Review

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Application of Heisenberg's Uncertainty Principle in the Diag-Nostic Dilemma of Children With Acute Appendicitis: Negative Appendectomy Versus Complicated Appendicitis Rates

Stylianos Roupakias *, Sotirios Fouzas, Eirini Kostopoulou, Despoina Gkentzi, Theodore Dassios, Ioannis Spyridakis, Xenophon Sinopidis

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Review

Application of Heisenberg's Uncertainty Principle in the Diagnostic Dilemma of Children with Acute Appendicitis: Negative Appendectomy versus Complicated Appendicitis Rates

Stylianos Roupakias [1,*], Sotirios Fouzas [2], Eirini Kostopoulou [2], Despoina Gkentzi [2], Theodore Dassios [2], Ioannis Spyridakis [3] and Xenophon Sinopidis [1]

[1] Department of Pediatric Surgery, University of Patras School of Medicine, Patras, Greece; xsinopid@upatras.gr
[2] Department of Pediatrics, University of Patras School of Medicine, Patras, Greece; sfouzas@upatras.gr (S.F.); eirini.kost@gmail.com (E.K.); gkentzid@upatras.gr (D.G.); tdassios@upatras.gr (T.D.);
[3] Department of Pediatric Surgery, Aristotle University of Thessaloniki School of Medicine, Thessaloniki, Greece; ispyrida@auth.gr
* Correspondence: stylroup@yahoo.gr

Abstract: Background. There is an inherent limit in the accuracy of our measurements, set by nature itself and predicted by Heisenberg's uncertainty principle, which defines the properties of nature in the microcosmos. There is a fundamental limit to the accuracy with which complementary physical quantities of a particle can be predicted from their initial conditions. As classical physics is essentially considered at borderline of quantum mechanics, so the power of uncertainty principle is limited in describing everyday life perceived or managed phenomena. **Method.** In this study, we apply Heisenberg's uncertainty principle to children under diagnostic uncertainty regarding appendicitis. We analyze this phenomenon in clinical practice. **Results.** Medical practice is full of uncertainty. False negative decisions correlate with delays in treatment and adverse outcomes in children with atypical appendicitis. On the other hand, false-positive surgery decisions result in negative appendectomies. With improvement of technology, the incidence of complicated appendicitis or negative appendectomies due to diagnostic uncertainty has decreased but cannot be ignored or eliminated. **Conclusions.** According to the principle, there is a fundamental limit to the accuracy with which the complementary variables of negative appendectomy and complicated appendicitis can be observed or measured simultaneously. What does all this mean for the physician?

Keywords: complicated appendicitis; negative appendectomy; Heisenberg's principle; diagnostic uncertainty; children

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The epoch of time, the incessant now of its flow,
that has already gone by before it's even arrived,
that startling point between the not yet
and the no more, are the Δp and Δq [1].

Dimitrios Liantinis
Philosopher

1. Heisenberg's Uncertainty Principle

The Heisenberg uncertainty principle is a fundamental theory in quantum mechanics that states that it is impossible to simultaneously measure certain pairs of complementary or canonically conjugated physical quantities with complete accuracy, but only within the smallest possible errors. The Uncertainty Principle corresponds to the smallest possible error in the determination of the position Δp and the momentum Δq of the electron, and their product could never be smaller than Planck's constant h ($\Delta p \times \Delta q \geq h$). The principle is not a limitation of science's measurement ability, but rather an actual property of the physical world. These uncertainty errors, although dominant in the microcosmos, appear on a very small scale in the macrocosmos of our daily life. This can be directly perceived from the mathematical expression, where the h-constant has a very small value with the quantities that we can practically measure outside the laboratory. Although these errors are negligible on a human scale, they cannot be ignored [2].

