Misdiagnosis of Appendicitis in Women in a Resource Limited Setting: Lessons from South Africa

This thesis is presented for the degree of

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at the University of Cape Town

by

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Contents

Acknowledgments

First and foremost, praise be to Allah the Almighty, the most Gracious, and the most Merciful for his guidance and blessings during this study.

To my supervisor, Professor Chu, for her patience, support, advice, and pearls of wisdom.

To my mother, my mother, my mother and my father for raising me, for guiding me and providing me with opportunities to thrive

And to my wife and son, for their unwavering support and love throughout my journey.

Declaration

I, Nazmie Kariem hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Signed: Dr Nazmie Kariem

Date: 29 December 2022

Abstract

Introduction: Acute appendicitis (AA) is a common surgical emergency. In low and middle-income countries, the diagnosis is often made clinically due to the lack of access to specialised imaging. Misdiagnosis in females is common, given the potential broad differential diagnosis. The rate of misdiagnosis varies between countries, but there is a paucity of data in the developing world. The aim and objectives of this study were to describe the routine workup of females with suspected AA at a South African government hospital and to determine factors associated with the misdiagnosis of AA.

Methods: A retrospective review of all females older than 12 years operated on by general surgeons with a suspected diagnosis of AA over a 2-year period was reviewed. Data including age, gender, presenting complaints and physical findings, laboratory and radiological results, pre and post-operative diagnoses were extracted and analysed using descriptive and inferential statistics.

Results: A total of 180 females were included and 48 (26.7%) of them were misdiagnosed with AA. Of these 48 that were misdiagnosed, 22 (46%) had pelvic inflammatory disease (PID), 15 (31%) had a normal appendix, 10 (21%) had ovarian cysts and (2%) had endometriosis. Gynaecologic bimanual examination was performed in 123 (68.3%) patients. Twelve (6.7%) patients had a CT scan and 16 (8.9%) had an abdominal ultrasound. In the multivariate model, the absence of nausea, vomiting and anorexia (odds ratio (OR)=2.43; p=0.023), the presence of cervical excitation tenderness (CET) (OR: 4.32; p=0.009) and adnexal tenderness (OR=3.06; p=0.021) were significantly associated with a diagnosis other than appendicitis. These factors remained significant in the multivariate model after adjusting for relevant covariates.

Conclusion: More than 25 % of females referred to general surgeons with suspected AA were misdiagnosed. Since imaging is not accessible at most resource-limited settings, it is imperative to conduct a gynaecologic examination on every female since adnexal and cervical tenderness were associated with PID and not AA.

Keywords: Appendicitis, misdiagnosis, South Africa, Appendectomy

Publication ready Manuscript

Introduction

Acute appendicitis (AA) is the most common emergency surgical condition worldwide and affects one in seven persons.[1]Appendectomy is the mainstay of treatment. Non-operative treatment with antibiotic therapy is an alternative option in early cases.[2, 3] However, its 27% failure rate [4] mandates close follow up, making it impractical in many low- and middle-income countries (LMICs) settings. Furthermore, in these settings, AA presents late and often with complications. [5, 6] Surgery is thus the most prudent treatment. However, the risk of surgery must be balanced with its benefits. Peri-operative mortality in Africa is twice as high as in other settings[7] and unnecessary surgery results in increased cost to the health system and patient morbidity.[8, 9] Therefore, minimizing misdiagnosis and unnecessary surgical exploration must be balanced with the risk of missing an AA diagnosis and failing to provide early definitive treatment.

