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EDGAR LIPPING

Postoperative antibacterial therapy in complicated appendicitis and appendectomy in pregnancy

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Department of Surgery. Institute of Clinical Medicine, Faculty of Medicine, University of Tartu

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LIST OF ORIGINAL PUBLICATIONS

The doctoral thesis is based on three original publications which are numbered and referred to in the text by Roman numerals (I–III).

1) Saar S, Mihnovitš V, Lustenberger T, Rauk M, Noor EH, **Lipping E**, Isand KG, Lepp J, Lomp A, Lepner U, Talving P. Twenty-four hour versus extended antibiotic administration after surgery in complicated appendicitis: A randomized controlled trial. ***Journal of Trauma and Acute Care Surgery.*** 2019 Jan; 86(1): 36–42.

2) **Lipping E**, Saar S, Reinsoo A, Bahhir A, Kirsimägi Ü, Lepner U, Talving P. Short Postoperative Intravenous Versus Oral Antibacterial Therapy in Complicated Acute Appendicitis – A Pilot Non-Inferiority Randomized Trial. ***Annals of Surgery.*** 2023 Sep 25.

3) **Lipping E**, Saar S, Rull K, Tark A, Tiiman M, Jaanimäe L, Lepner U, Talving P. Open versus laparoscopic appendectomy for acute appendicitis in pregnancy: a population-based study. ***Surgical Endoscopy.*** 2023 Aug; 37(8): 6025–6031.

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Paper I	participation in the study design, data collection and critical revision;
Papers II–III	contributed to the study conception and design, material preparation, data collection, data analysis, writing of the draft and critical revision, submissions and correspondence.

ABBREVIATIONS

AA	Acute appendicitis
AAS	Adult appendicitis score
AAST	American Association for the Surgery of Trauma
AIR	Appendicitis Inflammatory Response Score
ALARA	As low as reasonably achievable
ASA	American Society of Anesthesiology
APPIC	Appendicectomy in complex appendicitis
APSI	Appendicitis Severity Index
BMI	Body mass index
CAA	Classification of acute appendicitis
CCI	Comprehensive complication index
CD	Clavien-Dindo classification
CRP	C-reactive protein
CT	Computed tomography
DSS	Disease severity score
EAES	European Association of Endoscopic Surgery
EHIF	Estonian Health Insurance Fund
EMBR	Estonian Medical Birth Registry
ERAT	Endoscopic retrograde appendicitis treatment
ESTES	European Society for Trauma and Emergency Surgery
ESBL	Extended spectrum beta-lactamase
GALT	Gut-associated lymphoid tissue
HLOS	Hospital length of stay
IAA	Intra-abdominal abscess
ITT	Intention to treat
IQR	Interquartile range
LA	Laparoscopic appendectomy
LBW	Low birth weight
MRI	Magnetic resonance imaging
NEMC	North Estonia Medical Centre
OA	Open appendectomy
PP	Per protocol
PCR	Polymerase chain reaction
RCT	Randomized controlled trial
SAS	Scoring systems for appendicitis severity
SD	Standard deviation
SGA	Small for gestational age
SIRS	Systemic inflammatory response syndrome
SIS	Surgical Infection Society
SSI	Surgical site infection
STOP-IT	Study to Optimize Peritoneal Infection Therapy
US	Ultrasonography
WBC	White blood cell count
WHO	World Health Organization

INTRODUCTION

Acute Appendicitis (AA) is one of the most common abdominal surgical emergencies with a global prevalence of 8.7% (Guan et al. 2023). AA may lead to death or disability when left untreated. However, timely surgery leads to rapid recovery and early return to normal activities. AA affects mostly younger individuals who in general are socially active and productive members of the society (Bhangu et al. 2015). Thus, AA contributes to a significant burden to health care systems and optimal treatment of this cohort has an economic impact for the society. Although AA is a common pathology, management of patients with complicated appendicitis and pregnant patients with AA still challenge clinicians worldwide.

AA can be broadly divided into two different entities – uncomplicated and complicated, respectively. Uncomplicated AA is defined as inflamed appendix without signs of wall necrosis or perforation. Complicated AA is characterized by transmural necrosis, appendiceal wall perforation and abscess formation (Bhangu et al. 2015). Perforated AA may account for up to about 35% of cases of patients suffering acute appendicitis (Al-Omran, Mamdani, and McLeod 2003).

Appendectomy is the treatment of choice for AA despite numerous studies demonstrating the feasibility of conservative treatment of uncomplicated AA with antibiotics only (CODA Collaborative et al. 2020). About 39% of patients with uncomplicated AA treated initially with antibiotics only developed recurrent AA within 5 years and majority of those underwent eventually appendectomy (Salminen et al. 2018). Also, the recent prospective randomized APPAC III investigation suggests that uncomplicated AA may be treated even without antibiotics (Salminen et al. 2022).

All patients diagnosed with AA should be commenced on broad-spectrum antibiotics to reduce the rate of infectious complications (Di Saverio et al. 2020). Laparoscopic appendectomy (LA) is the mainstay treatment for AA when expertise and resources are available facilitating shorter hospital length of stay (HLOS) and improved quality of life with equal rate of postoperative infectious complications when compared to open appendectomy (OA) (Yu et al. 2017).

Postoperative antibacterial treatment is not indicated in uncomplicated AA, whereas patients with complicated AA are subjected to antibacterial therapy following surgery to prevent infectious complications. Current guidelines re–commend limiting postoperative intravenous antibacterial treatment to 3–5 days (Di Saverio et al. 2020).

Antibacterial resistance is a global health challenge (Larsson and Flach 2022). Optimizing antibacterial treatment on a global basis is a part of World Health Organization's (WHO) policy to reduce misuse and overuse of antimicrobials as the main drivers of antimicrobial resistance (World Health Organization 2019). Studies have shown variation in compliance with antibiotic guidelines with potential for improvement of antibacterial stewardship (Bass et al. 2023; Thong et al. 2020). Also, there is obvious need for pragmatical research to elucidate whether it is feasible to further abbreviate postoperative antibiotic course (Bhangu, Buchwald, and Ntirenganya 2023). There is evolving evidence that postoperative antibiotics are not associated with decreased wound complications in complicated AA (D. Y. Kim et al. 2015; Kimbrell et al. 2014).

In addition to general population with complicated AA, pregnant patients with AA are a subgroup of patients that pose a clinical challenge for the treating physician. The prevalence of AA is lower in pregnant patients than in general population (Zingone et al. 2015). Nevertheless, AA is the most common non-obstetrical surgical emergency among pregnant patients. Non-operative management with antibiotic therapy has shown an increased risk for adverse outcomes during pregnancy (Abbasi, Patenaude, and Abenhaim 2014). Thus, appendectomy remains the standard treatment of AA during pregnancy (Ball et al. 2019; Pearl et al. 2017). However, the optimal surgical approach has remained a matter of lively clinical and scientific debate. Although laparoscopic approach is considered safe during pregnancy, several systematic reviews comparing LA and OA have shown increased risk of fetal loss in pregnant women undergoing laparoscopic appendectomy (Augustin et al. 2020; Prodromidou et al. 2018; Walker et al. 2014; Walsh, Tang, and Walsh 2008; Wilasrusmee et al. 2012; Winter et al. 2017).

The aim of this doctoral thesis is to determine the optimal duration of postoperative antibacterial treatment following LA in complicated AA, to compare different routes of administration of postoperative antibacterial treatment following LA in complicated AA and to review the outcomes following LA vs OA in pregnant patients suffering AA.

REVIEW OF LITERATURE

Historical perspective

Disease of the appendix is likely as old as man. One of the earliest examples of AA is from an Egyptian mummy from Byzantine era – adhesions discovered in right lower quadrant of the abdomen likely caused by previous appendicitis. The first descriptions of the appendix date from the 15th century. First drawings of the appendix are contributed to Leonardo da Vinci (1492). In the 18th century the role of the appendix and the appropriate treatment regarding inflammation in the right lower quadrant, also called "iliac passion", was still ambiguous. Boerhaave (1709), a leading Dutch medical expert of the time, advised large and repeated bloodlettings, laxatives, cooling enemas, opiates and compresses. The first reported case of appendicitis was in a femoral hernial sac reported by Rene Jacques Croissant de Garengeot in 1731 (Rajan, Girn, and Ainslie 2009). The first documented incidental yet successful appendectomy was performed by Claudius Amyand in 1735 in a 11-year-old boy with an inguinal hernia (Michalinos, Moris, and Vernadakis 2014). Several surgeons have thereafter reported on drainage of abscess in right iliac fossa with various results – patients often still died of a septic shock despite of surgery. Two major advances took place in the mid-19th century that improved the outcomes of surgical patients. Firstly, the development of general anesthesia made surgery more applicable to patients. The second advancement came from the field of infectious diseases. In 1867, Joseph Lister published his first papers on antisepsis, e.g. sterilizing the surgeons hands and instruments with carbolic acid, that greatly improved the safety of surgical patients. During the first meeting of the Association of American Physicians in 1886, a Harvard pathologist Reginald Heber Fitz emphasized that the etiology of most right lower quadrant inflammatory disease was the appendix. He provided a comprehensible explanation of the clinical features of appendiceal disease, described in depth the pathological changes and coined the term "appendicitis". Also, he advocated early surgical removal of the inflamed appendix (Streck and Maxwell 2014). Charles Heber McBurney described the point of tenderness on the abdominal wall and proposed his original muscle splitting surgical technique in 1889 in his practice-changing scientific report in Annals of Surgery (Ellis 2020). During the 20th century more attention was paid to fluid resuscitation of surgical patients. The advent of antibiotics in the 1940s further improved outcomes of patients with AA. In 1980 Kurt Semm performed the first LA which has become the mainstay of treatment of AA (Semm 1983). In contemporary era, appendectomy is one of the most commonly performed surgical procedures with excellent outcomes.

Anatomy of the appendix

The appendix is a true diverticulum that arises from the posteromedial aspect of the caecum at the site of convergence of the tree taenia of the colon, about 2.5 cm inferior to the ileocaecal (Bauhini) valve. Histologically, it has the same layered structure as the caecum and the colon: columnar epithelium, lamina propria, muscularis mucosae, submucosa, muscularis propria (inner circular layer and outer longitudinal layer of smooth muscle) and serosa. The average length and diameter of the appendix is 7–8 cm and 6 mm, respectively. While the location of the appendiceal orifice is a constant anatomical feature, the tip of the appendix may be behind the ascending colon, pre-ileal, post-ileal, subcaecal or para-caecal with retrocaecal being the most common (Bazira 2023). The appendix is supplied by the appendicular artery, an end artery that arises from the ileocolic artery. The appendicular artery courses behind the terminal ileum and reaches the appendix through the mesoappendix. Venous and lymphatic drainage follow that of the arterial supply. The autonomic innervation of the appendix arises from the superior mesenteric plexus. Afferent sensory nerve fibers from the appendix enter the spinal cord at T10 which is the corresponding dermatome to the umbilical area (Hodge, Kashyap, and Khorasani-Zadeh 2023).

Function of the appendix

The appendix contains a high density of gut-associated lymphoid tissue (GALT), which develops in parallel with the intestinal microbiota. The appendix houses lymphoid tissue where T- and B-lymphocytes mature and B-lymphocytes produce antibodies. The columnar epithelia, enterocytes and goblet cells occupy the lamina propria and muscularis mucosae of the appendix, while macrophages and plasma cells generating immunoglobulin A and immunoglobulin G line the lamina propria. Also, the appendix contains a biofilm of commensal microbiota that is thought to facilitate the reinoculation of the intestine in the case of intestinal perturbation. Thus, the appendix is thought to contribute to the balance of intestinal pro- and anti-inflammatory activity to maintain the homeostasis of the gut (Vitetta, Chen, and Clarke 2019). Some evidence suggests that the appendix is involved in immunological priming in immune-mediated disease, specifically ulcerative colitis. Observational studies have shown protective effect of appendectomy against ulcerative colitis (Koutroubakis et al. 1999; N. M et al. 2001; Sahami et al. 2016). However, some evidence suggests that appendectomy is associated with elevated risk for developing Crohn’s disease (L et al. 2023).

Mechanisms of appendicitis

Appendiceal outlet obstruction has been proposed as the main cause initiating the inflammation of the appendix. The lumen of the appendix may be obstructed by fecaliths (solid feces), lymphoid hyperplasia, tumors or parasites. Lymphoid hyperplasia caused by an infection is thought to be more common cause for AA among younger patients, whereas appendiceal lumen in elderly patients is more likely obstructed by a fecalith. Fecaliths can be found in approximately 30% of cases of AA (Alaedeen, Cook, and Chwals 2008). Obstruction of the appendiceal lumen leads to bacterial overgrowth and increased intraluminal pressure, resulting in thrombosis of small intramural vessels. Vascular compromise progresses and the wall of the appendix may become ischemic and eventually necrotic leading to perforation together with bacterial translocation (Bhangu et al. 2015).

AA may be divided into two subgroups: uncomplicated and complicated AA. About 70–80% of cases of AA are uncomplicated. Uncomplicated AA is characterized by inflammation of the appendix without necrosis or perforation of the appendiceal wall. The European Association of Endoscopic Surgery (EAES) defined complicated AA as gangrenous AA with or without perforation, AA with an intraabdominal abscess and AA with periappendiceal contained phlegmon or purulent/free fluid (Gorter et al. 2016). The proportion of complicated appendicitis ranges from 15 to 35% (Zhuyin Li et al. 2021). An increasing amount of circumstantial evidence suggests that not all patients with AA will progress to perforation and that resolution may be a common event (Roland E. Andersson 2007). These findings have later been corroborated by the results of the MUSTANG study demonstrating the possible early perforation of complicated AA, affecting more elderly patients than the young. The development of perforation in the appendiceal wall might not be the result of a delayed treatment but rather have multiple factors leading to perforations, e.g. individual’s response to disease or co-morbid illnesses (Yeh et al. 2021).

