MAMA: Management of acute appendicitis in pregnancy

A multicentre service evaluation study of the management of appendicitis in pregnancy

mama

management of acute appendicitis in pregnancy

https://www.wrsc.info
info.wrsc@gmail.com
@WRSC_Research

https://ukarcog.org/
ukarcog.enquiry@gmail.com
@UKARCOG

Title page

Title	Management of Acute Appendicitis in Pregnancy
Acronym	MAMA
Protocol version	1.2
Date	12th March 2024
REC reference	056754 (University of Sheffield)
REC approval date	28th November 2023

Table of contents

Study Team

Project Lead	Ms Nilofer Husnoo, Clinical Research Fellow and Specialty Registrar in General Surgery, Academic Directorate of General Surgery, Research Office, 3rd Floor, Old Nurses' Home, Northern General Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Herries Road, Sheffield, S5 7AU. E-mail: nilofer.husnoo@nhs.net Tel; 0114 2267052
Trainee collaboratives	UKARCOG (UK Audit and Research Collaborative in Obstetrics and Gynaecology) and WRSC (White Rose Surgical Collaborative)
Study Steering Committee	Ms Nilofer Husnoo, Clinical Research Fellow and Specialty Registrar in General Surgery Mr Stephen Chapman, NIHR Clinical Lecturer and Specialty Registrar in General Surgery, WRSC chair Dr Babu Karavadra, Specialty Registrar in Obstetrics and Gynaecology, UKARCOG co-chair Dr Hajra Khattak, Specialty Registrar in Obstetrics and Gynaecology, UKARCOG co-chair Dr Ian Henderson, Specialty Registrar in Obstetrics and Gynaecology, UKARCOG committee member Dr Benjamin Rea, Consultant GI Radiologist, Sheffield Teaching Hospitals Dr Catriona Wright, Specialty Registrar in Radiology Miss Sonia Lockwood, Consultant General and Colorectal Surgeon, Bradford Teaching Hospitals Mr Arin Saha, Consultant General and Upper GI Surgeon, Calderdale and Huddersfield NHS FT
Protocol contributors	Study Steering Committee Michael Maginnis, Head of Information Governance/Data Protection Officer/Caldicott Guardian, Sheffield Teaching Hospitals NHS Foundation Trust
Individual hospital leads	Each participating site will have up two trainee collaborators (trainees in General Surgery +/- Obstetrics and Gynaecology), supported by a senior collaborator (Consultant General surgeon or Consultant in Obstetrics &/or Gynaecology). One of the trainee collaborators will be the "Hospital Lead" To check if your hospital is a participating centre, visit the following page: https://docs.google.com/spreadsheets/d/1FDdsetOOkZwd-NkRRH_mp-VdnO-qg8r1fxf4fnr_zRw/edit#gid=0 If your hospital is not listed, please consider joining as a Hospital Lead by contacting the Steering Committee (mama.study2024@gmail.com).

Study summary and timeline

08/01/2024	Project launch
08/01/2024-15/07/2024 ***Deadline extended – new dates TBC***	Participating hospital teams formed Applications for REDCap logins open Local teams seek information governance approval Data collection
31/08/2024 ***Deadline extended – new date TBC***	Final deadline for REDCap data uploads
31/08/2024 – 30/11/2024 ***New dates TBC***	Data analysis
01/12/2024 – 01/02/2025 ***New dates TBC***	Dissemination of results to collaborators Manuscript writing

1. Lay summary

Appendicitis usually causes pain in the lower tummy. A clinical examination and blood tests, sometimes alongside a scan, help to make the diagnosis. While appendicitis can sometimes be treated with antibiotics alone, an operation to remove the appendix is usually the preferred treatment option.

In pregnancy, it is difficult to make the diagnosis. This is because the appendix may sit in a different position in the tummy, as it is pushed by the womb. It can be harder to tell whether tummy pain is due to appendicitis or pregnancy-related causes. Blood tests and scans are harder to interpret. Scans that use radiation can be very good at diagnosing appendicitis, but they are usually avoided in pregnancy. Treating appendicitis in pregnancy is also challenging. Guidelines recommend an operation. In practice, many clinicians avoid operating, perhaps because the operation is riskier to the mother and the baby. When an operation is performed, it is unclear whether an open or keyhole approach is better. Research studies investigating the best approach to treat appendicitis in pregnancy are limited and are difficult to conduct.

As a result, it is possible that clinicians take longer than usual to diagnose appendicitis in pregnancy. Practice may also vary across hospitals and it is unclear whether this has any impact on the mother and unborn baby. The purpose of this study is to describe national practice in the UK and identify variations in practice. The project will be conducted through trainee research collaboratives.