Diagnosing AA remains a challenge universally. The misdiagnosis rate is 20-40% in high income countries (HIC) [10] despite routine imaging with CT scans that have 87-100% sensitivity and 83-98% specificity for AA.[11] In LMICs, CT scans are not readily available and clinical signs and symptoms are used to make the diagnosis. Clinical prediction rules (CPR) may play a role in improving diagnostic accuracy LMICs. There are at least 12 clinical prediction rules for AA[12], however, in females they are less accurate. In Zimbabwe and Iran, the misdiagnosis of females with appendicitis is 24%,[13] and 28% respectively.[14] Clinical features such as lower abdominal pain, elevated temperature and leukocytosis are common in both AA and pelvic inflammatory disease (PID), which contributes to appendicitis misdiagnosis.[15] PID is a common condition in LMICs where early treatment is just as important to prevent complications such as infertility and increased risk of ectopic pregnancy.[16] It is therefore prudent that an accurate diagnosis of lower abdominal pain in females is promptly made so that appropriate care can be expeditiously provided. Therefore the aim of this study was to describe the routine workup of females with suspected AA at a South African state hospital and to determine factors associated with AA misdiagnosis.

Methods

Study design and setting

This was a retrospective analysis of females who underwent surgical exploration by the general surgery service for suspected AA at New Somerset Hospital (NSH), a state hospital located in Cape Town, South Africa from 1 October 2015 to 30 September 2017. NSH is a regional level facility which receives referrals from two district hospitals and 15 community health centres. NSH serves a population of 500,000 people.[17] The surgical staff at NSH comprise 3 consultants and 4 registrars or medical officers. NSH has one CT scanner, which was only available during weekday working hours. All staff including trainees are taught to do the operation laparoscopically. It was the surgeon's discretion at each case to choose the approach taken.

Data collection

The prospective electronic operative database maintained at NSH by the general surgery registrars and consultants for monitoring and evaluation was used to identify the study population. Sex was determined through medical records and only those recorded as "female" were included in the study. All males, females under the age of 12 and those treated with antibiotics alone were excluded. Clinical and demographic information were obtained from medical records. Variables included age, gender, history and physical findings, laboratory and radiological results, pre and post-operative diagnoses.

History findings included anorexia, nausea and vomiting and sexual history. Physical findings included vital signs, presence of right iliac fossa tenderness and vaginal examination findings such as an abnormal vaginal discharge, cervical excitation tenderness and adnexal tenderness. Vaginal discharge was considered abnormal if the discharge was greenish and/or malodorous. Laboratory tests included white cell count /mm^3 and urinalysis. The presence of leucocytes or a combination of leucocytes and blood in the urinalysis was considered abnormal. Radiologic imaging included abdominal x-rays, transvaginal and abdominal ultrasounds, and abdominal CT scans. All radiology was done by the radiology service except for transvaginal ultrasounds done by the gynaecology service. By inclusion criteria, all study participants were evaluated by the general surgery service, the primary team that manages acute abdominal conditions. The primary outcome was misdiagnosis which was defined as a pre-operative diagnosis of AA but a post-operative diagnosis other than complicated or uncomplicated AA.

Data analysis

Data were extracted from the operative database and patient medical records onto a standardised data collection form and then imported into STATA 15 (College Park, TX, USA) for analyses. All variables including the outcome were summarised using descriptive statistics. Data were expressed as counts and proportions (%) for categorical variables, while continuous variables were summarised using mean (±standard deviation) and median (interquartile range). Chi-squared test was used to compare the categorical proportions and continuous variables were compared using student t-test. Univariate and multivariate logistic regression was used to determine the risk factors for misdiagnosis of appendicitis. Age was included *a priori* and other factors with p-value <0.1 on univariate analyses were included in the multivariate model. A p-value of <0.05 was considered statistically significant.

Ethical considerations

This study was approved by the University of Cape Town Research Ethics Committee (HREC R052/2016). Informed consent was waived for the study as there was no form of participant contact. Data were de-identified prior to statistical analysis.

Results

One hundred and eighty females were included in the study. The median age was 27 years (interquartile range 21-38). All 180 (100%) had an abdominal examination; 123 (68.3%) had a gynaecologic bimanual exam; 172 (95.6%) had a urine pregnancy test; and 178 (98.8%) had a urine analysis. Fifty (27.7%) patients had a formal consultation with the gynaecology service. Twelve (6.7%) females had a CT scan, and 16 (8.9%) had an abdominal ultrasound.

