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Review of Operative vs. Non-Operative Management of Appendicitis in Pregnancy

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Abstract

The last decade has marked a paradigm shift in the care for acute appendicitis in children and non-pregnant adults. Although surgical management remains the safest treatment modality for perforated or complicated appendicitis, antibiotic therapy has been proven to be safe in adult and pediatric patients with non-perforated appendicitis. However, controversy exists for the type of surgery (laparoscopic vs. open) and the post-operative antibiotic regimens which result in optimal patient care of pregnant as well as non-pregnant adults. As several authors have begun to evaluate a non-operative strategy for treating acute appendicitis, whether with antibiotic therapy alone or combined with image-guided percutaneous drainage, others have retrospectively analyzed these strategies to pregnant women with abdominal pain. This collective review presents the epidemiology and diagnostic challenges of acute appendicitis in the pregnant patient and a review of the data that supports non-operative management in non-pregnant adults and pediatric patients as well as the limited data that supports non-operative management in pregnant adults.

Keywords: Acute appendicitis; Laparoscopic appendectomy; Pregnancy; Fetal demise; Pre-term labor; Non-operative management

Introduction

Current estimates of the incidence of acute appendicitis in pregnant women are between 0.04% - 0.2% [1]. Acute appendicitis has a higher lifetime risk in males than females (8.6% vs. 6.7%), yet treatment with appendectomy is actually higher in women than in men (23% vs. 12%) [2,3]. Moreover, if treated without surgery at initial presentation, recurrence is higher for males [4]. Appendicitis in pregnancy is the most common cause of surgical intervention for an acute abdomen, followed by cholecystectomy, pancreatitis and bowel obstruction [5-8]. Non-obstetric surgery in pregnancy, for any gestational age, for a variety of indications, is performed for 1- 2% of all pregnancies [2].

Acute onset abdominal pain in the pre-menopausal woman presents a unique diagnostic challenge as there are a variety of gynecologic concerns and physiological changes during pregnancy that can confound diagnosis [9-13]. Other explanations for acute onset abdominal pain range from menstruation symptoms or endometriosis for any woman of child-bearing age, to the increased incidence of nausea and vomiting, urinary tract infection or complications of early pregnancy [14-18]. The presentation of acute appendicitis is altered in pregnancy due to the displacement of the appendix cephalad during uterine enlargement [19], so that by week 20 of gestation, the appendix sits at the level of the umbilicus and by the 37th week, the appendix sits below the right costal margin [12,20].

Appendectomy has been accepted as an effective treatment for acute appendicitis since Fitz described the technique 120 years ago [21]. However, treatment of acute appendicitis without surgery is as old as reports of treatment with surgery: In his autopsy reports, Fitz detailed previously inflamed appendix specimens that had healed without surgical management [21]. Until recently, there were few efforts to manage appendicitis non-operatively, with the exception of Coldrey in 1959, who published successful case series of non-operative management of acute appendicitis [22]. The last decade has presented compelling evidence for introducing non-surgical management into in the standard of care for acute appendicitis in children and non-pregnant adults. In a recent systematic review of several prospective randomized controlled trials, the American College of Surgeons concluded that an "antibiotic-first" approach was likely safe in the majority of patients with non-perforated appendicitis, but they and other authors of meta-analysis have maintained that appendectomy is still the gold standard for uncomplicated acute appendicitis [23,24]. While surgical management is standard of care for acute appendicitis in pregnant patients, controversy exists for the type of surgery (laparoscopic vs. open) and whether a non-operative strategy would be appropriate for this population.

Methods

Searches were conducted in PubMed using MeSH search for "appendicitis" + "pregnancy" yielding 997 papers. Filters were added and yielded the following number of papers: "humans" still yielded 997, "Randomized controlled trial" yielded 3 papers, "comparative study" yielded 37 papers, "systematic review" yielded 22 results and "clinical trial" yielded 8 papers. Due to the significant dilemma in diagnostic work-up, additional PubMed searches of "appendicitis" + "pregnancy" and either "tomography", "ultrasound" or "MRI" were also added to yield a total of 134 papers. Although the literature review started with randomized, prospective controlled trials prospective non-randomized trials were then addressed and finally retrospective case series and case reports. Due to the sparsity of Grade I articles, all of these types were included in review (Figure 1).

An Embase search was also conducted to examine Emtree (MeSH plus synonyms) terms. "Pregnancy" and "appendicitis" initially yielded 1,153 articles. Two prospective, randomized controlled trials were found that were not found in the PubMed search (Enochsson and Magary). The filters were then widened to just "prospective

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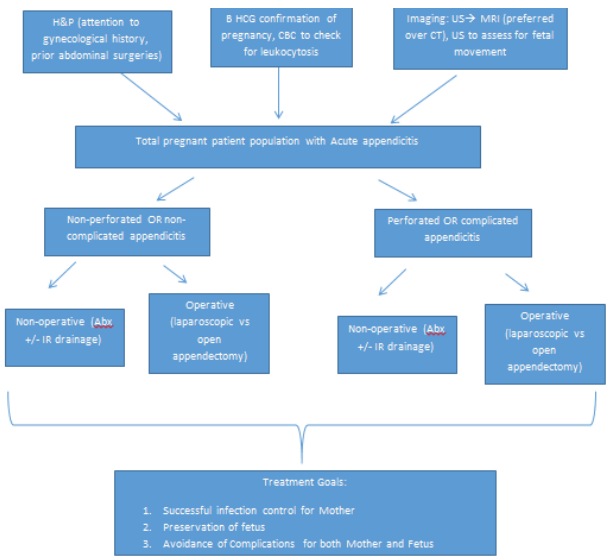

Figure 1: Diagnosis and Treatment Options for the Pregnant Patient with Acute Appendicitis

study" or "randomized controlled trial" with both "appendicitis" and "pregnancy", which yielded 17 and 8 articles respectively. All 23 of these studies were examined in the review. Finally, a PubMed search was conducted to examine the literature of non-operative management of acute appendicitis in non-pregnant adults. MeSH terms of "non-operative management" + "appendicitis" were used and yielded 24 total papers. All but 9 papers were reviewed, and those excluded were because of non-relevant subject matter (alternative causes of abdominal infection, SBO), inappropriate population (interval appendectomy in patients with cancer).