2. Medical Uncertainty

Medical practice is well known to be full of uncertainty [3]. A similar type of uncertainty principle appears to affect the medical relationship between a minority of patient's well-being and the diagnostic knowledge about the underlying disease [4]. In medicine, the uncertainty principle refers to the idea that there is always some level of uncertainty or error associated with medical diagnoses and treatments. The lack of complete knowledge or understanding regarding a patient's condition, prognosis, or the effectiveness of a particular intervention and early or late harmful consequences is a common occurrence in medicine. There is also a difficulty in distinguishing between medical and personal knowledge [5]. The basic process of prompt and appropriate diagnosis or treatment is sometimes complicated by understood or not understood factors and variables, which add an uncertainty to it [2]. These confounding factors are the variability of disease presentation and/or overlapping of symptoms from different diseases, the limitations of available diagnostic tests, the limitations of medical technology and/or knowledge, and the physician's inexperience and confusion in interpretation. Similarly, even with a clear diagnosis, there may be uncertainty around the best course of treatment, as different treatments may have different levels of effectiveness, or carry different risks and side effects.

The uncertainty principle in medicine underscores the importance for healthcare providers to make informed decisions which consider the uncertainties and risks associated with different possible diagnoses and treatments. This may involve ongoing monitoring and reassessment of the patient's condition, as well as a willingness to adjust treatment plans based on new information or changing circumstances. In addition, the uncertainty principle highlights the need for continued research and innovation in the field of medicine, to develop new diagnostic tools and treatments that can help reduce uncertainty and improve patient outcomes.

Medical uncertainty can be a source of anxiety and stress for healthcare professionals, as it may lead to delays in diagnosis, confusion about treatment options, and increased risk of adverse outcomes. Healthcare professionals may also feel uncertain about the best type and/or time of action and may need to rely on their clinical judgment and experience to make informed decisions. Future high technologies and precision medical knowledge practices, including high-end information and artificial intelligence, may reduce medical uncertainty, although may paradoxically bring up newer and unpredicted uncertainty [6]. Even in the era of the fourth industrial revolution, uncertainty in medicine may persist or even increase [6]. Medicine will obviously continue to be "science of uncertainty and art of probability".

3. Diagnostic Uncertainty in Children with Acute Appendicitis

Diagnostic uncertainty is an inherent dynamic state of medical practice, defined as a subjective perception of inability to provide accurate and timely patient health problem management [7]. It is especially obvious in emergency situations [4]. Uncertainty is not an uncommon challenge in appendicitis diagnosis, especially in children. Younger children have lower incidence of appendicitis, but less and non-specific symptoms, less reliable history, and more delayed diagnosis with perforation and complicated disease process [8–13]. Clinical examination of children requires special skills and patience, as small children are uncooperative and more irritable on touch and not able to localize the pain [8]. To help diagnose appendicitis, physicians often use a combination of physical examination and diagnostic tests, such as blood tests and imaging studies. A watchful waiting approach may be necessary in cases where the diagnosis is still uncertain, particularly in cases where the probability of appendicitis is borderline or when other comorbidities may be present. In these cases, an appendectomy may be recommended, as the definitive diagnostic and/or treatment approach for appendicitis.

It is important for physicians to understand the potential risks and benefits of different treatment options and decisions according to the level of uncertainty. There are concerns over the diagnostic uncertainty associated with medical management and how this uncertainty may result in a drift toward the over-diagnosis and over-treatment of presumed appendicitis [14], or the under-diagnosis and delayed treatment under special circumstances [15]. Perforated appendicitis rates due to physician's missed diagnosis are defined as underdiagnosis or false negative decisions errors, and negative appendectomy rates are defined as overdiagnosis or false positive decisions errors [15]. False negative decisions and the resulting delay in appendectomy constitute a leading source of expensive malpractice claims in emergency medicine in the United States of America [16].

4. Acute Appendicitis in Children

Acute appendicitis is one of the most common causes of abdominal pain and is the most common condition requiring emergent abdominal surgery in children [17]. It still remains an ongoing clinical and diagnostic challenge, due to potential atypical and/or clouding presentation with a wide range of differential diagnoses, with a high risk for delayed diagnosis/perforation and associated complications, increasing morbidity, prolonged hospitalization, and even mortality in young children [18]. The most common causes of acute abdominal pain in children mimicking appendicitis include gastroenteritis, constipation, mesenteric adenitis, ovarian cysts, or torsion, etc. [8].