2. Background

Acute appendicitis is the most common general surgical condition encountered in pregnancy (1). It is thought to affect 1 in 1000 pregnancies (2, 3). Reaching an accurate diagnosis in a timely fashion remains a challenge in this cohort. The appendix can have quite a variable anatomical course, but this is further exaggerated by the gravid uterus, which tends to progressively displace the appendix superiorly (4). This means that in pregnancy appendicitis is less likely to present in the classical way. Leucocytosis can be less helpful in making a diagnosis of appendicitis in pregnant patients as mild leucocytosis is common in pregnancy and both leucocyte and neutrophil counts gradually increase from first to third trimester (5).

Aside from the difficulties in making a clinical diagnosis, the accuracy of imaging modalities is also affected by the gravid uterus. Graded compression ultrasound scanning (US) is the initial imaging modality of choice for diagnosing acute appendicitis in the pregnant patient. However, the accuracy of US in this context is low. The overall sensitivity and specificity in a recent meta-analysis were 77.6% and 75.3%, respectively, and values for both steadily fell from first to third trimester (6). Magnetic resonance imaging (MRI) without gadolinium is the next preferred imaging modality in cases where diagnostic uncertainty remains. MRI in this context is highly sensitive and specific, with values of 96% and 97% respectively, reported in a meta-analysis of 21 studies (7). However, access to MRI scans can be very variable across centres, especially out of hours, potentially leading to delays in initiating the appropriate treatment. The rate of non-visualisation of the appendix with MRI is also higher in the 3rd trimester (8). The increasing diagnostic difficulty as pregnancy progresses is reflected by the increasing rate of perforation from first to third trimesters (9). Computed tomography (CT) would be the imaging of choice for diagnosing appendicitis in a non-pregnant patient, and is widely available, but there is a risk of ionising radiation with potential adverse foetal effects. Changes to the CT protocol can limit estimated foetal radiation exposure to less than 3 mGy, which is a significantly smaller dose than those known to potentially affect the foetus (10-12). However, data on its use in pregnancy is limited; in practice, it is likely that its use varies according to local expertise.

The rate of foetal loss increases significantly in complex or perforated appendicitis (10-35% (9, 13, 14)) compared to simple appendicitis (<5% (14, 15)). Guidelines commissioned by the British Society for Gynaecological Endoscopy (BSGE) and endorsed by the Royal College of Obstetricians & Gynaecologists (RCOG) therefore support operative management of appendicitis in pregnancy (16). This is backed by evidence from large series highlighting the higher maternal and foetal morbidity associated with conservative management (2, 17). Despite this, recent literature shows that non-operative management is still common practice (18, 19). This may be a reflection of diagnostic difficulties, inconsistencies in the evidence base and the general surgeon's reluctance to operate on the pregnant patient,

compounded by knowledge that negative appendicectomy is associated with poor foetal and neonatal outcomes (15, 20).

American guidelines support a laparoscopic over an open approach to appendicectomy (21). This view is supported by the World Society of Emergency Surgery (WSES) (22). Conversely, UK guidelines do not recommend one approach over the other (16), based on evidence from a systematic review which demonstrated an increased risk of miscarriage associated with laparoscopic appendicectomy when compared to open (23). However, the adverse findings were influenced by a single large study, raising questions about its transferability to other research settings and everyday practice (15).

2.1. Knowledge gap

Current evidence shows that diagnosing and managing the pregnant patient with suspected acute appendicitis in a timely fashion is extremely challenging. Each general surgeon will only encounter this condition a handful of times in their career, making it difficult to build their individual experience. There are also no national guidelines from general surgical societies in the UK to guide the management of acute appendicitis in pregnancy. The conduct of prospective studies on this relatively uncommon condition would be impractical, and randomised trials would bring about key ethical challenges. Present guidelines are therefore based on limited data and low quality evidence (purely observational studies). As a result, variations in current practice are likely to exist, with potential implications for maternal and foetal outcomes.