Results

Diagnostic challenges

Obtaining a definitive diagnosis using current laboratory and imaging modalities has remained at the crux of the challenges of evaluating a woman of child-bearing age with abdominal pain [25-30]. Several papers have revealed that there are few, if any, elements of a patient's clinical and laboratory examinations that can predict need for surgery [16,17]. Several studies have demonstrated that common findings used to diagnose acute appendicitis, such as leukocyte count, CRP and fever, were not helpful in establishing a correct diagnosis in a pregnant patient [16,31]. Others have found that appendicitis is very likely when two or more inflammatory laboratory variables are increased, but is very unlikely when two or more inflammatory variables are normal [32]. Diagnosis of acute appendicitis can be made by physical exam without expected laboratory values to corroborate the diagnosis in 20-33% of non-pregnant patients [33,34].

Ultrasound, CT and MRI serve as the three imaging options for assessing etiology of abdominal pain [5,35-37]. Elevated radiation risk to the fetus can cause teratogenic and carcinogenic effects if excessive CT imaging is used [6,12,14]. CT use has increased, so that now 50% of children receive CT dose radiation in the work-up of acute onset abdominal pain [38,39]. In response, the National Cancer Institute and the American Pediatric Surgical Association, as well as other authors, have advocated for non-radiation based imaging to be used wherever possible [6,40,41]. Currently, pregnant women with suspected appendicitis need no further imaging to confirm diagnosis if ultrasound reveals visualization of the inflamed appendix [42-44]. However, if ultrasound is non-diagnostic, MRI is recommended instead of CT imaging since it yields a high rate of diagnosis without radiation exposure [45-48]. In the past 25 years, there has been a decline in the rates of non-perforated appendicitis, with an increase in use of CT imaging and laparoscopic appendectomy, but no decrease in rate of perforation [6,49,50]. These findings have led toward efforts to identify two separate patterns for non-perforated and perforated appendicitis, thus identifying which type of patient would be most suited to non-surgical management [32,49,51].

Several scoring systems have been developed to help differentiate appendicitis from other causes of abdominal pain and minimize usage of imaging that exposes patients to radiation and hospital systems to excess cost [52]. These include the Appendicitis Inflammatory Response (AIR), Adult Appendicitis Score (AAS), and the Raja Isteri Pengiran Anak Saleha Appendicitis (RIPASA), with the most commonly used being the Alvarado Score (also known as MANTRELS) and the Pediatric Appendicitis Score (PAS) [53-63]. Of the clinical scoring systems used to aid in diagnosis of acute appendicitis, the Alvarado and Appendicitis Inflammatory Response scores have been the longest standing and most thoroughly evaluated [2,60,63-65]. According to the World Society of Emergency Surgery's recent Jerusalem guidelines for diagnosis of acute appendicitis, Alvarado or AIR scores can be used to triage patients into further treatment categories [66]. For patients with scores <5, no further imaging is needed and patients can be re-assessed in 6-8 hours or discharged. With scores 5-8, ultrasound is used to see if patients can be further observed or imaged with CT scan for more definitive imaging. Lastly, patients with a high probability of appendicitis and scores >8 can be considered for CT initially and expedited for surgical care. However, these scoring systems have only been validated by level 2 and 3 evidence and are plagued by inadequate or inconsistent definitions for clinical variables [67]. Moreover, no data exist that demonstrates improvement in outcomes after implementation of any of the scoring systems [2,68-70].

High-risk patients with high Alvarado scores may not require ultrasound, CT or MRI before surgery [66]. However, these images are routinely performed for pregnant and non-pregnant patients alike, particularly in the US [63]. Although this strategy has been recommended in young women, it presents significant risks and cost when compared to other strategies [71], and only established a diagnosis in 45%-95% of patients [72-75]. However, a "wait and see" approach with imaging was able to establish diagnosis 84% of the time [71].

Controversies in surgical management

Several landmark studies revealed the importance of surgical management in pregnant patients with acute appendicitis. In 1962, a retrospective study of 74,000 patients in California demonstrated higher rates of fetal loss and premature delivery, with the degree of prematurity proportionate to the delay in operating [76]. Ensuing papers through the 1970s- 2000s calculated the risk of fetal loss to be approximately 10% in simple appendicitis and greater than 30% in complicated appendicitis [5,77-79]. Surgical therapy was further encouraged to reduce complications associated with abscess, such as ureteric obstruction needing decompression of upper urinary tract [80]. Emphasis was placed on early surgical intervention because pregnant patients are more likely to present with appendiceal rupture, compared with non-pregnant patients, leading to increased risk of fetal loss [12,81]. In 1992,

a case series of over 700 pregnant patients demonstrated maternal death in 5 cases, all of which had perforated appendicitis [82]. By the late 1990s, there was documentation of decreased rates of maternal mortality, but the rates of negative appendectomy and appendiceal perforation were unchanged over past 50 years [15]. Other studies show decline in rate of perforated appendicitis in 25 years since 2007 [49].

Historically, pregnant women who were suspected of having acute appendicitis were treated with open appendectomy [71,77,79] with shorter time to treatment than for non-pregnant pts [83]. There have also been a variety of techniques introduced within the field of surgical treatment of appendectomy, including a McBurney (oblique), Rockey-Davis (transverse), modified McBurney (oblique following Langer's lines), "cul-de-sac" (transvaginal), multiport laparoscopy or single port laparoscopy [84-86]. As laparoscopy became adopted by general surgeons and gynecologists for non-obstetric procedures, controversy grew over optimal approaches to the treatment of acute appendicitis in the pregnant patient. Pregnancy was initially considered a contraindication to laparoscopy [87] and subsequent papers questioned whether laparoscopic appendectomy was feasible in pregnant patients [88]. Challenges of performing laparoscopy during pregnancy include difficult visualization due to gravid uterus with laparoscope and potential risk of decreased blood flow due to increased intraabdominal pressure, possible carbon dioxide absorption for the mother or fetus [89].