Epidemiology of appendicitis

The lifetime risk of developing AA has been estimated to range from 8.6% to 12% in males and 6.7% to 23.1% in females (Addiss et al. 1990; Sammalkorpi, Mentula, and Leppäniemi 2014). AA is a global disease. The incidence of AA escalated in Western countries in first half of the 20th century but then decreased in the second half without good explanation (Addiss et al. 1990; Williams 1983). The annual incidence of AA in the 21th century worldwide is approximately 100 cases per 100 000 adult population. The pooled incidence ranges from 105 in Eastern Europe to 151 in Western Europe. The pooled incidence is higher in newly industrialized countries in Asia (South Korea: 206), the Middle East (Turkey: 160) and South America (Chile: 202) (Ferris et al. 2017). AA related hospitalizations cost $3 billion per year within the United States of America alone (Davies, Dasbach, and Teutsch 2004).

Microbiology

The most frequent microorganisms responsible for infection in AA are aerobic and anaerobic Gram-negative enteric organisms. *Escherichia coli* is the most recurrent aerobic organism, and *Bacteroides fragilis* is the most frequent anaerobic suggesting that the bowel flora represents a key origin for infectious microorganisms. Also, other bacteria have been documented such as *Pseudomonas aeruginosa, Staphylococcus* and *Enterococcus* groups (Bratzler et al. 2013).

Uncomplicated and complicated AA have different appendiceal microbiome profiles suggesting the difference between the two entities (Vanhatalo et al. 2022). It has been demonstrated that complicated AA is associated with a significant local expansion of oral bacterial pathogens in the appendix, most strongly influenced by necrotizing *Fusobacterium spp.*, *Porphyromonas* and *Parvimonas*. However, uncomplicated appendicitis was associated with gut microbiomes (B. M et al. 2023).

Diagnostics of acute appendicitis

The presentation of AA generally follows a typical sequence of events: sudden onset of vague periumbilical or epigastric pain followed by anorexia, nausea or vomiting. About 24 hours after symptom onset, the pain migrates to the lower right quadrant of the abdomen with accompanying tenderness to palpation. The character and localization of the pain depends on the position of the appendix. During pregnancy, the point of maximum tenderness may be more cranial due to displacement of the caecum and appendix by the uterus. Fever is a consistent feature but may be absent at early stage of symptom onset. C-reactive protein (CRP) and white blood cell count (WBC) count remain the most commonly used laboratory markers, while elevated serum bilirubin level has been found to be associated with perforated AA (D'Souza, Karim, and Sunthareswaran 2013). Clinical diagnosis alone has been shown to lead to a negative appendectomy rate of 15 to 30%. The diagnosis is specially challenging for women of fertile age (J. Hoffmann and Rasmussen 1989; Raja et al. 2010; Seetahal et al. 2011).

Alvarado score, first described in 1986, combines eight predictive features from history, physical findings and laboratory results to stratify suspected appendicitis into probability groups (Alvarado 1986). More recently, Appendicitis Inflammatory Response Score (AIR) has been proposed to outperform Alvarado score in predicting AA (M. Andersson and Andersson 2008). AIR uses similar features as Alvarado with the inclusion of CRP. The most recent score, Adult Appendicitis Score (AAS) combines clinical features and laboratory findings (Sammalkorpi, Mentula, and Leppäniemi 2014). Scoring systems help to find patients who are most likely to have AA and also to avoid negative appendectomies without the use of radiographic imaging. Patients with a high probability of AA will undergo surgery or radiographic imaging, e.g. ultrasonography (US), computed tomography (CT) or magnetic resonance imaging (MRI). Although US is inexpensive and has no exposure to ionizing radiation, it is operator dependent and only has a specificity of 83% and a sensitivity of 78%. CT has a specificity of 90% and a sensitivity of 94%, but is more costly and exposes the patient to non-negligible ionizing radiation (Doria 2009; Rosen et al. 2011). Sensitivity of US for AA during pregnancy ranges from 46% to 63% and diminishes as the gestational age increases (Restrepo-Castro et al. 2018). According to Bayraktutan et al, a combination of diffusion-weighted and conventional MRI is the most sensitive (92%) and the most accurate (92%) for appendicitis (Bayraktutan et al. 2014).

Discriminating between uncomplicated or complicated appendicitis

Discriminating between uncomplicated and complicated AA is important as these two entities can be managed in different ways. There is emerging evidence on the feasibility of conservative treatment of uncomplicated AA (CODA Collaborative et al. 2020; Salminen et al. 2015). Also, uncomplicated AA may resolve even without antibacterial treatment (H. C. Park, Kim, and Lee 2017; Salminen et al. 2022). Patients with complicated AA are recommended to undergo urgent surgical treatment and patients with uncomplicated AA may receive conservative treatment with antibiotics. However, guidelines do not clearly advise how to differentiate between uncomplicated and complicated AA (Di Saverio et al. 2020; Gorter et al. 2016). Several studies have examined the performance of the AIR and Alvarado score on discriminating between uncomplicated and complicated AA (Deiters et al. 2019; W. Liu, Wei Qiang, and Xun Sun 2015; Yeşiltaş et al. 2018; Yılmaz et al. 2017). Nevertheless, imaging seems to be an integral part of differentiating uncomplicated AA from complicated AA. CT findings such as abscess, extraluminal air, intra- or extraluminal appendicolith and periappendiceal fluid have been found to be associated with complicated AA (H. Y. Kim et al. 2018). Appendicoliths have been found to be associated with complicated AA and are an independent risk factor for non-operative treatment failure (Mahida et al. 2016; Mällinen et al. 2019). Scoring systems for appendicitis severity (SAS) have been developed to distinguish between uncomplicated and complicated AA. SAS combines imaging with clinical and biochemical features: SAS-US utilizes US features and SAS-CT utilizes CT features (Atema et al. 2015). Appendicitis Severity Index (APSI) utilizes clinical, biochemical and CT findings to discriminate complicated AA from uncomplicated AA (Avanesov et al. 2018). A more recent study proposed a new classification of acute appendicitis (CAA) that is based solely on radiological findings on US or CT to clearly differentiate between uncomplicated and complicated AA (J. C. Hoffmann et al. 2021). However, these scoring systems are not externally validated. Also, a recent study by Bolmers et al demonstrated poor discrimination between uncomplicated and complicated AA of stepwise imaging (US, CT or MRI) in daily practice (Bolmers et al. 2022).

Appendicitis severity classification

Intraoperative findings during surgery offer the most accurate evaluation on the degree of inflammation severity of the appendix allowing for more clearer differentiation between uncomplicated and complicated AA. Disease severity score (DSS) for acute appendicitis was developed to grade intraoperative findings (Garst et al. 2013). Also, more recently the American Association for the Surgery of Trauma (AAST) developed an anatomic grading system to assess appendicitis severity through increasing grades of inflammation (Mouch et al. 2020). Both grading systems divide appendicitis into five grades. Grading allows for clinical benchmarking description of disease severity for acute appendicitis. Also, intraoperative findings of complicated AA have a better correlation with rate of postoperative complications when compared to histological classification (Silva et al. 2022). Bolmers et al. suggest that intraoperative evaluation of the appendix is the gold standard of diagnosing a complicated AA. Also, routine histological examination is not helpful in predicting complicated postoperative course and should be preserved to exclude malignancy (Bolmers et al. 2020).

Table 1. AAST anatomic severity grades and description

Grades	Operative AAST description of appendicitis
Normal	Normal appendix
I	Acutely inflamed appendix intact
II	Gangrenous appendix intact
III	Perforated appendix with local contamination
IV	Perforated appendix with periappendiceal phlegmon or abscess
V	Perforated appendix with generalized peritonitis

Treatment

LA is the mainstay of treatment for AA even for uncomplicated AA (Di Saverio et al. 2020; Fugazzola et al. 2020; Gorter et al. 2016). There is no consensus on the urgency of surgery. Not delaying surgery beyond 24 hours from admission is generally accepted. However, as demonstrated by Teixeira et al., delay of more than 6 hours resulted in a significant increase in surgical site infections (SSI) in patients with non-perforated AA (Teixeira et al. 2012). A recent well-designed prospective randomized PERFECT study found no difference in complication rates when comparing appendectomy scheduled <8 hours or <24 hours from admission indicating the safety of postponing possible night-time surgery to daytime (Jalava et al. 2023).

LA is associated with a lower incidence of wound infection and postoperative morbidity, shorter hospital stay and better quality of life scores when compared to OA (Jaschinski et al. 2015; Yu et al. 2017).

Postoperative management of patients with uncomplicated and complicated AA differs. Patients with uncomplicated AA who have undergone appendectomy are in lower risk of developing postoperative infectious complications and therefore do not need to receive antibacterial treatment following surgery, whereas patients with complicated AA need postoperative antibacterial treatment (Di Saverio et al. 2020; Fugazzola et al. 2020; Gorter et al. 2016). Current guidelines recommend limiting postoperative antibacterial treatment in complicated AA to 3–5 days (Di Saverio et al. 2020).

Endoscopic treatment

Endoscopic retrograde appendicitis treatment (ERAT) is a novel promising minimally invasive alternative for the treatment of AA. ERAT procedure is performed to resolve the appendiceal lumen obstruction by appendiceal luminal irrigation, fecalith removal and stenting for drainage if necessary (B.-R. Liu et al. 2012). The appendix is not removed. The procedure can be carried out without ionizing radiation which makes it a suitable treatment modality for pregnant patients with AA (Kong et al. 2022). ERAT has been shown to result in fewer complications and shorter recovery time when compared to appendectomy. However, similarly to non-operative management of uncomplicated AA with antibiotics, recurrence is an issue with ERAT. Interestingly, the procedure was introduced to public already in 2012 but has received little acceptance globally as all the published trials to date originate from China (B.-R. Liu et al. 2012; Xu, Jin, and Wu 2023).

Morbidity and mortality

Estimated postoperative mortality of AA in low-income sub-Saharan African countries is 54 per 1000 appendectomies compared to 3.03 per 1000 appendectomies performed in high-income countries (Uribe-Leitz et al. 2016). In the United States of America, mortality following appendectomy is 0.1%. Postoperative mortality of AA worldwide is estimated to be 0.3% (Alore et al. 2018; Sartelli et al. 2018).

Delaying intervention has been shown to produce worse surgical outcomes in patients with AA (Alore et al. 2018). An interval greater than 48 hours from the onset of symptoms to surgery results in a significant increase in the risk of appendiceal perforation and a two-fold increase in the risk of postoperative complications (Fair et al. 2015; Saar et al. 2016). Also, the rate of postoperative infectious complications correlates with DSS and AAST grading for AA with higher grades being associated with increased risk of complications (Garst et al. 2013; Mouch et al. 2020). Most common causes of morbidity following appendectomy are infectious complications, mostly SSI. The rate of 30-day postoperative infectious complications following LA is 14–19% (Giesen et al. 2017; Kleif et al. 2017; C. C. van Rossem et al. 2014; van Wijck et al. 2010).

Duration of postoperative antibiotic treatment

Misuse of antibiotics may lead to antibacterial resistance, disruption of normal microbiota that may result in *Clostridium difficile* or fungal infections, allergic reactions, organ toxicity but also may impact fertility and fetal development or have neurotoxic effects. In the recent years, resistance against antibiotics has developed due to extensive use of antibiotics in hospitals (Ansari et al. 2009). It has been evaluated that about 30–50% of the antibiotic consumption in hospitals is inappropriate (Hecker et al. 2003). Antibacterial resistance is a global health challenge (Larsson and Flach 2022). Thus, WHO aims to optimize antibacterial treatment to reduce worldwide misuse and overuse of antimicrobials as the main drivers of antimicrobial resistance. Restricting antimicrobial therapy to the shortest course associated with better outcomes is an important part of antimicrobial stewardship (Fernandez-Lazaro et al. 2019; Hanretty and Gallagher 2018). There have been several attempts over the past two decades to define the optimal duration of antimicrobial therapy by comparing abbreviated courses with traditional longer courses. There is data from randomized controlled trials (RCT) in specific conditions such as pneumonia, urinary tract infections, bacteremia and intraabdominal infections. In many of the trials, the abbreviated course was just as effective as the longer course but associated with fewer complications (Chastre et al. 2003; Choudhury et al. 2011; Kalil et al. 2016; Vaughn et al. 2019).

Earlier reports on postoperative antibacterial therapy following appendectomy in complicated AA have utilized a course ranging from 5 to 12 days (Piskun et al. 2001; Sleem et al. 2009; X. Wang et al. 2009). Guidelines during that period provided by Surgical Infection Society (SIS) and the Infectious Disease Society of America recommended treatment until clinical signs of infection had resolved such as elimination of fever, elevated WBC and ileus. In general, recommendations were to limit antibacterial treatment to 5–7 days (Solomkin et al. 2010). In 2015 Sawyer et al. published their results of a randomized Study to Optimize Peritoneal Infection Therapy (STOP-IT) trial to compare two strategies guiding the duration of antimicrobial therapy for the management of complicated intraabdominal infection, including patients with complicated AA. In this prospective trial patients were randomized to receive 4 full days of antimicrobial therapy after their index source-control procedure (experimental group) or to receive antimicrobial therapy until 2 days after the resolution of the physiological abnormalities related to systemic inflammatory response syndrome (SIRS) (control group). Consequently, 4 days of antibiotic treatment resulted in outcomes that were similar to those of a longer (traditional) course that was based on resolution of physiological abnormalities. The rate of 30-day postoperative complications was similar in both groups. Also, a shorter course was associated with significantly fewer days of antibiotic exposure (Sawyer et al. 2015).