Complicated appendicitis is defined as an inflammation accompanied by gangrene or perforation, and/or periappendicular phlegmon, perityphlic abscess, or free purulent fluid [19]. Children with complicated appendicitis are at increased risk of many complications such as wound infection, postoperative abscess formation, sepsis, wound dehiscence, prolonged ileus, and delayed bowel obstruction [20]. Reintervention rate is higher in complicated appendicitis cases [21,22]. The rate of pediatric perforated appendicitis often refers to 30%, with a range from 20% to 74% [23,24]. It may be much higher for younger children, ranging between 69-93% for children of age of 2 to 5 years and up to 100% for infants [23,24]. A study of 55,591 appendectomies in children found a 21% rate of perforated appendicitis [25]. Perforation and abscess formation occurs rarely during the first 12-24 hours of symptoms but is more likely with time thereafter (36-48 hours), and becoming very common after 48-72 hours [24,26–30]. Perforation rate is an index of poor outcome [20] and is doubled when in-hospital delay prior to surgery exceeded 24 hours [31]. A delay of up to 12 hours in children while antibiotics are given does not seem to influence the morbidity of a patient with uncomplicated appendicitis to any relevant extent [19]. Perforated appendicitis increases the postoperative wound infections rate from under 5% to 20% [32]. With an average perforation rate of 20%, the average abscess rate was about 7% [20]. Surgeons who delay operating to clarify the appendicitis diagnosis could miss the opportunity to remove an appendix before it perforated. Appendectomy delay is associated with a significantly increased risk of surgical site infection in patients with nonperforated appendicitis [33].

Negative appendectomy rates up to 25% were justified, in order to avoid the morbidity of missed perforated appendicitis [34]. The acceptable rate has been even higher in children [34]. However, the reported in pediatric literature rate of negative appendectomy has continued to vary widely from 1% to 40% [35–44]. In large populations of children with appendectomies, the reported negative

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appendectomy rate varied from 4.3% to 6.7% [35,45,46]. As with any surgery, however, complications such as infection, bleeding and iatrogenic injury may arise, rendering operative exploration for appendicitis not deprived of risk [34]. Complications are not lower when removing a normal than an inflamed appendix, with the same severity and reoperation rates [47]. A study presented increased length of stay and complication rates in a national review of patients that had undergone negative appendectomy compared with patients with uncomplicated appendicitis [42]. Furthermore, readmissions for persistent abdominal pain are remarkable after a normal appendix removal [34].

The vermiform appendix is no longer considered as a redundant remnant of evolution without essential function [48]. It is now recognized as an important part of the intestinal immune system [48,49]. Research has shown that the appendix contains a significant amount of lymphoid tissue which plays a crucial role in the body's immune response [48,49]. The appendix serves as a reservoir for beneficial bacteria that live in the gut, helping to repopulate the intestinal flora after an infection or antibiotic treatment [49]. Furthermore, the appendix may play a role in the development of the immune system during early childhood. It has been suggested that the appendix helps to train the immune system to recognize and tolerate harmless antigens, and also helps to stimulate the production of antibodies [49]. An early appendectomy is expected to significantly reduce the intestinal immune reactivity, alter the gut microbiome [50,51], and may be associated with on increased risk of several diseases [52,53]. Since the child is a growing organism with a long life-expectancy, any intervention such as appendectomy could cause a long-term impact.

Thus, if the adverse events (perforation, abscess formation, sepsis, prolonged ileus, delayed bowel obstruction etc.) are associated with physician false negative decisions, then unnecessary surgeries are associated with physician false positive decisions in abdominal pain evaluation [20]. In 1984, Berry and Malt interestingly found a primary relation between the physician higher ‘’diagnostic accuracy’’ and the higher perforation rate [54].

5. False Negative Decisions

False negative decisions regarding the diagnosis of appendicitis occur when a child who actually has appendicitis is incorrectly diagnosed as not having it. The diagnosis of appendicitis is missed in 3.8% to 15% of children [13,55,56]. Underdiagnosis of appendicitis can occur for several reasons including atypical symptoms, delayed seeking of medical attention, physician’s inadequate diagnostic training and experience, incomplete examination or lack of appropriate imaging tests, and misdiagnosis of other disease, leading to delayed surgical intervention. A study showed that the emergency physician delay in hospital admission is more significant cause of complicated appendicitis and postoperative complication rates than patient delay in presentation and surgeon delay in performing the operation [16]. False negative decisions by the physician occurred when the physician who first examined the patient did not make the diagnosis in a timely manner, resulting in delays of surgical intervention [20]. Failure of the initial examining physician to refer the patient for a surgical evaluation places the patient at increased risk of perforation and subsequent complications [20].