Several systematic reviews and meta-analyses showed higher rates of fetal loss with laparoscopy as compared to open appendectomy, with the rate of fetal loss with laparoscopy approximately 5.6% versus 3.1% with open appendectomy [50,90-93]. However, there was no difference in length of hospitalization, wound infection rate or APGAR scores between the two surgical techniques [93]. One study also calculated open appendectomy to be less expensive [94]. The latest Cochrane systematic review in 2014 determined that although there was no high grade evidence to support either laparoscopic or open appendectomy as the safer approach for treatment; however, there was low grade evidence that showed a higher rate of fetal loss [95].

However, advocates of the laparoscopic approach have cited long-term studies that demonstrate its safety for the fetus and mother, independent of trimester, and relate complications to the degree of underlying severity of appendicitis [93,95-98]. Several retrospective reviews have shown a lack of complications in newborns, including adequate weight for gestation age, well-being at birth [99-101] and one prospective paper showing no association with developmental delays of motor, sensory or social skills by 3 years of age [1]. Arguments for laparoscopic appendectomy include improved accuracy of diagnosis and preventing complications related to delayed diagnosis [14,71] in a population with many confounding diagnoses and incorrect pre-op diagnosis in as many as a quarter of the patients [16,102] as well as ability to identify other intra-abdominal pathology which may mimic appendicitis and harbor fetal loss [96]. Also, other studies show benefits of laparoscopic technique in other fields can be applied to these patients, including shorter hospital stay than for open [71,94,103] and shorter time to first flatus, earlier time to oral intake than for open appendectomy [101], less operating time, less use of post-operative analgesics [104] and lower rate of wound infection [93]. By 2004, some authors had termed it the "new standard of care" [105].

Challenges to surgical approaches

Proponents of early surgical intervention recommended this strategy because it was assumed that a negative appendectomy is well tolerated and that laparoscopy is safe for both the mother and fetus [5]. As a result of differing physiology as well as other confounding diagnoses, the rate of negative appendectomy is considerably higher in pregnant women when compared with non-pregnant women. Several studies have established the rate of negative appendectomy to be between 10-30% [71,93,98] and up to 56% in one study that performed histopathological confirmation [106]. These rates are in contrast to the rate of 18% negative appendectomy rate in women of childbearing age found in a retrospective review of over 94,000 women [90]. Interestingly, one study found no difference in the rate of negative appendectomy or perforation in high volume centers (>100 appendectomies / year) vs. low volume or between teaching vs. community hospitals [15]. In pregnant patients, negative appendectomy is associated with substantial complications: 6% infectious complications and 2% rate of reoperation, in addition to longer length of hospital stay and, of course, higher total admission charges [71]. One study also documented statistically significant increased risk of fetal loss with negative appendectomy [90]. These adverse consequences of surgical management are in light of the increased risks that have been published compared to non-operatively managed pregnant women including uterine infections, ovarian torsion [107], maternal shock, peritonitis and venous [108] and even necrotizing fasciitis [109].

Discussion

To help determine if literature that supports non-operative management could apply to pregnant patients is the question of whether appendicitis is the same disease in pregnant patients than in non-pregnant women. Changes in maternal physiology during pregnancy are dramatic, including a baseline increase in plasma volume of 45%, cardiac index by 40% and clotting factors by 50-200%, making the risk of any type of surgery higher than for a non-pregnant patient [50]. Large case registries have almost two-fold increase in sepsis, septic shock, transfusion requirement, pneumonia, bowel obstruction, post-operative infection and length of stay greater than 3 days [108]. Indeed, evidence exists for a possible common pathophysiology between ectopic pregnancy and appendicitis, which highlights the variability in causes of acute appendicitis [110]. However, a recent smaller series found equivalent duration of surgery, duration of antibiotic use and incidence of surgical site infection among pregnant women and non-pregnant women of child-bearing age [111]. And, recent literature has highlighted a common physiology for appendicitis in pregnant and non-pregnant patients [112].

Recently, the American College of Surgeons performed collective review on 6 key prospective randomized trials of antibiotic therapy vs. appendectomy in non-pregnant adults and concluded that antibiotic therapy is safe for approximately "3 out of 4 adults" [23,113-118]. One of the most compelling studies showed 91% efficacy of antibiotics alone with a 14% rate of recurrent appendicitis at 1 year, but it excluded populations (children and elderly) at high risk of perforation [114]. These data have been mirrored by success of non-operative treatment in children who have had symptoms for three or more days, or absence of diffuse peritonitis, bowel obstruction or mass; moreover, failure of conservative treatment has not been associated with increased morbidity [119]. Subsequent meta-analyses and Cochrane reviews in the 2010s revealed that antibiotics was safe in the majority of patients with uncomplicated appendicitis [51,120-122].

Additional trials showed that non-operative management was safe with 2 year follow up [54], and that no increase in complications was observed, even with perforation [16]. Moreover, complications

of laparoscopic appendectomy, such as stump appendicitis, can be managed with an antibiotics only strategy [123], and that interval appendectomy is not needed in adults [124] or children [125]. Additional review in 2014 revealed that patients who present with phlegmon, abscess <5 cm, who smoke, have generalized abdominal tenderness or tachycardia were more likely to fail non-operative management than patients without these features [126]. Other papers have demonstrated resolution of sepsis and abscess control with percutaneous drainage if an abscess has already developed [127,128]. One review demonstrated success with CT guided drainage if the patient failed to improve at 48-72 hours after diagnosis, and it found that percutaneous drainage was frequently not necessary [129].

Interestingly, some of these papers report usage of ultrasound in diagnosis and treatment, which would be of particular benefit in the pregnant population. Limiting doses of ionizing radiation as well as contrast agents that carry potential for fetal injury recommend ultrasound and MRI as preferred imaging techniques for pregnant patients [18,130-132]. Since rates of fetal loss and early delivery are higher in women with perforation, and negative appendectomy rate higher in pregnant women, reducing risk of fetal loss relates directly to accuracy of diagnosis, with particular attention to accurate imaging interpretation, as most women have undergone some kind of imaging prior to evaluation by a surgeon.