Van Rossem et al published results of a prospective observational study where they compared 3-day regimen of postoperative antibacterial treatment with 5-day regimen in complicated AA. The actual antibiotic duration in all patients ranged from 2 to 10 days. Also, 91% of patients in 3-day group received intravenous administration only, while 47% of patients in 5-day group received only intravenous administration of antibacterial treatment. Histologically, in total only 45% of study patients were considered complicated, whereas 55% of patients were uncomplicated. Thus, possibly a considerable number of patients received unnecessary postoperative antibacterial treatment. Nevertheless, postoperative complications were observed in 23% of patients. In patients with a perforated AA, the intraabdominal abscess rate was 16.0% in contrast to a rate of 3.8% when the appendix was intact. No differences in complication rates were observed after 3 or 5 days of antibiotic treatment. However, abbreviated postoperative antibacterial treatment resulted in shorter hospital length of stay (Charles C. van Rossem et al. 2016).

A recent appendicectomy in complex appendicitis (APPIC) study compared 2-day regimen of intravenous postoperative administration with 5-day regimen in a randomized controlled trial. A total of 95% of patients from that study underwent LA and received intravenous amoxicillin/clavulanate postoperatively. Fewer patients in the 2-day group compared to the 5-day group had adverse effects of antibiotics. Also, rates of infectious complications and reinterventions were similar in both groups. The authors concluded that a shorter course of postoperative antibacterial treatment in complicated AA could reduce adverse effects of antibiotics and reduce hospital length of stay (de Wijkerslooth et al. 2023).

Recently published results of SnapAppy, a prospective multicenter study conducted by European Society for Trauma and Emergency Surgery (ESTES) demonstrated a clear opportunity for improvement in postoperative antibiotic stewardship also in hospitals in high-income countries. Although not indicated, 49.7% of patients with uncomplicated AA received postoperative antibacterial treatment following appendectomy. In total, 71.4% – 100% of patients with complicated AA received postoperative antibacterial treatment in all participating centers. The mean duration of postoperative antibacterial treatment in complicated AA stratified according to AAST grading was 4.3 days in AAST grade II, 8.5 days in AAST grade III, 10.5 days in AAST grade IV and 11 days in AAST grade V. In general, the mean duration of postoperative antibacterial treatment following appendectomy in uncomplicated and complicated AA was 4.6 days. Management of AA in participating hospitals was compared with two major guidelines – that of the World Society of Emergency Surgery for the management of patients with AA and that of the Surviving Sepsis Campaign for the management of patients with sepsis or septic shock (Di Saverio et al. 2020; SCCM | Surviving Sepsis Campaign Guidelines 2021 n.d.). Accordingly, median length of hospital stay was significantly shorter in patients who received fully compliant care (1.2 days), compared with those who received partially compliant (2.0 days) or noncompliant care (4.3 days) (Bass et al. 2023).

Clinical parameters including absence of fever (temperature ≤38°C) for 24 hours and ability to tolerate oral intake have been used to guide postoperative antibacterial treatment in complicated AA. Postoperative antibacterial treatment can be safely discontinued and the patient discharged when these clinical criteria are met (Cunningham et al. 2020; Skarda et al. 2014). However, in a recent retrospective study discharge criteria (absence of fever, oral intake resumed, pain controlled) were met by a median of 2 days after appendectomy for complicated AA in an adult population. Nevertheless, this did not result in discontinuation of antibacterial treatment or discharge of the patients. Median HLOS and duration of postoperative antibacterial treatment were still both 5 days, respectively. Also, not meeting discharge criteria by day 2 was a risk factor for developing postoperative complications (Anne Loes van den Boom et al. 2023).

A small retrospective study compared durations of > 24 hours of postoperative antibacterial treatment in complicated AA with < 24 hours of treatment. There was no significant difference in the rate of intra-abdominal abscess (IAA) formation between the two study groups. The authors concluded that postoperative antibiotics may not provide an appreciable clinical benefit for preventing intraabdominal abscesses (Kimbrell et al. 2014). Also, patients with complicated AA receiving no postoperative antibacterial treatment may not have an increased risk of developing infectious complications when compared to patients who received postoperative antibacterial treatment (D. Y. Kim et al. 2015).

Recent guidelines consider gangrenous non-perforated AA as a complicated disease process and recommend postoperative antibacterial treatment (Di Saverio et al. 2020; Gorter et al. 2016; Rushing et al. 2019). There is, however, some evidence that gangrenous non-perforated AA can be treated as uncomplicated appendicitis. Restricting treatment to preoperative prophylactic antibacterial treatment only does not result in increased rate of postoperative infections or readmissions in gangrenous non-perforated AA (Liberman et al. 1995; Mui et al. 2005; Nordin et al. 2019).

Routine laboratory monitoring following appendectomy has not been recommended by multiple authors (Di Saverio et al. 2020; Rushing et al. 2019). Nevertheless, WBC count has been widely used to guide postoperative antibacterial treatment in complicated AA. Prolonging antibacterial treatment in patients with leukocytosis at time of discharge does not result in decreased rate of postoperative complications (Desai et al. 2015). However, as described by Bonasso et al., normal WBC count at time of discharge allows for discontinuation of postoperative antibacterial treatment and therefore results in significantly decreased exposure to antibiotics (Bonasso et al. 2019).

Infectious adverse events are the most common postoperative complications in complicated AA. However, the duration of postoperative antibacterial treatment in complicated AA has not been associated with complication rates in most studies (Giesen et al. 2017; C. C. van Rossem et al. 2014; Charles C. van Rossem et al. 2016). Thus, it is possible that reducing the duration of antibiotic treatment may not increase the rate of IAA in patients with AA, as the development of infectious complications following appendectomy is likely a multifactorial process. Several risk factors have been identified including preoperative CRP level, timing of appendectomy, technique of appendiceal stump closure, surgical approach (laparoscopic or open), the presence of a fecalith, longer operation time, uncomplicated or complicated AA, body temperature, American Society of Anesthesiology (ASA) classification, age, body mass index (BMI) and gender (A. L. van den Boom et al. 2015; Emil et al. 2014; Fraser et al. 2010; Giesen et al. 2017; Henry et al. 2007; Kelly et al. 2014; Margenthaler et al. 2003).

Associations and findings mentioned above clearly indicate the need to establish antibiotic stewardship programs to reduce misuse of antibiotics as antibiotic overtreatment increases the speed of emergence and selection of resistant bacteria (Dalgic et al. 2014; Goossens 2009).

Route of administration of antibiotic treatment

Postoperative antibacterial treatment is utilized in complicated AA to prevent infectious complications. Current common practice is to administer intravenous antibiotics for 3–5 days after adequate source control, often followed by oral antibiotics at discharge or when oral intake can be resumed (Iskandar et al. 2022; Q. Liu et al. 2020; Sawyer et al. 2015a; E. Taylor et al. 2004).

Studies comparing different durations of postoperative antibacterial therapy have used exclusively intravenous administration of antibiotics (Cho et al. 2016; Kroon et al. 2023; Ramson et al. 2021; Saar et al. 2019; de Wijkerslooth et al. 2023). However, there seems to be no consensus as to the optimal route of post-appendectomy antibiotic administration (Alamili, Gögenur, and Rosenberg 2010). Moreover, intravenous antibiotic treatment is associated with excessive medical expenses and increased hospital length of stay when compared to oral route (Adibe et al. 2008; Rice et al. 2001). A shift of the intravenous antibiotic therapy to oral therapy alone would be an advancement towards minimizing the use of medication and the need for hospitalization after surgery.

Research on oral antibacterial treatment following appendectomy in complicated AA has mostly studied the timing of transition from intravenous administration of antibiotics to the oral route. Also, most of the research is conducted in pediatric populations and therefore might not be generalizable to adults. The mean duration of postoperative antibacterial treatment in pediatric studies ranged from 5 to 15 days which is considerably longer than courses commonly used in adult populations. Nevertheless, as demonstrated in a systematic review by Wang et al., sequential intravenous-oral administration of postoperative antibacterial treatment does not result in increased rate of postoperative infectious complications when compared with completely intravenous antibacterial treatment (C. Wang, Li, and Ji 2019).

Several previous trials have demonstrated the feasibility and safety of early transition from intravenous to oral route of administration of antibiotics for the treatment of pneumonia, urinary tract infections and endocarditis (Athanassa et al. 2008; Ramirez et al. 1999; Spellberg et al. 2020). Transition from intravenous to oral antibacterial treatment is considered acceptable when the patient is hemodynamically stable, clinically improving, tolerates enteral intake and has a functional gastrointestinal tract. Patients should not be switched from intravenous to oral antibacterial treatment in case of life-threatening or deep-seated infection, neutropenia and intestinal failure (Barlow and Nathwani 2000; Mertz et al. 2009). Likewise, oral antimicrobials that are typically very well absorbed have been used as initial therapy in certain conditions (Itani et al. 2012; Sandberg et al. 2012).

In clinical guidelines, a combination of cephalosporin, piperacillin in combination with metronidazole is typically recommended for the postoperative antibacterial treatment in complicated AA (Bratzler et al. 2013). Ciprofloxacin, a second-generation fluoroquinolone, is active against both Gram-negative and Gram-positive bacteria. Ciprofloxacin is frequently combined with metronidazole that has a good anti-anaerobic activity (Matthaiou et al. 2006). For stable, non-critical patients presenting with no extended spectrum beta-lactamase (ESBL) associated risk factors, amoxicillin/clavulanate or ciprofloxacin plus metronidazole regimens are recommended. In critically ill patients, however, presenting with no ESBL-associated risk factors, treatment with piperacillin/tazobactam are recommended (Sartelli et al. 2011, 2012).

Most commonly used antibiotics used for postoperative treatment in complicated AA are affordable, widely accessible, have high bioavailability and can be administered orally, e.g. amoxicillin (Béïque and Zvonar 2015). Orally administered amoxicillin reaches peak plasma concentration within 1 hour and has a reported bioavailability of 70–93% making it an acceptable alternative for intravenous therapy (Arancibia et al. 1980; Spyker et al. 1977).

Contemporary literature comparing postoperative intravenous and oral antibacterial treatment in complicated AA in adults is scarce with only a single published RCT to date. In this trial, the authors demonstrated that oral antibacterial treatment after OA resulted in similar outcomes when compared to intravenous antibacterial treatment. However, the duration of postoperative antibacterial treatment ranged from 3 to 6 days for complicated AA in both study arms. The investigators concluded that oral antibacterial treatment may not only safely replace parenteral antibiotics in AA but it may also be a significantly more cost-effective drug utilization being also more convenient to the patient, reducing hospital length of stay by 1–2 days and 30% of overall costs (Banani and Talei 1999).

A recent retrospective study comparing three-day intravenous and oral postoperative antibacterial therapy in complicated AA observed oral administration to be noninferior to intravenous administration in terms of postoperative complications. The only risk factor in the multivariate analysis for wound infections was OA. Also, in patients without postoperative surgical complications oral administration of postoperative antibacterial treatment resulted in a significant reduction (88.7%) of HLOS (Kleif et al. 2017).

Acute appendicitis in pregnancy

AA occurs less frequently among pregnant women compared to non-childbearing women (R. E. Andersson and Lambe 2001; Zingone et al. 2015). Nevertheless, AA remains the most common non-obstetrical surgical emergency during pregnancy with an incidence ranging from 1:181 to 1:1700 pregnancies (Augustin and Majerovic 2007; Bonfante Ramírez et al. 1998; Mahmoodian 1992; Parangi et al. 2007). Also, earlier studies demonstrate that non-obstetric surgery during pregnancy increases the risk of adverse obstetrical outcomes, e.g. miscarriage, stillbirth, preterm birth, low birth weight (LBW) and a lower Apgar scores (Brodsky et al. 1980; Duncan et al. 1986; Mazze and Källén 1989).

Overall, spontaneous, frequently with unknown etiology, the first-trimester fetal loss occurs in 25% to 50% of all pregnancies (Allison, Sherwood, and Schust 2011). Laparoscopic surgery during pregnancy may increase intra-abdominal pressure, result in decreased maternal cardiac output and consequently decrease utero-placental perfusion (Cox et al. 2016; Walker et al. 2014). Animal studies have shown 40% decrease of uterine blood flow with increased abdominal pressure (S. H. Park et al. 2010). Moreover, gravid uterus poses a technical challenge with risk of inadvertent uterine injury (Friedman et al. 2002; Lemieux et al. 2009). Aforementioned features of pregnancy may explain the dogmatic resilience among providers to perform laparoscopy during the first and third trimester as it may be associated with higher rate of fetal loss and preterm delivery.

Abdominal pain in pregnancy may have several obstetrical and non-obstetrical differential diagnoses. Increase of WBC count is normal during pregnancy and is more common in the third trimester (Carey and Litzenberg 1936; Kuvin and Brecher 1962). During pregnancy, normal WBC ranges from 5.6 to 13.8×10^9/L (D. J. Taylor, Phillips, and Lind 1981). Nevertheless, increased WBC count may be associated with several obstetrical adverse events, e.g. gestational hypertension, preeclampsia, gestational diabetes mellitus, preterm birth and LBW (Y. Zhang et al. 2023). Thus, diagnosing AA in pregnancy remains challenging. Ultrasound has a moderate sensitivity for identifying appendicitis in pregnant women and may be utilized as an alternative diagnostic method. US for the diagnosis of AA has a sensitivity of 56% and a specificity of 88% and diminishes as the gestational age increases (Restrepo-Castro et al. 2018; J. Zhang et al. 2021). CT should not be the initial imaging modality for the pregnant patient, except when urgent information is required in case acute abdomen (Katz et al. 2013; Masselli et al. 2013). As low as reasonably achievable (ALARA) principles should be adhered to when exposing patients to ionizing radiation (Karamat 2015). Given the utility of US and MRI in the diagnosis of abdominal pain in the gravid patient, CT should be reserved for emergency cases or when MRI is unavailable (Groen, Bae, and Lim 2012). MRI without intravenous contrast agent accurately diagnoses AA in the general adult population and improves the identification of complicated AA (D. Kim et al. 2023).