The diagnosis of appendicitis is potentially missed in 4.4% of children during the initial emergency department visit [57], and its diagnosis can be made only after 2 or more visits in 15% of younger patient [13]. A missed diagnosis of appendicitis is more likely to occur in children younger than 5 years, in girls, in children with comorbidities, and in children experiencing abdominal pain accompanied by constipation [57]. Surgeon’s underconfidence refers to a situation where a surgeon lacks confidence in their abilities or decision-making skills and prefers a more conservative management of acute abdominal pain, leading to reluctance to perform a surgical procedure or to make decisions that may benefit early the patient. This can be caused by several factors, including shortage of experience, fear of making mistakes, or a lack of support from colleagues or superiors. A surgeon’s under-confidence can have serious consequences for patient outcomes, as the surgeon makes suboptimal decisions and may delay necessary procedures. The rate of false negative decisions ranges from 10.6% to 27.8% and this of more than 20 hours delay in hospital until surgery from 1.5% to 18.9% [20]. Overall, timely diagnosis and prompt surgical intervention are critical in preventing complications of appendicitis in children, but some cases of acute appendicitis will be missed under any circumstances.

6. False Positive Decisions

False positive decisions in the diagnosis of appendicitis occur when children are diagnosed with appendicitis, but in fact, they do not have the condition. A false positive diagnosis of appendicitis can lead to unnecessary surgical intervention that increases the medical costs and exposes patients to potential risks of intraoperative or postoperative complications and prolonged hospital stay. Overdiagnosis of appendicitis and negative appendectomy reveal a possible overreliance on clinical symptoms alone and the reluctance of the surgeon to risk missing a potentially more serious condition of complicated appendicitis.

Surgeon's overconfidence refers to the tendency of some surgeons to prefer a more aggressive management of acute abdominal pain since they believe they can easily perform a surgery without any hesitation, delay, and fear of potential complications. Surgeon's overconfidence can be influenced by a variety of factors, including experience, personality traits, and prior success rates. Surgeons with a lot of experience and a track record of successful surgeries may be more prone to overconfidence than those with less experience, as they may feel that they have seen it all before and know what to expect. The clinical judgment of an experienced clinician might warrant surgical intervention even in some cases without pathologic inflammatory markers [58].

A drift toward the overtreatment of children with increasingly early diagnosed appendicitis albeit with equivocal or borderline imaging results is also possible, as the threshold for initiating operative exploration is likely to be lower, especially when considering the consequences of a "wrong" treatment decision [14]. Physicians do not enjoy uncertainty, and instinctively decide to treat the possible major problem because they feel uncomfortable [2]. It is however important to see this as a convenience that may not always suit the patient [2]. Negative appendectomy rates in children have decreased over time, likely due to improvements in advanced imaging techniques.

7. Eliminating the Appendicitis Diagnostic Uncertainty Errors

Physicians who are intolerant to uncertainty tend to prescribe excessive amounts of diagnostic tests [59]. To minimize the risk of false positive and false negative decisions in management of children with acute abdominal pain, physicians may use a combination of diagnostic tools and physical examination to increase the accuracy of appendicitis diagnosis. They may use clinical scoring systems, such as the modified for children Alvarado score or Pediatric Appendicitis Score, to help identify patients who are more likely to have appendicitis and require surgery [60,61]. Both scoring systems can be of assistance in setting the diagnosis of acute appendicitis, but none has adequate predictive values in assessing acute appendicitis and none can be used as an exclusive standard in setting the diagnosis of acute appendicitis in children [62]. It seems evident that the opinion of an expert surgeon can never be replaced by a scoring system, and that the final decision whether to operate or not must rest on his criteria [62]. In addition, advanced imaging studies such as ultrasound (US), computed tomography (CT) scans, or magnetic resonance imaging (MRI) can help confirm the presence of appendicitis and rule out other conditions with similar symptoms. US and CT imaging have an ever-increasing role in the prompt and accurate diagnosis of acute appendicitis in the pediatric population, improving the rupture rates [17], and also reducing the negative appendectomy rates over the last decade [26].