Once a diagnosis is achieved, there is no consensus on the true risks that pneumoperitoneum and anesthetic agents are incompletely defined [1,133,134]. Risks to the fetus, however rare, are still present, such as case reports of accidental gas insufflation into amniotic cavity leading to fetal loss [135], or stump appendicitis leading to chorioamnionitis [136]. In five reviews of laparoscopic technique, all published since 2001, there was increased risks of miscarriage or premature labor [9,137-140]. In the most recent of these reviews, there have been rates of 8.2% for premature delivery and 2.5% of fetal loss, even with laparoscopic appendectomy [140]. Moreover, this review also found a rate of 3.9% for major birth defects among women who underwent surgery in the first trimester, and that surgery induced labor occurred at 4.6% during appendectomy [140].

Although no prospective randomized controlled trials exist for pregnant paitents receiving non-operative management, a small case series of pregnant women with ruptured appendicitis demonstrated successful management with antibiotic therapy alone, despite one needing repeat medical management for recurrence at 32 weeks gestation of her fetus [141]. Future prospective studies are needed to determine whether antibiotics alone or with percutaneous drainage is a non-inferior treatment to surgical therapy in pregnant patients with appendicitis. Although several different antibiotic regimens have been proposed [142-144], the type, duration and indications for these antibiotics are yet to be determined in pregnant patients.

Cost-effective analysis (cost per expected successfully treated patient) is beginning to appear in the literature [145] and will help determine the most cost-effective options given equivalent efficacy and safety. In a 2014 retrospective review of 231,678 patients with uncomplicated appendicitis, over 3 thousand of these patients were managed non-operatively; and of those patients, approximately 6% required appendectomy at that admission and 4.4% experienced recurrence of appendicitis after discharge during 7 year follow up. Of note, total charges were not statistically different between operative and non-operative patients, but length of stay was significantly longer in the non-operative group [146].

Conclusion

Management of acute onset abdominal pain the pregnant patient presents several diagnostic and treatment-based challenges. Pregnant women have a variety of other causes of acute onset abdominal pain that confound a diagnosis of acute appendicitis, compared to non-pregnant patients. Given the uncertainty of long-term risks to the fetus of radiation exposure in CT imaging, antibiotic therapy and general anesthesia and surgical manipulation, pregnant patients also present unique challenges with management of appendicitis once the diagnosis is made. Early studies of non-operative management revealed significantly higher rates of pre-term labor, fetal demise as well as maternal sepsis and abscess: Thus, the past decades have marked emergent laparoscopic appendectomy as the standard of care. However, new studies in pediatric and adult populations reveal that appendicitis can be safely managed with antibiotic therapy or a combination of antibiotic therapy with percutaneous drainage, if the appendix is already perforated. Given the unique risks and challenging facing pregnant women, optimizing management remains an important topic of future study in this population.

References

1. Choi JJ, Mustafa R, Lynn ET, Divino CM (2011) Appendectomy during pregnancy: Follow-up of progeny. J Am Coll Surg 213: 627-632.
2. Di Saverio S, Birindelli A, Kelly MD, Catena F, Weber DG, et al. (2016) WSES Jerusalem guidelines for diagnosis and treatment of acute appendicitis. World J Emerg Surg 11: 34.
3. Addiss DG, Shaffer N, BS Fowler, RV Tauxe (1990) The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol 132: 910-925.
4. Lien WC, Lee WC, Wang HP, Chen YC, Liu KL, et al. (2011) Male gender is a risk factor for recurrent appendicitis following nonoperative treatment. World J Surg 35: 1636-1642.
5. Vandeven CJ, Krupnick AS (2011) Greenfield's surgery: Scientific principles and practice. The Pregnant Patient (5thedn). Lippincott Williams & Wilkins, US.
6. Angelini DJ (2003) Obstetric triage revisited: update on non-obstetric surgical conditions in pregnancy. J Midwifery Womens Health 48: 111-118.
7. Kuczkowski KM (2006) The safety of anaesthetics in pregnant women. Expert Opin Drug Saf 5: 251-264.
8. Tamir IL, Bongard FS, Klein SR (1990) Acute appendicitis in the pregnant patient. Am J Surg 160: 571-575.
9. Kilpatrick CC, Orejuela FJ (2008) Management of the acute abdomen in pregnancy: a review. Curr Opin Obstet Gynecol 20: 534-549.
10. Cappell MS, Friedel D (2003) Abdominal pain during pregnancy. Gastroenterol Clin North Am 32: 1-58.
11. Oto A, Ernst RD, Shah R, Koroglu M, Chaljub G, et al. (2005) Right-lower-quadrant pain and suspected appendicitis in pregnant women: evaluation with MR imaging--initial experience. Radiology 234: 445-451.
12. Horowitz MD, Gomez GA, Santiesteban R, Burkett G (1985) Acute appendicitis during pregnancy: Diagnosis and management. Arch Surg 120: 1362-1367.
13. Musselman RC, Nunnelee JD, Ware DB (1998) Appendicitis during pregnancy. Clin Excell Nurse Pract 2: 338-342.
14. Tarraza HM, Moore RD (1997) Gynecologic causes of the acute abdomen and the acute abdomen in pregnancy. Surg Clin North Am 77: 1371-1394.
15. Hale DA, Molloy M, Pearl RH, Schutt DC, Jaqueset DP (1997) Appendectomy: A contemporary appraisal. Ann Surg 225: 252-261.
16. Urbach DR, Cohen MM (1999) Is perforation of the appendix a risk factor for tubal infertility and ectopic pregnancy? An appraisal of the evidence. Can J Surg 42: 101-108.
17. Pastore PA, Loomis DM, Sauret J (2006) Appendicitis in pregnancy. J Am Board Fam Med 19: 621-626.

18. Brown JJ, Wilson C, Coleman S, Joypaul BV (2009) Appendicitis in pregnancy: An ongoing diagnostic dilemma. Colorectal Dis 11: 116-122.

19. Oto A, Ernst RD, Ghulmiyyah LM, Nishino TK, Hughes D, et al. (2009) MR imaging in the triage of pregnant patients with acute abdominal and pelvic pain. Abdom Imaging 34: 243-250.

20. Lee RA, CE Johnson, Symmonds RE (1965) Appendicitis during pregnancy. Jama 193: 966-968.

21. Fitz R (1886) Perforating inflammation of the vermiform appendix with special reference to its early diagnosis and treatment. Trans Assoc Am Physicians 1: 107-144.