Forty-eight (26.7%) females were misdiagnosed and 132 (73.3%) had AA. In the misdiagnosed group, the most common diagnosis was PID (n=22, 46%), followed by normal pelvis (n=15, 31%), ovarian cyst (n=10, 21%) and endometriosis (n=1, 2%). Clinical characteristics such as heart rate, temperature, white cell count and normal urinalysis were statistically similar in the two groups. The proportion with right iliac fossa tenderness was also not significantly different. The lack of gastrointestinal symptoms was significantly associated with the misdiagnosis group (p=0.012). Clinical characteristics are shown in Table 1.

On univariate analyses, absence of nausea, vomiting or anorexia (odds ratio (OR)=2.36; p=0.013), absence of right iliac fossa (RIF) tenderness (OR 2.38; p<0.026), cervical excitation tenderness (CET) (OR=7.06; p<0.001), and adnexal tenderness (OR:4.40; p=0.001) and a transvaginal ultrasound (OR=2.94; p=0.004) were significantly associated with a diagnosis other than appendicitis. In the multivariate model, only the absence of nausea, vomiting and anorexia (OR=2.43; p=0.023), presence of CET tenderness (OR: 4.32; p=0.009) and adnexal tenderness (OR=3.06; p=0.021) were significantly associated with a diagnosis other than appendicitis (Table 3).

Discussion

AA can cause significant morbidity and mortality if left untreated[18]. In LMICs, AA presents late[6] and surgical care is the mainstay of treatment. Our study shows that the preoperative diagnosis of AA was incorrect in one out of four females. Other LMICs studies have reported similar findings (16-28%),[13, 14] which are comparable to those reported in HICs (20-40%),[10]

In our study, certain clinical findings were not useful in distinguishing AA from misdiagnosis in females such as tachycardia, fever, and leukocytosis. Clinical prediction rules (CPR), such as the Appendicitis Inflammatory Response (AIR) Score[19] and the Adult Appendicitis Score (AAS),[20] were created to rely on the history, physical and laboratory values and theoretically could play a role in diagnosing AA in resource-limited settings. The Alvarado score is one of the most common CPR and considered 68-96% sensitive and 58-89% specific in certain settings.[12] It is reported to be well-calibrated in men, inconsistent in children and with a tendency to overpredict AA probability in females.[21] A previous study in South Africa reported that the score may not be as useful in the Black African population and that severity of disease presentation may be a confounding factor.[1, 22] In our setting, CPRs that use laboratory tests such as neutrophil count or C-reactive protein were not useful as cost restraints made these tests unavailable on a routine basis .

Pelvic inflammatory disease (PID), resulting from infection of the fallopian tubes, was the most common differential diagnosis[23] for suspected AA in our study. While imaging can improve diagnostic accuracy, these tests are prohibitively costly or unavailable in many resource limited settings including in South African government hospitals.[24-26] In this study less than 10% of females had abdominal ultrasounds and less than 10% had

abdominal/pelvic CT scans. Reliance on clinical history and examination is therefore critical in diagnosing AA in these settings. However, in our study, only two thirds of females with suspected AA had a gynaecologic bimanual exam despite the presence of adnexal and cervical tenderness being associated with misdiagnosis. A standard workup that includes gynaecologic examinations should be implemented including a gynaecology consultation if any positive findings are noted.

Limitations

This study has certain limitations. Firstly, females who were initially diagnosed with a gynaecologic condition, such as PID, who ultimately had a surgical exploration and were found to have AA, were not included in this study. Also, we could not use CPR as a potential predictor for AA since the required laboratory parameters required were not available. We could also not calculate the sensitivity and specificity of imaging tests for AA since fewer than 10% had either. The diagnosis was also not confirmed histologically. Lastly, this was a single-centre study conducted in only one public hospital, therefore, findings may not be generalisable to other settings.

Conclusion

One in four females were misdiagnosed with AA. In our resource limited setting, only a minority of females had imaging so diagnostic accuracy needs to be improved through better clinical examination. A standard gynaecologic examination must be done on every female since adnexal and cervical tenderness were associated with misdiagnosis and any cases with these findings should be referred for formal gynaecology consultation. Routine neutrophil testing would allow use of CPRs such as the AIR and AAS scores. Further studies to ascertain its diagnostic accuracy in females in LMICs where late presentation is common are needed.