Guidelines on the management of AA in pregnancy do not recommend non-operative management of uncomplicated AA in pregnant women because of a higher rate of peritonitis, fetal demise, shock and venous thromboembolism when compared to operative management (Adamina et al. 2022; Cheng et al. 2015; Pearl et al. 2017). Also, a recent retrospective trial demonstrated an association of non-operative management of pregnant patients with complicated AA with higher odds of infectious complications, including amniotic infection and sepsis, when compared to immediate operative treatment. Failure of non-operative treatment was associated with significantly higher odds of preterm labor, preterm delivery and abortion. Non-operative management was also associated with longer HLOS and higher hospital costs (Ashbrook et al. 2022).

LA is the preferred treatment for pregnant patients with AA (Cox et al. 2016; Korndorffer, Fellinger, and Reed 2010). The size of the uterus, depending on the trimester of pregnancy, may increase the complexity of the operation accordingly. There are no restrictions as to the optimal timing of LA during pregnancy in terms of trimester of pregnancy (Adamina et al. 2022; Ball et al. 2019; Pearl et al. 2017). Most studies advocating for the safety of LA during pregnancy include patients in their first or second trimester. There is little published data on the feasibility and safety of LA performed during the third trimester (Cohen et al. 2020; Iwamura et al. 2018; Sekar et al. 2019). In general praxis, about 32% of appendectomies are performed during the first trimester, 43% during the second trimester and 25% during the third trimester, respectively. Most pregnant patients undergo OA, while LA accounts for 39% of all appendectomies. LA is more commonly used in the first (64%) and second trimester (47%), less frequently in the third trimester (16%) (Haataja et al. 2023).

Pregnant patients undergoing LA for AA have significantly shorter HLOS and lower rates of SSI when compared to OA. Although laparoscopic approach is considered safe during pregnancy, systematic reviews comparing obstetrical and surgical outcomes in OA and LA have unanimously demonstrated the increased rate of fetal loss in LA cohort (Chakraborty et al. 2019; Lee et al. 2019; Walker et al. 2014; Walsh, Tang, and Walsh 2008; Wilasrusmee et al. 2012; Zeng et al. 2021; J. Zhang et al. 2021). However, researchers have also noted that one large study have a potentially unfair impact on the results and conclusions of all systematic reviews due to a substantial number of patients included in the analysis (McGory et al. 2007). After exclusion of this particular study from the pooled analysis, no significant difference in the rate of fetal loss is observed when comparing OA to LA (Augustin et al. 2020).

As previously highlighted, McGory et al. reported higher rate of fetal loss after LA than OA (McGory et al. 2007). Despite having a great influence on meta-analyses owing to a large cohort, McGory et al. omitted gestational age in statistical analysis and have received criticism for methodology and selection bias (Eom et al. 2012; Sadot et al. 2010; Wilasrusmee et al. 2012). Also, the study analyzed surgeries conducted between 1995 and 2002 – time when LA was considered yet in its early stages, especially for pregnant patients.

The trial's definitions of an event of fetal loss and preterm delivery were indirect and unclear. The authors detected fetal loss as the presence of diagnostic codes for spontaneous abortion, intrauterine death or dilation and curettage. Early delivery was defined as procedure codes for Cesarean section or hysterectomy. The investigators reported that median length of stay for pregnant women was 3 days during which obstetric outcomes associated with the code for appendectomy were observed, therefore possibly underestimating rates of obstetric outcomes occurring beyond that hospital stay, in readmissions or outside of hospitals.

In addition, the study reported very low rates of fetal loss (LA 7% *versus* OA 3%) and preterm labor (LA < 1% *versus* OA 8%), which is lower than in the literature cited in the trial (fetal loss 3–15%, preterm delivery 15–45%). This adds to the previously mentioned underestimation of the actual rates. Thus, the results of the study of McGory et al. are advised to be taken with caution (Augustin et al. 2020).

Some recent evidence shows that surgery during pregnancy does not increase the rate of fetal loss, low Apgar scores or increase the rate of small for gestational age (SGA). Nevertheless, women who undergo non-obstetric surgery during pregnancy have an increased rate of stillbirth and preterm birth compared to women without surgery (Haataja et al. 2023). However, a recent systematic review analyzing absolute risks of adverse obstetrical outcomes following non-obstetrical surgery demonstrated higher rates of fetal loss and preterm birth for pelvic inflammatory conditions (e.g. AA) than for abdominal or nonurgent conditions. Also, surgery in the second and third trimesters was associated with lower rates of fetal loss (0.1%) and higher rates of preterm birth (13.5%) than surgery in the first and second trimesters (fetal loss 2.9%, preterm birth 5.6%) (Cusimano et al. 2023).

Summary of the review of the literature

Despite being a very common surgical condition in all age groups across the globe, the management of AA has significant scientific data gaps that warrant extensive further research. However, the previous research has addressed many aspects of the AA disease and treatments. Conservative treatment of uncomplicated AA has been studied extensively. Likewise, feasibility of non-operative management of uncomplicated AA with antibacterial treatment has been scrutinized in numerous trials. Also, previous research has noted that uncomplicated AA may even be treated without antibacterial therapy. Endoscopic management has been noted to be a promising novel alternative to surgical removal of the appendix that preserves the appendix which is considered to have a role in the functioning of the immune system and intestinal microbiota.

However, patients with complicated AA still undergo emergency surgery for source control by removal of the inflamed appendix. Perioperatively, AA can be graded according to AAST disease severity scale. The rate of postoperative complications is related to the severity of inflammation of the appendix. Postoperative antibacterial treatment is used to prevent postoperative infectious complications. However, there are several aspects of antibacterial treatment following surgery that warrant further research. Also, the debate continues on the optimal approach for appendectomy in pregnancy.

Based on the contemporary literature, there are following significant data gaps.

Firstly, there is a need for practical research to restrict the use of postoperative antibacterial treatment in complicated AA. Current guidelines recommend restricting postoperative antibacterial treatment in complicated AA to 3–5 days. According to the results of STOP-IT trial, antibacterial treatment may be discontinued after 4 days following adequate source control in the abdominal cavity. The investigators of APPIC trial concluded that 2 days of postoperative antibacterial treatment in complicated AA was not inferior to 5 days of antibiotics. Several studies have described the need to establish antibiotic stewardship programs to reduce misuse of antibiotics. Therefore, there is need for further research on the feasibility and safety of abbreviated courses of postoperative antibacterial treatment in complicated AA.

Secondly, trials comparing durations of postoperative antibacterial treatment in complicated AA use intravenous administration of antibiotics. Intravenous administration is considered to be related to higher treatment costs. Most trials study early sequential transition from intravenous to oral administration of antibacterial treatment. Only a few trials have looked at completely oral postoperative antibacterial treatment in complicated AA. There are no studies examining abbreviated courses of oral postoperative antibacterial treatment in complicated AA. A shift from intravenous administration to short oral therapy alone would be an advancement towards minimizing the use of medication and the need for hospitalization after surgery.

Thirdly, there is room for research regarding the optimal surgical approach to patients with AA in pregnancy. Although considered safe during pregnancy, LA for appendectomy in pregnant patients has been demonstrated to increase the rate of fetal loss in systematic reviews.

In conclusion, postoperative antibacterial treatment in complicated AA warrants further research in terms of necessary duration and optimal route of administration. Also, more data is needed to delineate the safe surgical approach to patients with AA in pregnancy.

AIMS OF THE STUDY

The main purpose of the study was to investigate the role of post-operative antibacterial treatment in complicated appendicitis in terms of length and route of administration. In addition, the study scrutinized the optimal approach for appendectomy in pregnant population.

The specific aims of the present study were:

1) To compare outcomes after abbreviated versus prolonged administration of intravenous antibiotics for postoperative antibacterial treatment in complicated AA after LA in adult population.
2) To analyze outcomes following short oral versus intravenous administration of antibiotics for postoperative antibacterial therapy in complicated AA after LA.
3) To assess the safety and effectiveness of OA and LA in a population-based cohort of pregnant patients suffering from AA.

MATERIAL AND METHODS

The dissertation is based on three original studies including adult patients with AA. Studies I and II included adult patients with complicated AA, study III included pregnant patients with AA regardless of the degree of inflammation of the appendix. The main characteristics of the studies are depicted in Table 2.

Table 2. Overview of the studies

Study	Study cohort	Study aim	Study design	Recruitment
Study I	Adults with AA	To compare short postoperative Abx to extended Abx in complicated AA	RCT, open-label	2016–2018, NEMC
Study II	Adults with AA	To compare short postoperative oral Abx to short intravenous Abx in complicated AA	RCT, open-label	2020–2023, NEMC
Study III	Pregnant patients with AA	To compare OA and LA in pregnancy	Retrospective	2010–2020, EHIF

AA – acute appendicitis, Abx – antibacterial therapy, RCT – randomized controlled trial, OA – open appendectomy, LA – laparoscopic appendectomy, NEMC – North Estonia Medical Centre, EHIF – Estonian Health Insurance Fund

Ethics

All the studies were approved by the Research Ethics Committee of the University of Tartu (study I approval number – 257/T-2, study II approval number – 323/T-23, study III approval number – 345/T-2) and were performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Patients and study design

Adult patients with complicated acute appendicitis (study I)

Study I enrolled all consecutive adult patients with AA at a tertiary teaching hospital (North Estonia Medical Centre, NEMC) from May 2016 to February 2018. Patients, when diagnosed with AA and scheduled for appendectomy, were consented prior to appendectomy for postoperative randomization when complicated AA was encountered at surgery.

Randomization to intravenous antibacterial therapy limited to 24 hours (short) versus >24 hours (extended) administration after appendectomy was performed with a computerized software within 24-hour period following surgery when both study groups received intravenous antimicrobial treatment per the study protocol. In patients allocated to short treatment, the antibiotic administration was terminated at 24 hours after surgery and those allocated to extended treatment interval were managed at the discretion of the treating physician. Appendicitis disease severity was classified using the DSS dividing AA into five grades: grade 1, inflamed; grade 2, gangrenous; grade 3, perforated with localized free fluid; grade 4, perforated with a regional abscess; and grade 5, perforated with diffuse peritonitis. For randomization we included grade 2, 3, and 4 constituting an entity of complicated appendicitis. The DSS grade was assessed during appendectomy by the surgeon performing the operation per the DSS grading protocol.

Exclusion criteria included age < 18 years, pregnancy, cognitive impairment, diabetes, immunodeficiency (primary or secondary), ongoing chemo- or radiotherapy for any oncological disease, radical treatment of an oncological disease within 5 years, penicillin allergy, presence of a mechanical heart valve or a synthetic vascular implants or grafts. Also, patients with grade 1 or grade 5 appendicitis per DSS were excluded (Figure 1).

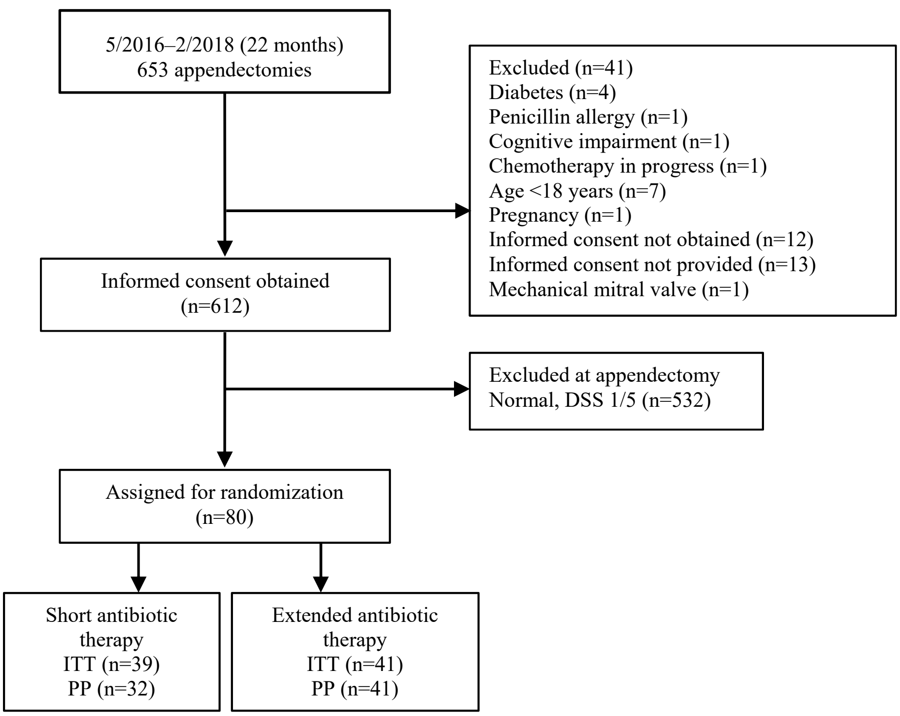

Figure 1. Flowchart of study I patient selection

Adult patients with complicated acute appendicitis (study II)

Study II enrolled all consecutive adult patients with AA at a tertiary teaching hospital (NEMC) from November 2020 to January 2023. Patients, when diagnosed with AA and scheduled for LA, were consented prior to surgery for postoperative randomization when complicated AA was encountered at operation.

Randomization to short intravenous postoperative antibacterial therapy limited to 24 hours versus short oral antibacterial therapy limited to 24 hours was performed with a computerized software immediately after appendectomy by the treating physician. In both groups, antibacterial treatment was terminated 24 hours after surgery. Appendicitis disease severity was classified using the DSS dividing AA into five grades: grade 1, inflamed; grade 2, gangrenous; grade 3, perforated with localized free fluid; grade 4, perforated with a regional abscess; and grade 5, perforated with diffuse peritonitis. For randomization we included grade 2, 3, and 4 constituting an entity of complicated appendicitis. The DSS grade was assessed during appendectomy by surgeon performing the operation per the DSS grading protocol.