22. EC (1959) Five years of conservative treatment of acute appendicitis. J Int Coll Surg 32: 255-261.

23. Ehlers AP (2016) Evidence for an antibiotics-first strategy for uncomplicated appendicitis in adults: A systematic review and gap analysis. J Am Coll Surg 222: 309-314.

24. Rocha LL, Bianco Rossi FM, Souza Pessoa CM, Campos FND, Fonseca Pires CE, et al. (2015) Antibiotics alone versus appendectomy to treat uncomplicated acute appendicitis in adults: what do meta-analyses say? World J Emerg Surg 10: 51.

25. Bongard F, Landers DV, Lewis F (1985) Differential diagnosis of appendicitis and pelvic inflammatory disease: A prospective analysis. Am J Surg 150: 90-96.

26. Webster DP (1993) Differentiating acute appendicitis from pelvic inflammatory disease in women of childbearing age. Am J Emerg Med 11: 569-572.

27. Rothrock SG, Green SM, Dobson M, Colucciello SA, Simmons CM (1995) Misdiagnosis of appendicitis in nonpregnant women of childbearing age. J Emerg Med 13: 1-8.

28. Dahlberg DL, Lee C, Fenlon T, Willoughby D (2004) Differential diagnosis of abdominal pain in women of childbearing age. Appendicitis or pelvic inflammatory disease? Adv Nurse Pract 12: 40-45.

29. Poortman P, Oostvogel HJ, Bosma E, Lohle PN, Cuesta MA, et al. (2009) Improving diagnosis of acute appendicitis: results of a diagnostic pathway with standard use of ultrasonography followed by selective use of CT. J Am Coll Surg 208: 434-441.

30. Kessler N, Cyteval C, Gallix B, Lesnik A, Blayac PM, et al. (2004) Appendicitis: Evaluation of sensitivity, specificity, and predictive values of US, Doppler US, and laboratory findings. Radiology 230: 472-478.

31. Hallan S, Asberg A (1997) The accuracy of C-reactive protein in diagnosing acute appendicitis--a meta-analysis. Scand J Clin Lab Invest 57: 373-380.

32. Andersson RE, MG Petzold (2007) Nonsurgical treatment of appendiceal abscess or phlegmon: A systematic review and meta-analysis. Ann Surg 246: 741-748.

33. Velanovich V, Satava R (1992) Balancing the normal appendectomy rate with the perforated appendicitis rate: implications for quality assurance. Am Surg 58: 264-269.

34. Kirkil C, Karabulut K, Aygen E, İlhan YS, Yur M, et al. (2013) Appendicitis scores may be useful in reducing the costs of treatment for right lower quadrant pain. Ulus Travma Acil Cerrahi Derg 19: 13-19.

35. Albiston E (2002) The role of radiological imaging in the diagnosis of acute appendicitis. Can J Gastroenterol 16: 451-63.

36. Krajewski S, Brown J, Phang PT, Raval M, Brown CJ (2011) Impact of computed tomography of the abdomen on clinical outcomes in patients with acute right lower quadrant pain: a meta-analysis. Can J Surg 54: 43-53.

37. Tan WJ, Pek W, Kabir T, Goh YC, Chan WH, et al. (2013) Alvarado score: A guide to computed tomography utilization in appendicitis. ANZ J Surg 83: 748-752.

38. Kotagal M, Richards MK, Flum DR, Acierno SP, Weinsheimer RL, et al. (2015) Use and accuracy of diagnostic imaging in the evaluation of pediatric appendicitis. J Pediatr Surg 50: 642-646.

39. Kotagal M, Richards MK, Chapman T, Finch L, McCann B, et al. (2015) Improving ultrasound quality to reduce computed tomography use in pediatric appendicitis: the Safe and Sound campaign. Am J Surg 209: 896-900.

40. Kim ME, Orth RC, Fallon SC, Lopez ME, Brandt ML, et al. (2015) Performance of CT examinations in children with suspected acute appendicitis in the community setting: a need for more education. AJR Am J Roentgenol 204: 857-860.

41. Nielsen JW, Boomer L, Kurtovic K, Lee E, Kupzyk K, et al. (2015) Reducing computed tomography scans for appendicitis by introduction of a standardized and validated ultrasonography report template. J Pediatr Surg 50: 144-148.

42. Freeland M (2009) Diagnosis of appendicitis in pregnancy. Am J Surg 198: 753-758.

43. Mallin M, Craven P, Ockerse P, Steenblik J, Forbes B, et al. (2015) Diagnosis of appendicitis by bedside ultrasound in the ED. Am J Emerg Med 33: 430-432.

44. Terasawa T, Blackmore CC, Bent S, Kohlwes RJ et al. (2004) Systematic review: Computed tomography and ultrasonography to detect acute appendicitis in adults and adolescents. Ann Intern Med 141: 537-546.

45. Spalluto LB, Woodfield CA, DeBenedectis CM, Lazarus E (2012) MDMR imaging evaluation of abdominal pain during pregnancy: Appendicitis and other nonobstetric causes. Radiographics 32: 317-334.

46. Theilen LH, Mellnick VM, Longman RE, Tuuli MG, Odibo AO, et al. (2015) Utility of magnetic resonance imaging for suspected appendicitis in pregnant women. Am J Obstet Gynecol 212: 345.

47. Chang ST, RB Jeffrey, Olcott EW (2014) Three-step sequential positioning algorithm during sonographic evaluation for appendicitis increases appendiceal visualization rate and reduces CT use. AJR Am J Roentgenol 203: 1006-1012.

48. Leeuwenburgh MM, Wiezer MJ, Wiarda BM, Bouma WH, Phoa SS, et al. (2014) Accuracy of MRI compared with ultrasound imaging and selective use of CT to discriminate simple from perforated appendicitis. Br J Surg 101: 147-155.

49. Livingston EH, Woodward WA, Sarosi GA, Haley RW (2007) Disconnect between incidence of nonperforated and perforated appendicitis: implications for pathophysiology and management. Ann Surg 245: 886-892.

50. Juhasz-Boss I, Solomayeret E, Strik M, Raspé C (2014) Abdominal surgery in pregnancy--an interdisciplinary challenge. Dtsch Arztebl Int 111: 465-472.

51. Varadhan KK, Neal KR, Lobo DN (2012) Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: Meta-analysis of randomised controlled trials. Bmj 344: 2156.

