from the Eastern Association for the Surgery of Trauma demonstrated first that a low rate of women developed appendicitis while pregnant [51]. Additionally, the authors concluded that in comparison to non-pregnant women with appendicitis, the severity was not dissimilar [51]. Further, pregnant women were more likely to undergo non-operative management compared to non-pregnant women. Operative outcomes were similar as well during inpatient duration and at thirty days. Data on fetal outcomes were not available nor were the rates of successful non-operative management. In the study by Abbasi et al., those patients with appendicitis who were managed non-operatively during pregnancy demonstrated increased rates of sepsis, development of peritonitis, and venous

thromboembolism [14]. This highlights greater severity and persistent symptom confers significant maternal risk.

Authors from Korea assessed the use of antibiotics alone for pregnant patients with uncomplicated appendicitis (non-perforated) [52]. The authors utilized MRI to define the severity of disease. Intravenous antibiotics was administered for two days and at 48 h, if an elevated C-reactive protein was found, failure of antibiotic therapy was determined and an operative to remove the appendix was performed. Twenty women were evaluated with three not responding to antibiotic therapy and underwent an operation whereas five (25%) demonstrated recurrent appendicitis during follow-up. This study demonstrated that, for a select population, antibiotic therapy for non-perforated appendicitis appeared to work and reduced the rates of appendectomy, risk of fetal loss, and preterm delivery [52]. Similarly, in Greenland, a single case report of a geographically isolated pregnant woman with appendicitis was treated with antibiotics until the weather permitted travel to a referral center for evaluation. The patient eventually underwent appendectomy and carried the fetus to term [53]. In 2009, two cases of pregnant women with perforated appendicitis were successfully managed with antibiotic therapy alone [54]. One patient, however, developed recurrent appendicitis not refractory to additional antibiotic therapy and subsequently underwent a Cesarean section at 34 weeks of gestation due to breech positioning. Several other authors report successful management of non-complicated appendicitis in pregnant patients [55]. While the data for sole antibiotic therapy for appendicitis in pregnant patients are not widely studied, the available data do suggest its use over the past decade and in well-selected patients who are adequately monitored and, most important, who do not progress (i.e., perforate, become intolerant to diet, and do not have worsening physiology), antibiotic therapy may be provided. A carefully designed trial would best serve to answer this question.

Limitations and Future Directions to the majority of operative studies

In several of the recent meta-analyses evaluating laparoscopic versus open appendectomy, the concept of disease severity was broached. Available data on appendicitis severity in the pregnant patient are virtually nil, save for the recent study by EAST [51]. Current data lack granular measurement of appendicitis severity. This limits meaningful conclusions regarding maternal and fetal outcomes for pregnant patients with appendicitis. Going forward, accurate measurement of disease severity should be reported allowing for more equitable comparisons [56]. A clinical, imaging, operative, and pathologic grading system

exists to better classify disease severity for common emergency general surgery diseases and assignment of a patients' disease severity should be routinely done to improve communication and outcome reporting [56–58].

Conclusion

In the pregnant patient with appendicitis, accurate and rapid diagnosis is the most important first step. Judgment regarding operative versus non-operative management appears to be dependent on the availability of system resources. For well-monitored patients without subjective and objective progression of appendicitis, antibiotic therapy alone may serve to adequately treat patients although the data are sparse and low quality. With respect to operative management, the life of the mother remains essential. Therapies, resuscitation, and operative intervention should most effectively treat the fetus. There is still debate regarding the potential risk of fetal loss during a laparoscopic compared to open approach, however, as the reports are conflicted. The safest technique should be employed by the operating surgeon and the risks and benefits thoroughly described to the patient. Additional assistance from obstetrics or maternal fetal medicine physicians may prove best to optimize outcome for both the fetus and mother. Future studies evaluating appendicitis in pregnant patients should incorporate well-studied criteria to estimate the severity of appendicitis and improve the outcome reporting in this infrequent disease.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no conflicts of interest.

Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Recently published papers of particular interest have been highlighted as:

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