Exclusion criteria included age < 18 years, pregnancy, cognitive impairment, diabetes, immunodeficiency (primary or secondary), ongoing chemo- or radiotherapy for any oncological disease, radical treatment of an oncological disease within 5 years, penicillin allergy, presence of a mechanical heart valve or a synthetic vascular implants or grafts. Also, patients with grade 1 or grade 5 appendiciti s per DSS were excluded (Figure 2).

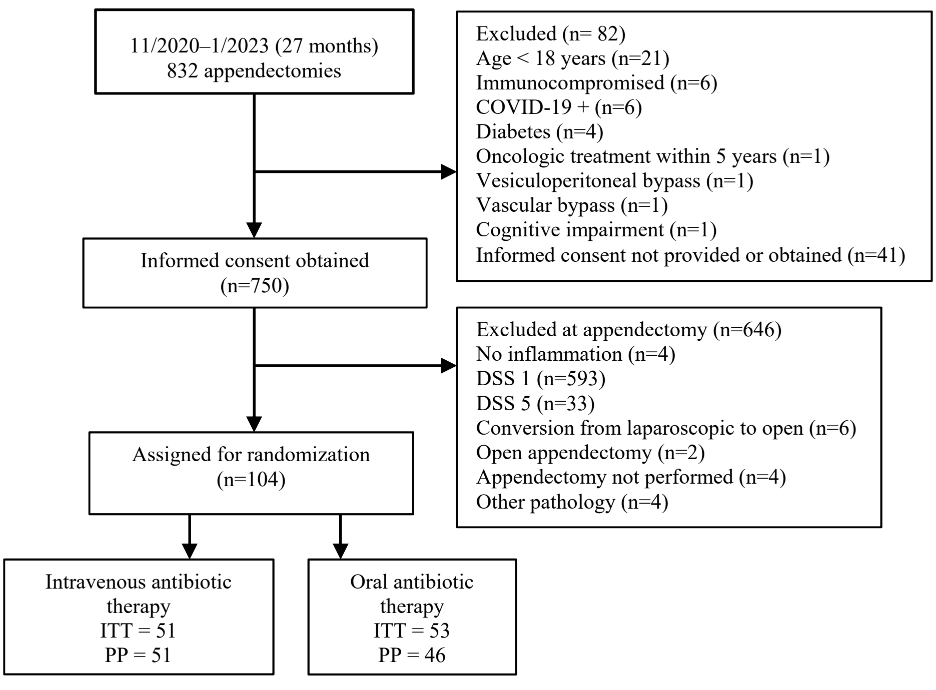

Figure 2. Flowchart of study II patient selection

Pregnant patients with acute appendicitis (study III)

Study III enrolled all pregnant patients undergoing appendectomy in 2010–2020 in Estonia. Patients' data was accrued from the Estonian Health Insurance Fund (EHIF) database and from the Estonian Medical Birth Registry (EMBR). The study subjects were identified as patients who had a medical bill with ICD-10 code for AA (K35) preceding a medical bill with ICD-10 code for delivery (O80-O84) or cessation of pregnancy (O00-O06). The individuals where appendectomy for AA remained in the preceding 9 months before delivery or 5 months before termination of pregnancy were extracted.

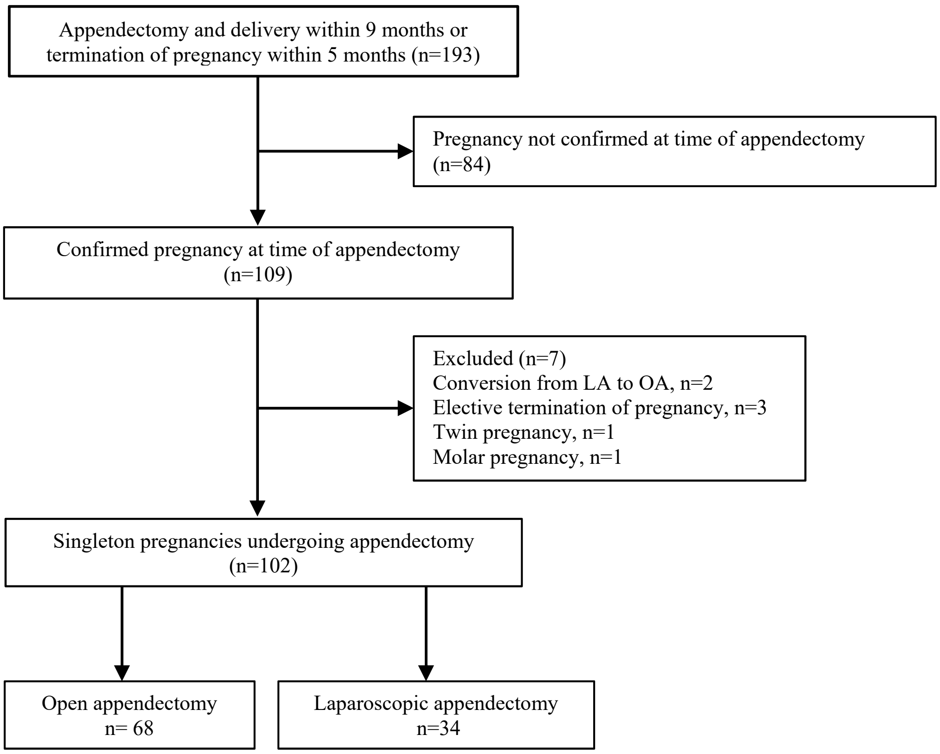

Figure 3. Flowchart of study III patient selection

Data collection

Adult patients with complicated acute appendicitis (study I and II)

Prospective data collection included demographics, laboratory markers (WBC and CRP), antibiotic therapy, surgical treatment, complications per Clavien-Dindo classification (CD), comprehensive complication index (CCI) and HLOS. Complications were screened from the hospital's electronic records.

Follow-up phone-call survey was performed 30 days after surgery and all complications and readmissions were documented. SSI, including superficial and deep incisional and organ/space SSI (IAA), was defined per Centers for Disease Control and Prevention guideline.

Primary outcomes were 30-day postoperative complications per CD and CCI. Secondary outcome was HLOS.

Pregnant patients with acute appendicitis (study III)

Data collection included demographics, clinical characteristics, laboratory and radiological findings, surgical and obstetrical outcomes. Alvarado score was calculated based on patient's record. Surgical outcomes included time from onset of symptoms to operation (time to operation), operative time, DSS, histological findings, HLOS and 30-day post-operative complications. Obstetrical outcomes included preterm delivery, fetal loss, Apgar score, birth weight, gestational age at delivery, SGA estimation and perinatal mortality. Preterm delivery was defined as delivery of a viable fetus before 37 completed weeks of gestation. Fetal loss (miscarriage) was defined as spontaneous loss of pregnancy before 22 weeks of gestation. Perinatal mortality was defined as the number of fetal deaths past 22 completed weeks of pregnancy plus the number of deaths among live-born children up to 7 completed days of life.

Primary outcomes were preterm delivery, fetal loss and perinatal mortality. Secondary outcomes included operative time, HLOS and 30-day postoperative complications.

Statistical methods

Adult patients with complicated acute appendicitis (study I)

In study I, the outcome analysis was performed per intention to treat (ITT) and per protocol (PP) follow-up. The p values for continuous variables were derived from the Student's t test or Mann-Whitney tests and for categorical values $\chi 2$ or 2-sided Fisher's exact test were used. P values less than 0.05 were considered statistically significant. Values are reported as a percentage for categorical variables and as mean ± standard deviation (SD) for continuous variables.

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS for Mac) version 16.0 (SPSS Inc., Chicago, IL).

Adult patients with complicated acute appendicitis (study II)

In study II, the REDCap electronic data collection instrument was utilized for the data collection. The outcome analysis was performed per ITT and PP follow-up. The Fisher's exact test was used to compare categorical values. All continuous variables were expressed as medians with the interquartile range (IQR) and comparisons between groups were assessed using the Mann-Whitney U test. P-values <0.05 were considered statistically significant.

All statistical analyses were performed with R Studio (RStudio Team, Boston, MA).

Pregnant patients with acute appendicitis (study III)

The Fisher's exact test was used to compare categorical values. The Student's t-test was used to compare numerical values with normal distribution and the Mann-Whitney U test for numerical values without normal distribution. Shapiro–Wilk test was utilized to confirm a normal distribution for numerical values. P-values < 0.05 were considered statistically significant. Multiple linear regression was used to define related factors for primary and secondary outcomes. Because of a low incidence of fetal loss, preterm delivery, and perinatal mortality, no multivariate regression analysis was performed for these outcomes. Likewise, due to a low incidence of complications, no multivariate regression analysis was deployed for these outcomes. After a univariate regression analysis, significant variables to predict HLOS and operative time were selected for multiple linear regression analysis.

All statistical analyses were performed with R Studio (RStudio Team, Boston, MA).

RESULTS

Twenty-four hour versus extended antibiotic administration after surgery in complicated appendicitis

During the study period, a total of 80 patients were enrolled with 39 and 41 cases in the short and the extended therapy group, respectively (Figure 1). The average length of antibiotic therapy in the extended group was 6 ± 3 days. Thirty-day follow-up by phone-call survey was available in all patients. All demographic and laboratory variables were similar between the study groups depicted in the Table 3. Majority of the cases had LA with similar rates in both study groups per ITT and PP analyses. Overall, grades 2, 3, and 4 appendicitis per DSS constituted 66.3%, 21.3%, and 12.5% of the cases, respectively, and did not differ significantly between the study groups.

HLOS and detailed description of surgical complications per CD and CCI are listed in Table 4. HLOS was significantly reduced in the short therapy group (61 ± 34 hours vs. 81 ± 40 hours, $p = 0.005$ per ITT and 51 ± 21 hours vs. 81 ± 40 hours, $p < 0.001$ per PP analysis). Mean CCI and complication rate per CD did not differ significantly between the study groups and the respective follow-up analyses. Grade II complications predominated in both study groups. None of the patients had higher than grade IIIa complication. No mortalities were encountered. When only gangrenous perforated appendicitis cases (grades 3 and 4) were stratified and compared between the study arms, the mean CCI was 5.86 and 7.14 ($p = 0.72$) and the rate of complications was 27.2% and 37.5% ($p = 0.69$) in the short and extended treatment groups, respectively.

Allocation to the short treatment group was violated in seven (17.9%) cases where antibiotic therapy was extended by the treating physician. The most frequent causes for protocol violation were persistent fever in five patients and elevated postoperative CRP (250 mg/L) in two patients after 24 hours of antibiotic treatment. None of the patients had complications during the 30-day follow-up. Thus, PP analysis included 32 patients in the short interval group and 41 in the extended interval group, respectively.

Overall, superficial and deep SSI occurred in 12.8% (n = 5) and 7.3% (n = 3) in the short and extended treatment groups, respectively ($p = 0.47$). Organ/space SSI rate was likewise similar, at 7.7% (n = 3) and 12.2% (n = 5) in the 24-hour and extended treatment groups, respectively ($p = 0.71$). No difference in SSI was noted per ITT and PP analyses. Postoperative diarrhea occurred only in one patient in the extended treatment group with a negative *Clostridium difficile* polymerase chain reaction (PCR) test. Other complications included one pneumonia and four postoperative ileus cases in the extended group. The overall readmission rates were similar at 7.7% (n = 3) and 7.3% (n = 3) in fixed and extended treatment groups, respectively ($p = 1.00$). Readmissions did not differ in ITT and PP analyses. Organ/space SSI caused all rehospitalizations and interventions included percutaneous drain placement in four and antimicrobial therapy in two patients (Table 4).

Table 3. Demographic profile, laboratory values, surgical interventions and classification of appendicitis severity per Disease Severity Score of all patients

	Intention to treat			**Per protocol**		
n	**Short** n=39	**Extended** n=41	***p*-value**	**Short** n=32	**Extended** n=41	***p*-value**
Age (years)	44.2 ± 15.2	45.8 ± 15.3	0.627	42.8 ± 14.4	45.8 ± 15.3	0.384
Gender (male)	56.4%	63.4%	0.523	59.4%	63.4%	0.913
Charlson's co-morbidity index > 0	38.5%	39.0%	0.959	34.4%	39.0%	0.870
Time from onset of symptoms to surgery (hrs)	43.2 ± 31.2	48.4 ± 44.3	0.832	45.2 ± 32.8	48.4 ± 44.3	0.623
Time from ED admission to surgery (hrs)	9.7 ± 6.9	9.1 ± 5.1	0.675	10.3 ± 7.2	9.1 ± 5.1	0.446
Mean admission WBC x 10^9/L	14.7 ± 4.4	14.3 ± 3.7	0.641	14.4 ± 4.5	14.3 ± 3.7	0.901
Mean admission CRP mg/L	92 ± 99	87 ± 101	0.829	82 ± 93	87 ± 101	0.408
Laparoscopic appendectomy	89.7%	95.1%	0.426	87.5%	95.1%	0.455
Open appendectomy	10.3%	4.9%	0.426	12.5%	4.9%	0.394
Conversion to open appendectomy	2.6%	0	0.488	3.1%	0	0.438
Length of operation (min)	52 ± 19	54 ± 20	0.680	51 ± 19	54 ± 20	0.433
DSS grade 2	71.8%	61.0%	0.306	75.0%	61.0%	0.310
DSS grade 3	20.5%	22.0%	0.875	15.6%	22.0%	0.561
DSS grade 4	7.7%	17.1%	0.313	9.4%	17.1%	0.499

ED – Emergency Department; WBC – white blood cell count; CRP – C-reactive protein; DSS – Disease Severity Score