52. Debnath J (2015) Alvarado score: Is it time to develop a clinical-pathological-radiological scoring system for diagnosing acute appendicitis? Am J Emerg Med 33: 839-840.

53. Kittisupamongkol W (2009) Modified alvarado score for acute appendicitis. Colorectal Dis 11: 788.

54. Di Saverio S, Sibilio A, Giorgini E, Biscardi A, Villani S, et al. (2014) The NOTA Study (Non Operative Treatment for Acute Appendicitis): Prospective study on the efficacy and safety of antibiotics (amoxicillin and clavulanic acid) for treating patients with right lower quadrant abdominal pain and long-term follow-up of conservatively treated suspected appendicitis. Ann Surg 260: 109-117.

55. Alvarado A (1986) A practical score for the early diagnosis of acute appendicitis. Ann Emerg Med 15: 557-564.

56. Andersson M, RE Andersson (2008) The appendicitis inflammatory response score: a tool for the diagnosis of acute appendicitis that outperforms the Alvarado score. World J Surg 32: 1843-1849.

57. Chong CF, Adi MI, Thien A, Suyoi A, Mackie AJ, et al. (2010) Development of the RIPASA score: A new appendicitis scoring system for the diagnosis of acute appendicitis. Singapore Med J 51: 220-225.

58. Sammalkorpi HE, Mentula P, Leppaniemi A (2014) A new adult appendicitis score improves diagnostic accuracy of acute appendicitis--a prospective study. BMC Gastroenterol 14: 114.

59. Atema JJ, van Rossem CC, Leeuwenburgh MM, Stoker J, Boermeester MA (2015) Scoring system to distinguish uncomplicated from complicated acute appendicitis. Br J Surg 102: 979-990.

60. Ohle R (2011) The Alvarado score for predicting acute appendicitis: A systematic review. BMC Med 9: 139.

61. Samuel M (2002) Pediatric appendicitis score. J Pediatr Surg 37: 877-881.

62. Kollár D, McCartan DP, Bourke M, Cross KS, Dowdall J (2015) Predicting acute appendicitis? A comparison of the alvarado score, the appendicitis inflammatory response score and clinical assessment. World J Surg 39: 104-109.

63. Scott AJ, Mason SE, Arunakirinathan M, Reissis Y, Kinross JM, et al. (2015)

Risk stratification by the Appendicitis Inflammatory Response score to guide decision-making in patients with suspected appendicitis. Br J Surg 102: 563-572.

64. McKay R, Shepherd J (2007) The use of the clinical scoring system by Alvarado in the decision to perform computed tomography for acute appendicitis in the ED. Am J Emerg Med 25: 489-493.

65. Trout AT, Sanchez R, Ladino-Torres MF (2012) Reevaluating the sonographic criteria for acute appendicitis in children: a review of the literature and a retrospective analysis of 246 cases. Acad Radiol 19: 1382-1394.

66. Ebell MH, Shinholser J (2014) What are the most clinically useful cutoffs for the alvarado and pediatric appendicitis scores? A systematic review. Ann Emerg Med 64: 365-372.

67. Gwynn LK (2001) The diagnosis of acute appendicitis: clinical assessment versus computed tomography evaluation. J Emerg Med 21: 119-123.

68. de Castro SM, Ünlü Ç, Ph Steller E, van Wagensveld BA, Vrouenraets BC (2012) Evaluation of the appendicitis inflammatory response score for patients with acute appendicitis. World J Surg 36: 1540-1545.

69. Jones RP, Jeffrey RB, Shah BR, Desser TS, Rosenberg J, et al. (2015) Journal Club: The Alvarado score as a method for reducing the number of CT studies when appendiceal ultrasound fails to visualize the appendix in adults. AJR Am J Roentgenol 204: 519-526.

70. Di Saverio S, Arianna B, Alice P, Fausto C, Andrea B, et al. (2016) How reliable is alvarado score and its subgroups in ruling out acute appendicitis and suggesting the opportunity of nonoperative management or surgery? Ann Surg.

71. Gaitán HG, Reveiz L, Farquhar C (2014) Laparoscopy for the management of acute lower abdominal pain in women of childbearing age. Cochrane Database Syst Rev.

72. Borgstein PJ, Gordijn RV, Eijsbouts QA, Cuesta MA (1997) Acute appendicitis--a clear-cut case in men, a guessing game in young women. A prospective study on the role of laparoscopy. Surg Endosc 11: 923-927.

73. Moberg AC, Ahlberg G, Leijonmarck CE, Montgomery A, Reiertsen O, et al. (1998) Diagnostic laparoscopy in 1043 patients with suspected acute appendicitis. Eur J Surg 164: 833-840.

74. Sellors J (1991) The accuracy of clinical findings and laparoscopy in pelvic inflammatory disease. Am J Obstet Gynecol 164: 113-120.

75. Spirtos NM, Eisenkop SM, Spirtos TW, Poliakin RI, Hibbard LT (1987) Laparoscopy--a diagnostic aid in cases of suspected appendicitis. Its use in women of reproductive age. Am J Obstet Gynecol 156: 90-94.

76. King RM, Anderson GV (1962) Appendicitis and pregnancy. Calif Med 97: 158-162.

77. Townsend JM, Greiss FC (1976) Appendictiis in pregnancy. South Med J 69: 1161-1163.

78. Mohammed JA, Oxorn H (1975) Appendicitis in pregnancy. Can Med Assoc J 112: 1187-1188.

79. Melton GB, Harmon JW (2011) Cameron's current surgical therapy: Acute appendicitis (10thedn).

80. Dueholm SP, Bagi P, Nordsten M (1987) Ureteric obstruction as a complication to the appendicular abscess. Case report. Acta Chir Scand 153: 557-559.

81. Mazze RI, Kallen B (1991) Appendectomy during pregnancy: A Swedish registry study of 778 cases. Obstet Gynecol 77: 835-840.

82. Mahmoodian S (1992) Appendicitis complicating pregnancy. South Med J 85: 19-24.

83. Hiersch L, Yogev Y, Ashwal E, From A, Ben-Haroush A, et al. (2014) The impact of pregnancy on the accuracy and delay in diagnosis of acute appendicitis. J Matern Fetal Neonatal Med 27: 1357-1360.