The incidence of negative appendectomies due to diagnostic uncertainty has significantly decreased, but still remains remarkable [20]. According to a study on a huge sample of children with appendectomies, the negative appendectomy rate has decreased from 21.4% in 1987 to 6.5% in 2009 [25]. At the same time, the diagnosis of many cases of acute appendicitis is still missed [20]. A current pediatric study presented an improvement of missed appendicitis diagnosis rate to 4.8% among 816 children, which had missed opportunities to diagnose their condition at earlier medical visits [55]. Sometimes, just waiting and seemingly doing nothing is an alternative therapeutic modality, which does not necessarily mean doing nothing [55]. Because of the fear of missing a treatable disease, we have forgotten the precept of masterly inactivity [63]. Close observation with serial abdominal clinical examinations (preferably by the same surgeon) is indicated for a child with acute abdominal pain and not a definite diagnosis, due to the absence of convincing clinical findings or presentation of confused imaging results or lack of advanced imaging modalities. Intensive observation with reexaminations every 8 hours is safer and more effective than the approach of once per day reassessment in hospital [64]. Although less frequently, imaging tests interpretation can be subjective and may lead to false positive or negative appendicitis diagnosis as well.

The final diagnosis will be still uncertain in a minority of children because there will be no pathologic imaging diagnosis to provide a "check and balance" against trends in overreading by well-meaning radiologists, or to acting on such reads by equally well-meaning pediatric surgeons [14]. However, there comes a time when a therapeutic decision needs to be made and further investigations are unlikely to yield more certainty [64]. Simultaneous prompt and accurate diagnosis cannot be precise and comes with relative uncertainty. This uncertainty medical situation cannot be time consuming. Surgeons who can navigate the often-narrow channel between insecurity and overconfidence are best equipped to conquer uncertainty and serve children well, either by judicious immediate intervention or with masterly inactivity [65].

8. Application of Heisenberg Uncertainty Principle in Pediatric Appendicitis

The application of Heisenberg uncertainty principle in pediatric appendicitis describes a trade-off between negative appendectomy and complicated appendicitis. The incidence of both complicated appendicitis and negative appendectomies due to diagnostic uncertainty has been significantly decreased but cannot be ignored and especially eliminated. There is an inherent uncertainty in nature that we cannot limit below a value. Perforated appendicitis due to physician's missed diagnosis as underdiagnosis errors and negative appendectomies as overdiagnosis errors, are the Δp and Δq [15]. Their product could never be zero. Complicated appendicitis rates (Δp) x negative appendectomy rates (Δq) > ε ($\varepsilon \rightarrow 0$). According to the Heisenberg uncertainty principle, there is a fundamental limit to the accuracy by which the "conjugated variables" of negative appendectomy and complicated appendicitis cannot be further reduced simultaneously. *If we try to eliminate negative appendectomies, the complicated appendicitis incidence increases. If we try to catch up with complicated appendicitis, the negative appendectomies rate increases.* One of the critical components involving clinical decision making is diagnostic reasoning, as a thinking process performed in medical practice by healthcare professionals. It forms the core of professional autonomy [66]. The Heisenberg uncertainty principle "indicates by signs" a small limit of complete pediatric surgeon's reasoning autonomy and responsibility of choice.

9. Gain the Limit by Imaging

But what exactly is this threshold, and what does it depend on? Below the ε threshold, if the value of one of the errors increases then the value of the other error decreases. Once acute appendicitis is suspected, no single history, physical examination, laboratory finding, or score can eliminate the need for imaging studies [67]. Appendectomy should not be undertaken without imaging to confirm the clinical suspicion, but there will never be a single globally accepted strategy for evaluation of possible appendicitis in children [68,69]. There is no imaging modality with simultaneously 100% sensitivity and specificity, and thus potential ability to absolutely exclude or confirm the disease.