For continuous variables mean (±SD) was reported. Percentages might not total 100 because of rounding.
* For categorical variables p values were based on Fisher's exact test, for continuous variables p values were based on Mann-Whitney U test

Table 4. Hospital length of stay, complications per Clavien-Dindo classification, Comprehensive Complication Index and interventions in all readmitted patients

	Intention to treat			Per protocol		
	Short	**Extended**	***p*-value***	**Short**	**Extended**	***p*-value***
n	n=39	n=41		n=32	n=41	
HLOS (hours)	61 ± 34	81 ± 40	**0.005**	51 ± 21	81 ± 40	**<0.001**
Any CD complication	17.9%	29.3%	0.234	21.9%	29.3%	0.475
Grade I per CD	2.6%	9.8%	0.360	3.1%	9.8%	0.377
Grade II	10.3%	14.6%	0.738	12.5%	14.6%	1.000
Grade IIIa	5.1%	4.9%	1.000	6.3%	4.9%	1.000
Grade IIIb-V	0	0	-	0	0	-
Superficial/deep SSI	12.8%	7.3%	0.476	15.6%	7.3%	0.287
Organ/space SSI	7.7%	12.2%	0.713	9.4%	12.2%	1.000
Diarrhea	0	2.4%	1.000	0	2.4%	1.000
Pneumonia	0	2.4%	1.000	0	2.4%	1.000
Postoperative ileus	0	9.8%	0.116	0	9.8%	0.126
Mean CCI	3.93 ± 8.93	5.46 ± 9.57	0.298	4.79 ± 9.67	5.46 ± 9.57	0.579
Readmitted patients	7.7%	7.3%	1.000	9.4%	7.3%	1.000
Interventions in all readmitted patients						
Antimicrobial therapy	2.6% (1)	2.4% (1)	1.000	3.1% (1)	2.4% (1)	1.000
Percutaneous drainage + antimicrobial therapy	5.1% (2)	4.9% (2)	1.000	6.3% (2)	4.9% (2)	1.000

HLOS – Hospital Length of Stay; CD – Clavien-Dindo; SSI – Surgical site infection; CCI – Comprehensive Complication Index

For continuous variables mean (±SD) was reported. Percentages might not total 100 because of rounding.
* For categorical variables p values were based on Fisher's exact test, for continuous variables p values were based on Mann-Whitney U test

During the study period, a total of 104 patients were enrolled with 51 and 53 cases in intravenous and oral administration groups, respectively (Figure 2). Demographic and laboratory values were similar between the study groups with the exception of time from symptom onset to surgical treatment which was significantly longer in the oral antibacterial study group (p=0.005; Table 5). Positive finding for acute appendicitis on US was present in 69% and 75% of cases in intravenous and oral groups, respectively (p=0.735). CT investigation was obtained in 55% and 49% of cases in intravenous and oral groups, respectively (p=0.689).

There was no significant difference in duration of surgery in either of the study groups with an average LA lasting for 50 minutes. Overall, DSS grades 2, 3 and 4 accounted for 74%, 16% and 10% of all included cases respectively and did not differ significantly between the study groups. Appendiceal stump was closed with DS Appendectomy clips (B Braun, Melsungen, Germany) in 80% of cases with occasional use of Endoloop® ligature (Johnson & Johnson, New Brunswick, NJ, USA) or endoscopic stapler in both groups. There was no statistically significant difference between appendiceal stump closure techniques and the rate of complications (p=0.461). Histological examination revealed phlegmonous inflammation, gangrenous inflammation, and malignancy (neuroendocrine tumors in both groups) in 25%, 73% and 2% of cases, respectively, with no significant difference between the study groups (Table 5).

Thirty-day postoperative surgical complications and HLOS are listed in Table 6. Overall, the rate of complications was 15.7% and 15.1% in intravenous and oral groups, respectively (p=0.999). Median CCI did not differ between the two cohorts. Superficial/deep SSI accounted for 8% of cases in oral group and 4% in intravenous group (p=0.679). The overall readmission rates were similar with 10% and 9% in intravenous and oral groups, respectively. Unplanned readmissions were all but one due to postoperative organ/space SSI. Overall, 67% of patients with a postoperative organ/space SSI had a DSS grade 3 or 4 at the time of surgery. The incidence of postoperative organ/space SSI was 10% and 9% in intravenous and oral groups respectively with no significant difference between the two study groups. HLOS was similar in both groups with a median of 1.2 days and 1.3 days in intravenous and oral group, respectively.

Table 5. Demographics, laboratory values, classification of appendicitis per DSS and results of histological analysis

Variables	ITT			PP		
	Intravenous n = 51	Oral n = 53	p-value*	Intravenous n = 51	Oral n = 46	p-value*
Age (years)	47 (32–61)	45 (33–53)	0.400	47 (32–61)	45 (32–53)	0.382
Gender (male), n (%)	28 (55)	39 (74)	0.065	28 (55)	34 (74)	0.060
Charlson's comorbidity index > 0	22 (43)	16 (30)	0.243	22 (43)	12 (26)	0.092
White blood cells (x10^9/L)	13.4 (11.1–15.0)	13.8 (11.9–16.4)	0.296	13.4 (11.1–15.0)	13.8 (11.9–16.1)	0.443
C-reactive protein (mg/L)	48 (13.5–100.5)	48 (17.0–100.0)	0.972	48 (13.5–100.5)	46 (17.0–95.5)	0.820
Temperature (Celsius)	36.8 (36.5–37.2)	36.9 (36.5–37.3)	0.577	36.8 (36.5–37.2)	36.8 (36.5–37.3)	0.848
Time from symptom onset to operation (hours)	27 (21–48)	38 (25–60)	**0.005**	27 (21–48)	34 (24–59)	0.119
Time from admission to operation (hours)	9 (7–12)	10 (7–16)	0.557	9 (7–12)	9.5 (7–16)	0.658
Operation duration (minutes)	50.0 (36.5–63.5)	48.0 (35.0–55.0)	0.242	50.0 (36.5–63.5)	46.5 (35.0–55.0)	0.182
DSS, n (%)						
DSS 2	38 (74)	39 (74)		38 (74)	35 (76)	
DSS 3	10 (20)	7 (13)	0.395	10 (20)	6 (13)	0.532
DSS 4	3 (6)	7 (13)		3 (6)	5 (11)	
Rinsing, n (%)	6 (12)	6 (11)	0.999	6 (12)	4 (9)	0.744
Drainage, n (%)	2 (4)	3 (6)	0.999	2 (4)	2 (4)	0.999
Histological analysis, n (%)						
Phlegmonous	13 (25)	13 (25)		13 (25)	11 (24)	
Gangrenous	37 (73)	39 (73)	0.999	37 (73)	34 (74)	0.999
Malignancy	1 (2)	1 (2)		1 (2)	1 (2)	

DSS – disease severity score

For continuous variables median (IQR) was reported. Percentages might not total 100 because of rounding.

* For categorical variables p values were based on Fisher's exact test, for continuous variables p values were based on Mann-Whitney U test

Table 6. Thirty-day postoperative complications, management of infectious complications and hospital length of stay

Variables	ITT			PP		
	Intravenous n = 51	Oral n = 53	p-value*	Intravenous n = 51	Oral n = 46	p-value*
No complications, n (%)	43 (84.3)	45 (84.9)	0.999	43 (84.3)	41 (89.1)	0.561
Overall complications, n (%)	8 (15.7)	8 (15.1)	0.999	8 (15.7)	5 (10.9)	0.561
Complications per CD, n (%)						
Grade I	3 (38)	3 (38)		3 (38)	1 (20)	
Grade II	3 (38)	1 (13)		3 (38)	1 (20)	
Grade IIIa	1 (13)	3 (38)	0.785	1 (13)	3 (60)	0.456
Grade IIIb	1 (13)	1 (13)		1 (13)	0 (0)	
Grade IV – V	0 (0)	0 (0)		0 (0)	0 (0)	
Comprehensive Complication Index	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.915	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.509
Postoperative ileus, n (%)	1 (2)	3 (6)	0.618	1 (2)	2 (4)	0.602
Pneumonia, n (%)	1 (2)	0 (0)	0.490	1 (2)	0 (0)	0.999
Superficial/deep SSI, n (%)	2 (4)	4 (8)	0.679	2 (4)	2 (4)	0.999
Organ/space SSI, n (%)	5 (10)	4 (9)	0.739	5 (10)	3 (7)	0.718
Readmission rate, n (%)	5 (10)	4 (9)	0.739	5 (10)	4 (9)	0.999
Organ/space SSI management, n (%)						
Conservative	3 (60)	1 (25)		3 (60)	1 (33)	
Percutaneous drainage	1 (20)	2 (50)	0.571	1 (20)	2 (67)	0.679
Laparoscopic drainage	1 (20)	0 (0)		1 (20)	0 (0)	
Open drainage	0 (0)	1 (25)		0 (0)	0 (0)	
Hospital length of stay (days)	1.2 (1.0–1.6)	1.3 (1.0 -1.8)	0.543	1.2 (1.0–1.6)	1.1 (1.0–1.7)	0.965

CD – Clavien-Dindo, SSI – surgical site infection

For continuous variables median (IQR) was reported. Percentages might not total 100 because of rounding.
* For categorical variables p values were based on Fisher's exact test, for continuous variables p values were based on Mann-Whitney U test

When diagnosed with a postoperative complication, patients received a new course of antibiotics in 10% and 9% of cases in intravenous and oral therapy groups respectively without any significant difference between the study groups. Median new course of antibiotics was 8 and 9 days in intravenous and oral groups respectively (p=0.781).

When only perforated (DSS grade 3 and 4) appendicitis cases were stratified and compared between the study arms, the median CCI was not significantly different. Postoperative organ/space SSI rate for patients with perforated appendicitis was 31% and 14% in intravenous and oral groups respectively (p=0.385).

In terms of histological examination, specimens of clinically perforated appendices (DSS grade 3 and 4) were phlegmonous in 19%, gangrenous in 75% and malignant in 6% of cases. Likewise, postoperative organ/space SSI was observed in 22% of phlegmonous, 67% of gangrenous and 11% of malignant cases of acute appendicitis.

Allocation to short oral antibacterial treatment was violated in 13% (n=7) of cases with extended oral or intravenous antibiotics continued by the treating physician. There were no violations of allocation in intravenous group. Most common causes of violation were fever > 38^{o}C and high inflammatory markers (CRP and WBC) on first postoperative day. There were two complications among those treated with an extended course of antibiotics – one superficial/deep SSI and one organ/space SSI. The latter required open drainage under general anesthesia. Thus, PP analysis included 51 patients in intravenous group and 46 patients in oral group.

Open versus laparoscopic appendectomy for acute appendicitis in pregnancy

During the 11-year study period, 102 patients were included for the final analysis (Figure 3). OA and LA ratio were 67% and 33%, respectively. The rate of LA increased in recent years compared to OA (Figure 4).

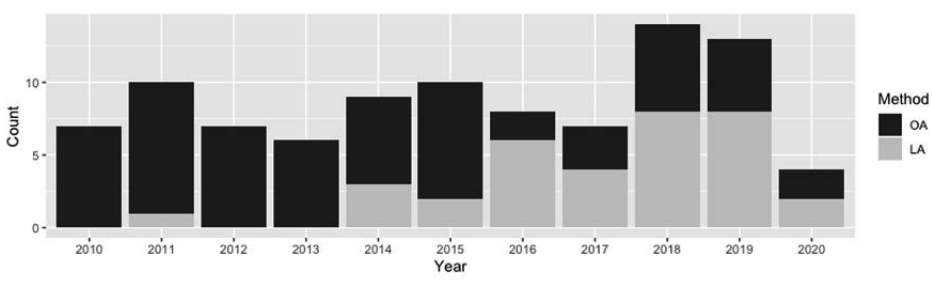

Figure 4. Distribution of open (OA) and laparoscopic appendectomies (LA) from 2010 to 2020 (R Studio)

Demographical data are depicted in Table 7. The mean age was similar in both cohorts being 27 and 29 years in the OA and LA cohort, respectively (p = 0.089). The mean gestational age during appendectomy and proportion of patients with third trimester pregnancy were significantly higher in the OA cohort. The rate of patients with previous laparoscopic intervention was higher in the LA cohort (p = 0.032).

Data about inflammatory markers and radiological investigations is shown in Table 8. The only significantly different variable was the incidence of positive US for acute appendicitis being significantly higher in the LA cohort (p = 0.008).

Overall, 153,790 deliveries and 75,464 pregnancy losses (elective abortions and terminations due to medical indications) were recorded during the study period in Estonia. Thus, the prevalence of AA during pregnancy was 0.05% (95% CI 0.04%–0.06%).

Table 7. Patients' characteristics upon admission in open (OA) and laparoscopic appendectomy (LA) cohorts

Variable	OA N=68	LA N=34	p-value*
Age (years)	27 .18 ±5.47	29.21± 5.66	0.089
History of miscarriage n (%)	7 (11)	9 (26)	0.082
Body mass index (kg/m^2)	23.12±4.11	25.71±4.79	0.074
Gestational age at appendectomy (weeks)	17.44±8.56	12.97±5.90	**0.002**
1st trimester n (%)	23 (35)	17 (50)	0.199
2nd trimester n (%)	31 (46)	16 (47)	1
3rd trimester n (%)	13 (19)	1 (3)	**0.031**
Previous laparoscopy n (%)	3 (4)	7 (21)	**0.032**
Previous laparotomy n (%)	1 (1)	3 (9)	0.119

For continuous variables mean ± SD was reported

* For categorical variables p values were based on Fisher's exact test, for numerical variables p values were based on Student's t-test or Mann-Whitney U test

Table 8. Patients' clinical findings upon admission in open (OA) and laparoscopic appendectomy (LA) cohorts

Variable	OA N=68	LA N=34	p-value*
Alvarado score	7.11±1.62	6.67±1.78	0.274
Body temperature (Celsius)	36.87±0.45	36.94±0.56	0.495
C-reactive protein (mg/L)	33.50±53.43	33.23±35.64	0.332
White blood cells (x10^9/L)	14.11±3.72	14.43±4.78	0.426
Ultrasound performed n (%)	57 (84)	29 (85)	1
Ultrasound positive for acute appendicitis n (%)	19 (33)	19 (66)	**0.008**
Computed tomography performed n (%)	2 (3)	1 (3)	1
Magnetic resonance imaging performed n (%)	4 (6)	2 (6)	1

For continuous variables mean ± SD was reported

* For categorical variables p values were based on Fisher's exact test, for numerical variables p values were based on Student's t-test or Mann-Whitney U test

Obstetrical outcomes

Among patients undergoing OA one pregnancy complicated with chorioamnionitis on week 20 and one with a subchorionic hematoma on week 18, both leading to termination of pregnancy before 22 gestational weeks. There were no fetal losses in the LA cohort.