84. Lowry S, Bavidov R, Shiroff AM (2011) Appendicitis and appendiceal abscess, in fischer's mastery of surgery. In: Fischer JE, Pomposelli FB (eds.). Lippincott Williams & Wilkins, US.

85. Amir-Jahed AK (1977) The cul-de-sac approach for appendectomy. Am J Surg 134: 656-658.

86. Koh AR, Lee JH, Choi JS, Eom JM, Hong JH (2012) Single-port laparoscopic appendectomy during pregnancy. Surg Laparosc Endosc Percutan Tech 22: 83-86.

87. Holthausen UH, Mettler L, Troidl H (1999) Pregnancy: A contraindication? World J Surg 23: 856-862.

88. Franca Neto AH, Amorim MM, Nobrega BM (2015) Acute appendicitis in pregnancy: Literature review. Rev Assoc Med Bras 61: 170-177.

89. Fatum M, Rojansky N (2001) Laparoscopic surgery during pregnancy. Obstet Gynecol Surv 56: 50-59.

90. McGory ML, Zingmond DS, Tillou A, Hiatt JR, Ko CY, et al. (2007) Negative appendectomy in pregnant women is associated with a substantial risk of fetal loss. J Am Coll Surg 205: 534-540.

91. Machado NO, Grant CS (2009) Laparoscopic appendicectomy in all trimesters of pregnancy. Jsls 13: 384-390.

92. Wilasrusmee C, Sukrat B, McEvoy M, Attia J, Thakkinstian A (2012) Systematic review and meta-analysis of safety of laparoscopic versus open appendicectomy for suspected appendicitis in pregnancy. Br J Surg 99: 1470-1478.

93. Walsh CA, Tang T, Walsh SR (2008) Laparoscopic versus open appendicectomy in pregnancy: A systematic review. Int J Surg 6: 339-344.

94. Reissfelder C, Mc Cafferty B, von Frankenberg M (2009) Open appendectomy. When do we still need it? Chirurg 80: 602-607.

95. Walker HG, Al Samaraee A, Mills SJ, Kalbassi MR (2014) Laparoscopic appendicectomy in pregnancy: A systematic review of the published evidence. Int J Surg 12: 1235-1241.

96. Sadot E, Telem DA, Arora M, Butala P, Nguyen SQ, et al. (2010) Laparoscopy: A safe approach to appendicitis during pregnancy. Surg Endosc 24: 383-389.

97. Kirshtein B, Perry ZH, Avinoach E, Mizrahi S, Lantsberg L (2009) Safety of laparoscopic appendectomy during pregnancy. World J Surg 33: 475-480.

98. Lemieux P, Rheaume P, Levesque I, Bujold E, Brochu G (2009) Laparoscopic appendectomy in pregnant patients: a review of 45 cases. Surg Endosc 23: 1701-1705.

99. Moreno-Sanz C, Pascual-Pedreño A, Picazo-Yeste JS, Seoane-Gonzalez JB (2007) Laparoscopic appendectomy during pregnancy: between personal experiences and scientific evidence. J Am Coll Surg 205: 37-42.

100. Wu JM (2005) Laparoscopic appendectomy in pregnancy. J Laparoendosc Adv Surg Tech A 15: 447-450.

101. Chung JC, Cho GS, Eung JS, Kim HC, Song OP (2013) Clinical outcomes compared between laparoscopic and open appendectomy in pregnant women. Can J Surg 56: 341-346.

102. Golash V, Willson PD (2005) Early laparoscopy as a routine procedure in the management of acute abdominal pain: a review of 1,320 patients. Surg Endosc 19: 882-885.

103. Cheng HT, Wang YC, Lo HC, Su LT, Soh KS, et al. (2015) Laparoscopic appendectomy versus open appendectomy in pregnancy: a population-based analysis of maternal outcome. Surg Endosc 29: 1394-1399.

104. Eom JM, Hong JH, Jeon SW, Choi JS, Lee JH, et al. (2012) Safety and clinical efficacy of laparoscopic appendectomy for pregnant women with acute appendicitis. Ann Acad Med Singapore 41: 82-86.

105. Rollins MD, Chan KJ, Price RR (2004) Laparoscopy for appendicitis and cholelithiasis during pregnancy: A new standard of care. Surg Endosc 18: 237-241.

106. Al-Mulhim AA (1996) Acute appendicitis in pregnancy: A review of 52 cases. Int Surg 81: 295-297.

107. de Perrot M, Jenny A, Morales M, Kohlik M, Morel P (2000) Laparoscopic appendectomy during pregnancy. Surg Laparosc Endosc Percutan Tech 10: 368-371.

108. Abbasi N, PatenaudeV, Abenhaim HA (2014) Management and outcomes of acute appendicitis in pregnancy-population-based study of over 7000 cases. BJOG 121: 1509-1514.

109. Penninga L, Wettergren A (2006) Perforated appendicitis during near-term pregnancy causing necrotizing fasciitis of the lower extremity: A rare complication of a common disease. Acta Obstet Gynecol Scand 85: 1150-1151.

110. Riggs JC, Schiavello HJ, Fixler R (2002) Concurrent appendicitis and ectopic pregnancy: A case report. J Reprod Med 47: 510-514.

111. Kumamoto K, Imaizumi H, Hokama N, Ishiguro T, Ishibashi K, et al. (2015) Recent trend of acute appendicitis during pregnancy. Surg Today 45: 1521-1526.

112. Segev L, Segev SY, Rayman S, Nissan A, Sadot E (2016) Acute appendicitis during pregnancy: Different from the nonpregnant state? World J Surg 41: 75-81.

113. Turhan AN, Kapan S, Kütükçü E, Yiğitbaş H, Hatipoğlu S, et al. (2009) Comparison of operative and non operative management of acute appendicitis. Ulus Travma Acil Cerrahi Derg 15: 459-462.

114. Hansson J, Körner U, Khorram-Manesh A, Solberg A, Lundholm K (2009) Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. Br J Surg 96: 473-481.

115. Salminen P, Paajanen H, Rautio T (2015) Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: The APPAC randomized clinical trial. Jama 313: 2340-2348.