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Appendices

Table 1

Table 1: Clinical workup of females with suspected appendicitis

		Suspected Appendicitis		
	Total	**Appendicitis**	**Misdiagnosis**	**p-value**
Clinical features N (%)	180 (100.0)	132 (73.3)	48 (26.7)	
Age (years)[a]	27 (21-38)	27 (20-43)	28 (22-34)	
Heart rate (beats/minute)[b]	98.8 (18.1)	98.7 (18.5)	99 (17.2)	0.903
Temperature (^oC)[b]	37.2 (1.0)	37.2 (1.0)	37.3(0.8)	0.685
White blood cell count (x 10^9/L)	14.0 (10.0-19.0)	13.0 (10.0-18.0)	15.0 (9.0-22.0)	0.984
Normal Urinalysis	162 (91.0)	120 (92.3)	42 (87.5)	0.320
Gastrointestinal work-up N (%)				
RIF tenderness	140 (77.8)	108 (81.8)	32 (66.7)	0.104
Nausea/vomiting/anorexia	120 (66.7)	95 (80.0)	25 (52.1)	**0.012**
Gynaecological work-up N (%)				
Bimanual pelvic examination	123 (68.3)	87 (65.9)	36 (75)	
Radiological examinations performed N (%)				
Abdominal Ultrasound	16 (8.9)	11 (8.3)	5 (10.4)	0.664
Transvaginal Ultrasound	43 (23.9)	24 (18.2)	19 (39.6)	**0.003**
CT scan	12 (6.7)	10 (7.6)	2 (4.2)	0.417

RIF, right iliac fossa; CT, computed tomography

[a]Median (Interquartile range); [b]Mean (Standard deviation)

Table 2

Table 2: Gynaecologic findings in females with suspected acute appendicitis

	Post-operative Diagnosis			
	Appendicitis	**Non-appendicitis**	**Total**	**p-value**
Sexually active	42 (31.8)	29 (60.4)	71 (39.4)	**0.001**
Gynaecology referral	25 (18.9)	25 (52.1)	50 (27.8)	
Bimanual pelvic examination	**87**	**36**	**123**	
Adnexal tenderness	20 (22.9)	20 (55.6)	40 (32.5)	**0.001**
Cervical excitation tenderness	8 (9.2)	15 (41.7)	23 (18.7)	**<0.001**
Non-physiologic vaginal discharge	10 (11.5)	6 (16.7)	16 (13.0)	0.272

Table 3

Table 3: Factors associated with misdiagnosis of appendicitis in females

	Univariate			**Multivariate**		
	OR	**95%CI**	**p-value**	**OR**	**95%CI**	**p-value**
Age (years)	0.99	0.97-1.02	0.432	0.99	0.97-1.02	0.730
Heart Rate (beats/minute)	1.00	0.98-1.02	0.902			
Temperature (^{o}C)	1.07	0.76-1.51	0.683			
Abnormal urinalysis	1.71	0.59-5.00	0.324			
White blood cell count (10^{9}/L)	1.01	0.96-1.06	0.675			
No nausea/vomiting/anorexia	2.36	1.19-4.67	**0.013**	2.48	1.16-5.28	**0.019**
No right lower quadrant tenderness	2.38	1.11-4.97	**0.026**	1.63	0.70-3.82	0.382
Adnexal tenderness	4.40	1.83-9.56	**0.001**	3.29	1.31-8.25	**0.010**
Vaginal discharge	1.57	0.52-4.72	0.419			
Cervical excitation tenderness	7.05	2.59-19.31	**<0.001**	4.77	1.61-14.10	**0.005**

Ethics Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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15 December 2017

HREC REF: 862/2017

Prof K Chu
Department of General Surgery
New Somerset Hospital
Portswood Road-Greenpoint

Dear Prof Chu

PROJECT TITLE: MISDIAGNOSIS OF APPENDICITIS IN FEMALES: DO WE NEED BETTER DIAGNOSTIC ALGORITHMS

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 December 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

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