Obstetrical outcomes including preterm delivery, gestational age at delivery, delivery mode (vaginal *versus* caesarean), newborn's Apgar score and birth weight were similar between the LA and OA cohorts. There were two events of perinatal mortality in the OA cohort: one after a preterm delivery at 26 gestational weeks and the other after a delivery of 42 gestational weeks. There were no perinatal mortality events in the LA cohort. However, the difference in the frequency of perinatal mortality in the two cohorts was not significant (p = 0.548).

When compared to all deliveries in Estonia from 2010 to 2020 (n = 153,790), pregnant women with AA had more hypertensive disorders, including preeclampsia, gestational and chronic hypertension (10.7% vs 3.4%, p = 0.008, Table 9). There was no difference in preterm rate, delivery mode, birth weight, low Apgar score and overall perinatal mortality rate.

Table 9. Obstetrical outcomes in open (OA) and laparoscopic appendectomy (LA) cohorts

Variable	OA N=68	LA N=34	p-value*	All appendectomies n=102	All deliveries N=153790	p- value
Fetal loss before 22 gestational week n (%)	2 (3)	0 (0)	0.548	2	NA	
Gestational diabetes n (%)	3 (4)	5(15)	0.122	8	10027 (6.50)	0.548
Hypertensive disorders ** n (%)	9(13)	2 (6)	0.327	11 (10.7)	5256 (3.40)	**0.0008**
Preterm delivery n (%)	5 (7)	4(12)	0.489	9 (9)	8316 (5.40%)	0.128
Delivery V/C n (%)	55 (82) / 12 (18)	29 (86) / 5 (14)	0.782	84 (83) /17 (17)	123438 (80.30)/ 30352 (19.70%)	0.534
Gestational age at delivery (weeks)	38.51±4.39	38.82±1.51	0.066		NA	
Apgar 1	8.50±1.36	8.21±1.45	0.087	10 (10)	NA	
Low APGAR 1 (≤7) n (%)	5 (7)	5 (22)			15206 (9.80) ***	1
Apgar 5	9.05±0.86	8.88±0.98	0.277	3 (3)	NA	
Low APGAR 5 (≤7) n (%)	2 (3)	1 (3)			5132 (3.30) **	
Birth weight (grams)	3489.16±382.52	3445.35±495.78	0.655		3511.20 ±6.90	1
Small for gestational age new-born n (%)	0 (0)	1 (3)	0.358	NA	NA	NA
Perinatal mortality n (‰)	2 (0.3)	0 (0)	0.548	2	667 (0.043)	0.070

For continuous variables mean ± SD was reported

*For categorical variables p values were based on Fisher's exact test, for numerical variables p values were based on Student's t-test or Mann-Whitney U test

** includes cases of preeclampsia (n=3061), eclampsia (n=23), gestational and chronic hypertension

*** total number of liveborn babies n=155785

Delivery V/C – Vaginal / Caesarean

Surgical outcomes

The time from onset of symptoms to operation, DSS and use of surgical drains were similar between patients in the OA and LA cohort. Duration of appendectomy and HLOS were significantly shorter in the LA cohort compared to patients in the OA cohort (34.6 minutes versus 44.7 minutes; p = 0.038 and 2.2 versus 3.0 days, p = 0.016).

Overall rate of 30-day post-operative complications including SSI and IAA was very low in both cohorts – a total of five events in both cohorts (Table 10).

Table 10. Surgical outcomes in open (OA) and laparoscopic appendectomy (LA) cohorts

Variable	OA N=68	LA N=34	p-value*
Time to operation (hours)	28.19±17.47	28.64±17.93	0.921
Operative time (minutes)	44.66±23.25	34.63±11.85	**0.038**
Drain usage n (%)	5 (7)	5 (15)	0.286
Disease severity score			
1) No appendicitis n (%)	2 (3)	3 (9)	0.331
2) Grade 1 n (%)	51 (76)	23 (67)	0.475
3) Grade 2 n (%)	12 (18)	6 (18)	1
4) Grade 3 n (%)	0 (0)	2 (6)	0.111
5) Grade 4 n (%)	2 (3)	0 (0)	0.548
6) Grade 5 n (%)	0 (0)	0 (0)	
Pathohistological findings			
1) Normal n (%)	3 (6)	1 (3)	1
2) Phlegmonous n (%)	40 (78)	25 (76)	0.794
3) Gangrenous n (%)	8 (16)	6 (18)	0.772
4) Neoplasia n (%)	0 (0)	1 (3)	0.392
Hospital length of stay (days)	2.96±1.83	2.15±1.42	**0.016**
Surgical site infection n (%)	2 (3)	1 (3)	1
Intra-abdominal abscess n (%)	2 (3)	0 (0)	0.551

For continuous variables mean ± SD was reported

* For categorical variables p values were based on Fisher's exact test, for numerical variables p values were based on Student's t-test or Mann-Whitney U test

Multiple linear regression model fitted for HLOS found time to operation, operative time and surgical drain usage to increase significantly the HLOS. However, LA was associated with decreased HLOS (Table 11). Multiple linear regression model fitted for operative time found no significant variables related to operative time.

Table 11. Multiple linear regression model fitted for hospital length of stay

	Estimate	Standard error	p-value*
(Intercept)	1.383608	0.391441	0.000703
Laparoscopic appendectomy	-0.930136	0.299937	0.002716
Time to operation	0.020543	0.008754	0.021576
Operative time	0.020616	0.007258	0.005796
Drain usage	2.304671	0.468705	0.000

*Only significantly related variables presented

DISCUSSION

In this dissertation, three relevant aspects of the management of AA in adult population, including abbreviated course of postoperative antibacterial treatment, the role of oral administration of postoperative antibiotics, and the optimal surgical approach for appendectomy in pregnancy, were investigated.

Twenty-four hour versus extended antibiotic administration after surgery in complicated appendicitis

Antibacterial resistance is a global health challenge (Larsson and Flach 2022). As the poor Global stewardship of antimicrobials is the main driver of growing resistance to antibiotics, there is clear need for research to establish the optimal role of perioperative antibacterial treatment. Approximately 30–50% of the antibiotic consumption in hospitals is inappropriate (Hecker et al. 2003). Thus, reducing unnecessary administration of postoperative antibacterial treatment may contribute to the decrease of growing antibacterial resistance.

Patients with complicated AA may not benefit from a longer course of postoperative antibacterial treatment in complicated AA. Duration of postoperative antibacterial treatment in complicated AA is not an independent risk factor affecting complication rate in most studies (Giesen et al. 2017; C. C. van Rossem et al. 2014; Charles C. van Rossem et al. 2016). The current trial supported the hypothesis of noninferiority of a short, 24-hour therapy, compared to an extended antibacterial treatment after source control in complicated AA. The rate of postoperative complications did not differ between the two study arms. Also, the study demonstrated significantly reduced HLOS in the short therapy group providing a significant cost-saving perspective and an antimicrobial stewardship potential in patients suffering from a common surgical emergency, i.e. complicated AA.

Postoperative administration is indicated according to the guidelines in complicated AA. However, randomized controlled trials are lacking to guide the best practice in terms of treatment duration. The extent of postoperative antimicrobial therapy in complicated AA is a subject of an ongoing debate. Recent investigations have observed noninferiority of short antibacterial therapy in mixed groups of patients with intraabdominal infections after adequate source control (Sawyer et al. 2015b). Nevertheless, prospective randomized studies specific to complicated appendicitis are scarce. Recently, the results of the APPIC trial demonstrated the safety of a shorter course of postoperative antibacterial treatment in complicated AA limited to 2 days when compared to 5-day course (de Wijkerslooth et al. 2023). A large prospective observational study by van Rossem et al. comparing 3-day antibiotic treatment with 5-day therapy in complicated AA observed no benefit on infectious complications in extended administration (Charles C. van Rossem et al. 2016).

The need for postoperative antibacterial treatment in complicated AA has also been brought into question. A small retrospective study by Kimbrell et al.

reported similar rate of postoperative complications among patients receiving antibiotics for 24 hours or less compared to extended administration after appendectomy for complicated AA (Kimbrell et al. 2014).

Current trial randomized patients to receive antibiotics per fixed 24-hour course versus extended course and observed no difference in the rate of post-operative complications in the two study arms. HLOS was significantly shorter in the short antibiotic therapy group, indicating a potential for cost saving perspective. Also, antibiotics utilized in the current study are rather inexpensive and widely available providing opportunities for a global implementation of the results.

The analysis included both ITT and PP follow-up with no significant difference in outcomes. The short therapy group treatment was violated per treating physicians in seven cases with most frequent cause being fever, however, none of the patients developed complications. A fever in the postoperative period is a common entity and may be related with non-infectious etiology including respiratory complications, drug fever, endocrine abnormalities or surgical insult with no indications for antimicrobial therapy (Johnson and Cunha 1996).

Short postoperative intravenous versus oral antibacterial therapy in complicated acute appendicitis

The current prospective randomized controlled trial supports the hypothesis of non-inferiority of 24-hour oral antibiotic treatment compared to 24-hour intravenous antibiotic treatment in complicated AA after adequate surgical source control. Oral administration of antibiotics was not associated with an increased risk of postoperative infections when compared to intravenous antibiotic treatment of the same length after LA in complicated AA. The rate of postoperative organ/space SSI in this study was 10% and 9% in intravenous and oral groups respectively which is comparable to 7–12% observed in the recent literature (Kleif et al. 2017; Saar et al. 2019; de Wijkerslooth et al. 2023). The overall rate of complications was 15% in both study groups which is comparable to 14–19% in previous studies (Giesen et al. 2017; Charles C. van Rossem et al. 2016; van Wijck et al. 2010).

Patients in the oral group had a longer time from symptom onset to surgical treatment in this trial. The extended time interval between onset of symptoms and surgery has been previously shown to increase the rate of complications, duration of surgery and hospital length of stay (Saar et al. 2016). However, our findings did not demonstrate a higher rate of perioperative morbidity in the oral group. Nevertheless, time difference from the onset of symptoms to surgery between the study arms may potentially impact the study results.

According to the study protocol, patients randomized to oral group were discharged only after completion of antibacterial treatment at the hospital. Following appropriate validation of the study results, oral antibacterial therapy could be administered as an outpatient regimen resulting in a significant reduction in HLOS and overall costs savings when compared to intravenous treatment.

Optimizing antibacterial treatment is a part of WHO's policy to reduce worldwide misuse and overuse of antimicrobials as the main drivers of antimicrobial resistance (World Health Organization 2019). Studies have shown variation in compliance with antibiotic guidelines with potential for improvement of antibacterial stewardship (Bass et al. 2023; Thong et al. 2020). Also, there is obvious need for pragmatical research whether it is possible to further abbreviate postoperative antibiotic course (Bhangu, Buchwald, and Ntirenganya 2023). There is evidence that postoperative antibiotics are not associated with decreased wound complications in complicated appendicitis (D. Y. Kim et al. 2015; Kimbrell et al. 2014).

The optimal route of administration of postoperative antibacterial therapy in complicated AA is still a matter of debate. Most studies combine intravenous with oral administration of antibiotics with alteration to oral antibiotics when diet is resumed (E. Taylor et al. 2004; van den Boom, de Wijkerslooth, and Wijnhoven 2020). A retrospective study comparing three-day intravenous and oral postoperative antibacterial therapy in complicated appendicitis observed oral administration to be noninferior to intravenous administration (Kleif et al. 2017).

Orally administered amoxicillin reaches peak plasma concentration within 1 hour and has a reported bioavailability of 70–93% making it an acceptable alternative for intravenous therapy (Arancibia et al. 1980; Spyker et al. 1977). Antibiotics used in the current study are relatively affordable and widely accessible providing opportunities for a worldwide application of the study results. A shift of the intravenous antibiotic therapy to oral therapy alone would be an advancement towards minimizing the use of medication and the need for hospitalization after surgery.

Research on comparing postoperative intravenous and oral antibacterial treatment in complicated AA in adults is very scarce with only a single published prospective study to date (Banani and Talei 1999). The current study is the pioneering randomized controlled trial to exclusively compare 24-hour postoperative oral treatment to 24-hour intravenous administration of antibacterial therapy in complicated AA.

Open versus laparoscopic appendectomy for acute appendicitis in pregnancy

LA is considered as the treatment of choice for acute appendicitis in settings with laparoscopic capabilities. During the study period the percentage of LA for AA has risen from 10% in 2010 to 80% in 2020 in general population in Estonia (Estonian Health Insurance Fund 2023). The extended overall experience with laparoscopic approach has had an impact on the treatment of AA also in pregnant patients with a clear increase of LA rates as seen in Figure 4. Recent guidelines recommend against non-operative management of AA in pregnant women (Di Saverio et al. 2020; Pearl et al. 2017). Although LA is considered safe for pregnant patients, several reviews and meta-analyses have concluded that there is low-grade evidence suggesting that LA in pregnant women may be associated with a higher risk of fetal loss.