116. Eriksson S, Granstrom L (1995) Randomized controlled trial of appendicectomy versus antibiotic therapy for acute appendicitis. Br J Surg 82: 166-169.

117. Styrud J, Eriksson S, Nilsson I, Ahlberg G, Haapaniemi S, et al. (2006) Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. World J Surg 30: 1033-1037.

118. Vons C, Barry C, Maitre S, Pautrat K, Leconte M, et al. (2011) Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. Lancet 377: 1573-1579.

119. Emil S, Duong S (2007) Antibiotic therapy and interval appendectomy for perforated appendicitis in children: a selective approach. Am Surg 73: 917-922.

120. Wilms IM, de Hoog DE, de Visser DC, Janzing HM (2011) Appendectomy versus antibiotic treatment for acute appendicitis. Cochrane Database Syst Rev.

121. Ansaloni L, Catena F, Coccolini F, Ercolani G, Gazzotti F, et al. (2011) Surgery versus conservative antibiotic treatment in acute appendicitis: a systematic review and meta-analysis of randomized controlled trials. Dig Surg 28: 210-221.

122. Mason RJ, Moazzez A, Sohn H, Katkhouda N (2012) Meta-analysis of randomized trials comparing antibiotic therapy with appendectomy for acute uncomplicated (no abscess or phlegmon) appendicitis. Surg Infect (Larchmt) 13: 74-84.

123. Rios RE, Villanueva KM, Stirparo JJ, Kane KE (2015) Recurrent (stump) appendicitis: a case series. Am J Emerg Med 33: 480.

124. Kaminski A, Liu IL, Applebaum H, Lee SL, Haigh P (2005) Routine interval appendectomy is not justified after initial nonoperative treatment of acute appendicitis. Arch Surg 140: 897-901.

125. Puapong D, Lee SL, Haigh PI, Kaminski A, Liu IL, et al. (2007) Routine interval appendectomy in children is not indicated. J Pediatr Surg 42: 1500-1503.

126. Maxfield MW, Schuster KM, Bokhari J, McGillicuddy EA, Davis KA (2014) Predictive factors for failure of nonoperative management in perforated appendicitis. J Trauma Acute Care Surg 76: 976-981.

127. Bagi P, Dueholm S (1987) Nonoperative management of the ultrasonically evaluated appendiceal mass. Surgery101: 602-605.

128. Shuler FW, Newman CN, Angood PB, Tucker JG, Lucas GW (1996) Nonoperative management for intra-abdominal abscesses. Am Surg 62: 218-222.

129. Yamini D, Vargas H, Bongard F, Klein S, Stamos MJ (1998) Perforated appendicitis: is it truly a surgical urgency? Am Surg 64: 970-975.

130. Patel SJ (2007) Imaging the pregnant patient for nonobstetric conditions: algorithms and radiation dose considerations. Radiographics 27: 1705-1722.

131. Katz DS, Klein MA, Ganson G, Hines JJ (2012) Imaging of abdominal pain in pregnancy. Radiol Clin North Am 50: 149-171.

132. Wang PI, Chong ST, Kielar AZ, Kelly AM, Knoepp UD, et al. (2012) Imaging of pregnant and lactating patients: part 2, evidence-based review and recommendations. AJR Am J Roentgenol 198: 785-792.

133. Lemaire BM, WF van Erp (1997) Laparoscopic surgery during pregnancy. Surg Endosc.

134. Barnes SL, Shane MD, Schoemann MB, Bernard AC, Boulanger BR (2004) Laparoscopic appendectomy after 30 weeks pregnancy: Report of two cases and description of technique. Am Surg 70: 733-736.

135. Al-Fozan H, Tulandi T (2002) Safety and risks of laparoscopy in pregnancy. Curr Opin Obstet Gynecol 14: 375-379.

136. Belli S, Yalçinkaya C, Ezer A, Bolat F, Çolakoğlu T, et al. (2011) Stump appendicitis and chorioamnionitis due to incomplete appendectomy: a case report. Turk J Gastroenterol 22: 540-543.

137. Weber Sánchez A, Garteiz Martínez D, Itzkovich RN, Núñez Vargas E (2001) Analysis of the increasing role of laparoscopy in the management of acute abdomen in pregnancy. Ginecol Obstet Mex 69: 422-430.

138. Augustin G, Majerovic M (2007) Non-obstetrical acute abdomen during pregnancy. Eur J Obstet Gynecol Reprod Biol 131: 4-12.

139. Sharp HT (2002) The acute abdomen during pregnancy. Clin Obstet Gynecol 45: 405-413.

140. Cohen-Kerem R, Railton C, Oren D, Lishner M, Koren G (2005) Pregnancy outcome following non-obstetric surgical intervention. Am J Surg 190: 467-473.

141. Young BC, Hamar BD, Levine D, Roqué H (2009) Medical management of ruptured appendicitis in pregnancy. Obstet Gynecol 114: 453-456.

142. Malangoni MA, Song J, Herrington J, Choudhri S, Pertel P (2006) Randomized controlled trial of moxifloxacin compared with piperacillin-tazobactam and amoxicillin-clavulanate for the treatment of complicated intra-abdominal infections. Ann Surg 244: 204-211.

143. Teppler H, Meibohm AR, Woods GL (2004) Management of complicated appendicitis and comparison of outcome with other primary sites of intra-abdominal infection: Results of a trial comparing ertapenem and piperacillin-tazobactam. J Chemother16: 62-69.

144. Cohn SM, Lipsett PA, Buchman TG, Cheadle WG, Milsom JW, et al. (2000) Comparison of intravenous/oral ciprofloxacin plus metronidazole versus piperacillin/tazobactam in the treatment of complicated intraabdominal infections. Ann Surg 232: 254-262.

145. Paladino JA, Gilliland-Johnson KK, Adelman MH, Cohn SM (2008) Pharmacoeconomics of ciprofloxacin plus metronidazole vs. piperacillin-tazobactam for complicated intra-abdominal infections. Surg Infect (Larchmt) 9: 325-333.

146. McCutcheon BA, Chang DC, Marcus LP, Inui T, Noorbakhsh A, et al. (2014) Long-term outcomes of patients with nonsurgically managed uncomplicated appendicitis. J Am Coll Surg 218: 905-913.