Computed Tomography: CT is the most accurate mode of imaging for suspected cases of appendicitis [70]. There is a significant inverse relationship between the annual increase in the rate of CT use and the annual decrease in the overall rates of false positive diagnosis of appendicitis and perforated appendicitis [71]. A meta-analysis demonstrated a significantly higher negative appendectomy rate during the pre-CT era compared to the post-CT era (21.5% vs 10%), but simultaneously the incidence of appendiceal perforation was reported as unchanged significantly [72]. In the USA, CT is routinely performed in 20–95% of patients, presumably contributing to the less than 5% rate of negative appendectomies [73]. According to a study, 1.3% of children with potentially missed appendicitis had received a CT scan at the index visit [57]. The long-term effects

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of CT ionizing radiation in the pediatric population must be taken into consideration when balancing the risk of future malignancy with missing the appendicitis diagnosis [74]. For children younger than 15 years, the estimated risk of death from radiation-induced malignancy ranges from 0.07%-0.10% [75]. Risk of abdominal CT on one-year-old child lifetime mortality from cancer is 0.18% (1 in 550) [75]. In a recent retrospective cohort study, the estimated risk for children younger than 15 developing leukemia and brain tumors tripled if a child had undergone more than two CTs [76]. Exposure to potentially hazardous contrast material is another disadvantage [8]. The sensitivity, specificity and accuracy of non-enhanced CT is 97%, 100% and 98% respectively [77]. There is no good evidence to support the routine use of CT scan in children [78], which should be reserved as the last option [8].

Ultrasound imaging: Increasing concerns over medical radiation led to a shift away from CT and toward ultrasonography as the diagnostic method of first choice, particularly in children [14,79]. On diagnostic confusion, serial examination with US monitoring can decrease the CT use without increase in undue risk to the patient [80]. As US findings are more subjective and dependent on operator experience, they have been associated with a much higher rate of indeterminate and false-positive results as compared with CT [14]. In a study, 11.2% of children with US positive appendicitis had CT negative appendicitis, and 31.9% of children with US negative appendicitis had CT positive appendicitis [81]. A US negative finding may not suffice to rule out appendicitis [67,82]. Furthermore, the appendix is often difficult to visualize in children with retrocecal appendices [57]. CT is performed more often in obese patients, because the ultrasonographic signs of appendicitis are hard to evaluate in this patient group [83]. In a prospective multicenter study of US performance in children, 51% of them were found to have indeterminate results [84]. Another retrospective review of all sonograms for acute appendicitis in children showed that the appendix was identified only in 246 / 1.009 cases (24.4%), with 35 of them false-positives and 54 false-negatives [85]. In 223 pediatric performed appendectomies, the negative appendectomy rate was 3.6% and the complicated appendicitis rate was 5.8%, with US as the only imaging modality [86]. Nowadays, US sensitivity in children is estimated at about 83–99%, and its specificity about 87–100% [79]. A serial (initial and interval) US diagnostic pathway in suspected appendicitis has a significantly higher diagnostic accuracy (97% sensitivity, 91% specificity) than that of the initial US, and results in fewer CT scans [87]. In experienced hands, accuracy of US approaches to that of CT/MRI scan [88]. The use of US in children is accurate and safe in terms of perforation rates, emergency department re-visits, and negative appendectomy rates [89].

Ultrasound combined with Computed Tomography: According to an imaging cooperative protocol, also known as Poortman's model [90], clear US signs cannot be used to "rule out" appendicitis and CT is then employed [70,90]. After implementation of the US/CT imaging protocol in children with suspected appendicitis, the perforation rate decreased from 35.4% to 15.5% and the negative appendectomy rate decreased from 14.7% to 4.1% [91]. In a population of 385 boys (8-14 years) that achieved a negative appendectomy rate of only 1%, 30% of them underwent CT, 51% had only US, 12% had both US and CT, and 7% had no imaging in their evaluation [92].