The only previous population-based study comparing OA and LA for AA in pregnancy was published by Cheng et al. using the database of Taiwan's National Health Research Institute without examination of individual patients' medical records (Cheng et al. 2015). While this resulted in a larger cohort than previous studies, the reported data does not include any perinatal information e.g. Apgar scores or birth weight. However, the reported surgical and obstetrical outcomes were similar to our study with LA cohort having a shorter HLOS and no increased risk of obstetrical complications when compared to OA cohort. Based on the epidemiological data the incidence of AA during pregnancy in Taiwan was 0.075% being considerably higher than 0.05% in Estonia.

Overall, spontaneous, frequently with unknown etiology, the first-trimester fetal loss occurs in 25% to 50% of all pregnancies (Allison, Sherwood, and Schust 2011). Laparoscopic surgery during pregnancy may increase intra-abdominal pressure, result in decreased maternal cardiac output and consequently decrease utero-placental perfusion (Cox et al. 2016; Walker et al. 2014). Animal studies have shown 40% decrease of uterine blood flow with increased abdominal pressure (S. H. Park et al. 2010). Moreover, gravid uterus poses a technical challenge with risk of inadvertent uterine injury (Friedman et al. 2002; Lemieux et al. 2009). Most studies advocating for the safety of LA during pregnancy include patients in their first or second trimester. There is little published data on the feasibility and safety of LA performed during the third trimester (Cohen et al. 2020; Iwamura et al. 2018; Sekar et al. 2019). McGory et al reported higher rate of fetal loss after LA than OA. Despite having great influence in meta-analyses, McGory et al omitted gestational age in statistical analysis and have received criticism for methodology and selection bias (Eom et al. 2012; Sadot et al. 2010; Wilasrusmee et al. 2012) .

This study included all pregnant women with AA undergoing appendectomy regardless of their length of gestation. In fact, the mean gestational age at surgery was 12 weeks in the LA cohort. There were no events of fetal loss in the LA cohort. Also, patients in the LA cohort had a smaller pregnancy than OA cohort in terms of gestational weeks (17 weeks versus 12 weeks), indicating the safety of laparoscopy during early weeks of pregnancy. In terms of fetal size, when compared at week 12 and 17, the difference is of marginal clinical significance (Assessment of Gestational Age by Ultrasound | GLOWM n.d.). On the other hand, there were more patients in the OA cohort in their third trimester at the time of appendectomy than in the LA cohort (19% versus 3%) reflecting a more traditional approach.

Pregnant women who underwent LA had shorter operative time and HLOS than patients who received OA. However, all but one of the patients in their 3rd trimester underwent OA. Technical challenges due to increased volume of the gravid uterus may increase the operative time. Also, there were more positive

US scans for AA in the LA cohort. While many of the admitted patients without a confirmed diagnosis of AA were actively monitored for worsening of symptoms, patients with a positive US finding could proceed to surgery quicker and thus have a shorter HLOS.

The increased rate of positive finding for acute appendicitis in US in LA cohort might be explained by the study cohort. All but one pregnant woman in their 3rd trimester underwent OA. Sensitivity of US for AA during pregnancy ranges from 46% to 63% and diminishes as the gestational age increases (Restrepo-Castro et al. 2018). A considerable number of patients in our study were operated for AA despite inconclusive findings on ultrasound – 66% and 33% in OA and LA cohorts respectfully. Nevertheless, negative appendectomy rate in our study was 6% and 3% in OA and LA cohort respectively which is considerably lower than the reported up to 30% in the literature (Pedrosa et al. 2009; Tankel et al. 2019). Negative appendectomy during pregnancy is associated with adverse neonatal outcomes, such as lower neonatal birthweight, lower neonatal gestational age and fetal loss (McGory et al. 2007; Rottenstreich et al. 2022).

The results of multiple regression analysis demonstrated a strong relationship between surgical drain utilization after appendectomy and increase of HLOS. The finding is coherent with previous publications. The use of abdominal drainage after appendectomy for complicated AA hasn't shown any significant reduction in prevention of IAA or SSI but an increase of the HLOS and the cost of operation (Abdulhamid and Sarker 2018; Zhe Li et al. 2018; Zhuyin Li et al. 2021). Interestingly, gestational age was not related to either operative time or HLOS in a multivariate linear regression analysis.

Limitations

Studies of this dissertation are limited to a low number of recruited patients. We acknowledge the risk of the studies being underpowered to allow for any final conclusions. Also, the majority of the results are applicable only to a rather healthy adult population. Patients with diabetes or immunodeficiency may benefit from a longer course of antibiotic therapy (Ho et al. 2020). The application of 24-hour oral or intravenous postoperative antibacterial treatment in children with complicated AA remains a topic for further investigations.

Nevertheless, to the best of our knowledge trials in this dissertation are the very first randomized studies to compare postoperative short antimicrobial therapy interval with extended treatment and short oral administration of antimicrobial therapy with intravenous in complicated appendicitis. Thus, our studies have the potential to modify postoperative management of acute complicated appendicitis in the era of rising antimicrobial resistance and to initiate large multi-center investigations to confirm our findings.

The strength of the third study can be seen in its population-based extensive cohort that was achieved by using the billing information of all the pregnant patients undergoing appendectomy from 2010 to 2020 at different hospitals across the country. Also, by examining each patient record, this study reports detailed perioperative surgical and obstetrical outcomes. The limitations of the third study are retrospective nature and rather low number of patients resulting in failure to analyze rare obstetrical events like preterm birth and fetal loss.

Future perspectives

Postoperative antibacterial treatment in complicated AA has seen a significant decrease of duration in the last decade. Shorter durations of postoperative antibacterial treatment in complicated AA result in similar results when compared to longer courses. As the duration of postoperative antibacterial treatment in complicated AA is not an independent risk factor for postoperative infectious complications, the need for postoperative antibacterial treatment has been brought into question. The necessity of postoperative antibacterial treatment after an adequate source control in complicated AA warrants scientific investigations.

Also, most trials advocating for the safety of LA in pregnancy for AA report results from patients in their first or second trimester. More research on LA performed in the third trimester is warranted to delineate the role of LA in pregnancy.

CONCLUSIONS

1) Short (24-hour) antibiotic administration following appendectomy did not result in a higher rate of postoperative infectious complications in complicated AA when compared to an extended course of antibacterial treatment. The short interval administration resulted in a significant reduction in HLOS with a major cost-saving and antibacterial stewardship perspective.
2) Short (24-hour) oral antibiotic administration resulted in a similar rate of postoperative infectious complications when compared to short (24-hour) intravenous administration of antibiotics after LA in complicated AA.
3) LA for AA in pregnancy was associated with a significantly shorter operative time and a shorter HLOS while OA and LA cohorts experienced comparable obstetrical outcomes in terms of preterm delivery, fetal loss and perinatal mortality. There was no significant difference between OA and LA cohorts in terms of postoperative infectious complications.

SUMMARY IN ESTONIAN

Operatsioonijärgne antibakteriaalne ravi komplitseeritud apenditsiidi korral ja apendektoomia rasedatel

Sissejuhatus

Äge apenditsiit ehk pimesoolepõletik on kõige levinum erakorralist kirurgilist sekkumist vajav ägeda kõhu põhjus. Elu jooksul haigestub apenditsiiti 7–14% inimestest. Hoolimata mitte-komplitseeritud apenditsiidi konservatiivse ravi võimalikkusest, on ägeda apenditsiidi ravi jätkuvalt apendektoomia. Komplitseeritud apenditsiidi korral rakendatakse operatsioonijärgselt infektsioossete tüsistuste ennetamiseks antibakteriaalset ravi. Rasedatel on äge apenditsiit kõige levinum mitte-günekoloogiline ägeda kõhu põhjus, esinedes 1:181 kuni 1:1700 raseduse kohta.

Eesmärgid

Käesoleva uurimustöö eesmärk on uurida komplitseeritud apenditsiidi operatsioonijärgse antibakteriaalse ravi manustamisviisi ja ravikuuri pikkust. Lisaks võrdleb uurimustöö avatud ja laparoskoopilist apendektoomiat rasedatel.

Spetsiifilised eesmärgid on järgnevad:

1. Võrrelda lühikese ja pika operatsioonijärgse veenisisese antibakteriaalse ravi tulemusi komplitseeritud apenditsiidi korral.
2. Võrrelda lühikese suukaudse ja veenisisese operatsioonijärgse antibakteriaalse ravi tulemusi komplitseeritud apenditsiidi korral
3. Võrrelda laparoskoopilise ja avatud apendektoomia ohutust ja tõhusust rasedatel

Uuritavad ja meetodid

Uurimustöö põhineb kahel juhuslikustatud kontrolluuringul ja ühel retrospektiivsel rahvastikuülesel uuringul.

Esimeses juhuslikustatud kontrolluuringus võrreldi 24-tunnist operatsioonijärgset antibakteriaalaset ravi pika operatsioonijärgse antibakteriaalse raviga komplitseeritud apenditsiidi korral. Komplitseeritud apenditsiidiga täiskasvanud patsiendid juhuvaliti saama lühikest (24 tundi) või tavapärast pikka (>24 tundi) operatsioonijärgset antibakteriaalset ravi.

Teises juhuslikustatud kontrolluuringus võrreldi lühikest (24 tundi) suukaudset operatsioonijärgset antibakteriaalset ravi lühikese (24 tundi) veenisisese operatsioonijärgse antibakteriaalse raviga komplitseeritud apenditsiidi korral. Komplitseeritud apenditsiidiga täiskasvanud patsiendid juhuvaliti saama lühikest suukaudset või veenisisest operatsioonijärgset antibakteriaalset ravi. Mõlema eelpool mainitud uuringu esmasteks tulemiteks olid operatsioonijärgsed tüsistused 30 päeva vältel operatsioonist, nagu näiteks haavainfektsioon, soolesulgus. Teiseseks tulemiks oli haiglasviibimise aeg.

Kolmandas, retrospektiivses uuringus võrreldi laparoskoopilist ja avatud apendektoomiat ägeda apenditsiidi korral rasedatel. Retrospektiivselt uuriti kõikide Eestis vahemikus 2010–2020 apendektoomia läbiteinud rasedate andmeid. Uuritavate haiguslugude leidmiseks kasutati Tervisekassa 2010–2020 raviarveid, millel oli raseduse katkemise (O00-O06) või sünnituse (O80-O84) ja ägeda apenditsiidi (K35) RHK-10 diagnoosikood. Esmasteks tulemiteks (rasedustulemid) olid enneaegne sünnitus, raseduse katkemine, perinataalne suremus. Teisesteks tulemiteks (kirurgilised tulemid) olid operatsiooniaeg, haiglasviibimise aeg ja operatsioonijärgsed tüsistused.

Tulemused

Esimesse juhuslikustatud kontrolluuringusse kaasati 80 uuritavat, kellest 39 uuritavat juhuvaliti lühikese operatsioonijärgse antibakteriaalse ravi (24 tundi) gruppi ja 41 uuritavat juhuvaliti pikka gruppi (>24 tundi). Üldine operatsioonijärgsete tüsistuste osakaal oli 17.9% ja 29.3% lühikeses ja pikas grupis vastavalt (p=0.29). Haiglasviibimise aeg oli oluliselt lühem lühikese antibakteriaalse ravi grupis (p=0.005 ITT analüüsi järgi ja p<0.001 PP analüüsi järgi).

Teise juhuslikustatud kontrolluuringusse kaasati 104 uuritavat, kellest 53 uuritavat juhuvaliti 24-tunni suukaudse operatsioonijärgse antibakteriaalse ravi gruppi ja 51 uuritavat juhuvaliti 24-tunni veenisisese operatsioonijärgse antibakteriaalse ravi gruppi. Uuritavate gruppide operatsioonijärgsete tüsistuste osas erinevus puudus (p=0.999 ITT analüüsi järgi ja p=0.561 PP analüüsi järgi).

Kolmandasse, retrospektiivsesse rahvastikuülesesse uuringusse kaasati 102 rasedat uuritavat, kellest 68 (67%) teostati avatud apendektoomia ja 34 (33%) teostati laparoskoopiline apendektoomia ägeda apenditsiidi raviks. Laparoskoopiline apendektoomia oli seotud oluliselt lühema operatsiooniaja (p=0.038) ja haiglasviibimise ajaga (p=0.016). Rasedustulemid olid mõlemas grupis sarnased.

Järeldused

Komplitseeritud apenditsiidi korral ei ole lühike operatisoonijärgne antibakteriaalne ravi halvem pikast antibakteriaalsest ravist. Operatsioonijärgsete tüsistuste osas puudub erinevus lühikese ja pika antibakteriaalse ravi vahel. Lühike operatsioonijärgne antibakteriaalne ravi on seotud oluliselt lühema haiglasviibimise ajaga.

Komplitseeritud apenditsiidi korral ei ole 24-tunnine suukaudne operatisoonijärgne antibakteriaalne ravi halvem 24-tunnisest veenisisesest antibakteriaalsest ravist. Lühikese suukaudse ja veenisisese antibakteriaalse raviga esineb operatsioonijärgseid tüsistusi võrdselt.

Uuringu tulemused soovitavad laparoskoopilist apendektoomiat ägeda apenditsiidi raviks rasedatel. Rasedustulemid avatud ja laparoskoopilise apendektoomia korral omavahel ei erine. Laparoskoopiline apendektoomia raseduse ajal on seotud lühema operatsiooniaja ja lühema haiglasviibimise ajaga. Operatsioonijärgseid tüsistusi esineb laparoskoopilise ja avatud apendektoomiaga raseduse ajal võrdselt.

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My friends and family
You are my true gems! Thank you all for the love and support!

PUBLICATIONS

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Professional career

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Research and development work

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List of publications

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Peamised uurimisvaldkonnad: trauma ja erakorraline kirurgia

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