Magnetic Resonance Imaging: To overcome the CT hazardous effect, MRI is gaining popularity [8]. A recent study showed high MRI accuracy in children with 96% sensitivity and specificity [93]. In a study of 77 performed MRI, one patient had false-positive result and two false-negative results [94]. MRI holds promise but has limited use because of availability and cost considerations [52]. Children under the age of five years often require sedation or general anesthesia for MRI to be performed [19].

Ultrasound and Magnetic Resonance Imaging: A staged radiation free US and unenhanced MRI imaging algorithm for the appendicitis diagnosis seems to be feasible, effective, and preferable in children [95,96]. The negative appendectomy rate in a cohort study was 0.2% (four of 1982 cases), that was lower than the institutional previous reported overall rate of less than 2% [94]. A US/MRI algorithm presented 98% sensitivity and 97% specificity, with 45 false-positive and seven false negative results [94].

10. Diagnostic Laparoscopy

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Are our surgical eyes better than the radiologist's eyes? About 68% of negative appendectomies could initially be diagnosed intra-operatively as inflamed appendicitis and later prove to be non-inflamed on histological examination [97]. On the other hand, in 18-29% of macroscopically normal appendix cases, histological study reveals appendicitis or other appendiceal pathology (neoplasia, endometriosis, parasites, appendicolith) [19]. About 10% of histopathologic perforated appendicitis cases could not be detected during the surgery [98]. Does laparoscopy reduce the rate of removal of normal appendices? Intraoperative laparoscopic assessment of the appendix can be difficult [98]. In more than half of the microscopic healthy appendices, the surgeon was convinced of the diagnosis appendicitis during surgery [99]. According to 200 consecutive laparoscopic appendectomies, 7.2% of inflamed macroscopically appendices were found microscopically normal and 25% of normal macroscopically appendices were found microscopically inflamed [100].

11. Histological Diagnosis of Acute Appendicitis

Large database studies report only the discharge letter diagnosis or intraoperative appearance of the appendix without analyzing the histology report [97]. Additionally, there is controversy over the diagnostic criteria required for the histological diagnosis of acute appendicitis and this contributed to variation in reported negative appendectomy rates. Some pathologists define as acute appendicitis the transmural inflammation (neutrophilic infiltration of the muscularis propria), and other indicate that mucosal inflammation in correlation with patient's presented symptoms must considered as early appendicitis [101,102]. Inflammation of the mucosa of the appendix is often assigned a differential diagnosis of enteritis or inflammatory bowel disease [101,102]. Pinworms, granuloma, or malignancy can occasionally cause transmural inflammation of the appendix owing to obstruction [34]. The American Association for the Surgery of Trauma developed an appendicitis grading system, based upon specific clinical, radiologic, operative, and pathologic criteria [103]. This grading system focused on adult pathology but is also applicable in children. It describes pathologically the acutely inflamed intact appendix with the presence of neutrophils at the base of crypts, submucosa, and occasionally in the muscular wall [104].

12. Concerns

Contrary to expectation, some authors conclude that the frequency of appendicitis misdiagnosis leading to unnecessary appendectomy has not changed with the introduction of computed tomography, ultrasonography, and laparoscopy, nor has the frequency of perforation decreased and nor has the outcome been changed [105,106]. Is it probable that the final decision to overcome uncertainty will continue to depend significantly on the opinion of an expert pediatric surgeon?

Few studies have shown 0% negative appendectomy or missed CT appendicitis rates, but not perforated appendicitis rates [107–109]. However, the number or characteristics of patients of their study populations was limited. Studies with larger populations and no exclusion criteria obviously reveal increased negative appendectomy rates.

13. Conclusions

How can a pediatric surgeon be absolutely certain? Werner Heisenberg was not. Despite advanced imaging and surgical technology improvements, neither negative appendectomies nor complicated appendicitis rates can be turned to zero. A systematic pediatric institutional approach should be associated with improved perforation rates and appendicitis outcomes while favoring reduced rates of negative appendectomy, due to the potential harmful long-term effects of appendectomy in children. Uncertainty may lose ground by achieving the limit of the balance between the unnecessary removal of too few normal appendices and the late removal of too few perforated appendices.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, S.R.; methodology, S.R. and X.S.; software, S.R.; validation, S.R., S.F. and X.S.; formal analysis, S.R..; investigation,

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