A large UK retrospective study (24) reported outcomes of non-obstetric surgery in pregnancy, using Hospital Episodes Statistics (HES) spanning from 2002-2012 (24). The authors reported an increased risk of adverse birth outcomes in patients undergoing abdominal surgery, with laparoscopic surgery contributing mostly to this risk. However, this study reported on all non-obstetric surgeries and did not focus specifically on appendicitis. While the use of HES data can provide a useful snapshot on a national level, more detailed relevant information such as the imaging modality used to make a diagnosis and the time taken to obtain radiological imaging cannot be obtained. This study also only reported outcomes in patients who had surgery and not those who were managed non-operarively with the same conditions. A retrospective Canadian study (Abbasi et al., 2014), comparing outcomes and management practices among pregnant and non-pregnant women with acute appendicitis using the national “Healthcare Cost and Utilisation project” database, has similar limitations in terms of richness of data. Other large-scale studies reporting outcomes of non-obstetric surgery during pregnancy were performed in the pre-laparoscopic era (Duncan et al., 1986; Mazze et al., 1989) and may no longer be generalisable to current modern practice.

There is certainly a need for more recent and more in-depth data to provide insight into the variations in current practice and to understand the reasons for these variations. Such data

would be key in initiating quality improvement work, standardising practice and establishing areas warranting further research.

3. Aims and Objectives

Aim:

The aim of this study is to describe national practice in the UK and identify variations in practice with regards to the management of acute appendicitis in pregnancy

Objectives:

The objectives are to:

1. Describe variation in the resources that are available and subsequently used to diagnose acute appendicitis in pregnancy
2. Describe variations in management strategies (non-operative versus operative, laparoscopic versus open) to treat acute appendicitis in pregnancy
3. Describe surgical and obstetric outcomes in patients with acute appendicitis during pregnancy

4. Methods

4.1. Summary

This is a multicentre retrospective study of the management of acute appendicitis in pregnancy over a ten year period (1st October 2013- 30th September 2023 inclusive). There will be two components:

1. A site-level resource profile questionnaire to describe access to diagnostic services and organisation of cross-specialty care within each hospital. This will be completed by each participating site
2. A retrospective service evaluation, using routinely available data on patients diagnosed with acute appendicitis during pregnancy between 2013 and 2023.

4.2. Site resource profile questionnaire

A site-specific questionnaire will be disseminated to senior leads at all participating centres (Appendix I). The purpose of this questionnaire will be to collect information about:

1. resources and imaging modalities available in and out of hours to manage acute appendicitis in pregnancy
2. local protocols and treatment pathways to manage this patient cohort
3. organisation of cross-specialty care within each trust

This will provide context for the findings from the retrospective study. The questionnaire will be administered using Qualtrics, which is a secure online platform, enabling participants to complete the questionnaire via a computer, or mobile device. A link to the online questionnaire will be emailed to the senior lead at each participating centre.

4.3. Retrospective study

This will be a service evaluation project (as per definitions produced by the Health Research Authority (HRA) (25)) that will aim to provide a snapshot of management practices in the UK for acute appendicitis in the pregnant patient. Data will be obtained from a review of patients' notes (i.e. using data that have been routinely collected as part of the patient's care).

4.3.1. Eligibility criteria

1. Patients aged 18 years and above with a diagnosis of acute appendicitis (made clinically, radiologically, histologically or intra-operatively) during any stage of a confirmed pregnancy, in a UK secondary care or tertiary care setting.
   OR
   Patients aged 18 years and above who had an appendicectomy during any stage of a confirmed pregnancy for suspected/possible or confirmed appendicitis, in a UK secondary care or tertiary care setting.

2. The diagnosis should have been made between 01/10/2013 and 30/09/2023 (inclusive)
3. In instances where the diagnosis was purely clinical, it should have been made by a member of the general surgical team

4.3.2. Outcomes of study:

1. Time delay between presentation and imaging
2. Length of stay
3. Rate of pre-term births (<37 weeks gestation) and small for gestational age (as per the Intergrowth-21st international standard (26))
4. 30-day medical, surgical and obstetric complication rate (including rates of foetal loss)*
5. Acute readmission within 30 days*
6. Readmission during pregnancy with acute appendicitis
7. Incidence of complicated appendicitis (defined as perforated or with abscess formation)

*Within 30 days of admission with suspected appendicitis, or within 30 days of presentation with suspected appendicitis if patient was already an inpatient when symptoms started

4.3.3. Data collection

Patients will be identified using coding (see Appendix III for the proposed search strategy). Eligibility will be confirmed using hospital electronic or paper records. Data will be collected from a combination of electronic records and paper records. Anonymised data will be entered into the REDCap database. A table of the fields that data will be collected on is included in Appendix II.

4.3.4. Data analysis

The data will be analysed using descriptive statistics, including rates, averages, and proportions. Outcomes will be stratified by management strategy (non-operative vs laparoscopic surgery vs open) and severity of appendicitis (simple vs complicated vs negative). Multivariate logistic regression will be used to identify predictors for the outcomes of interest. All statistics will be performed on SPSS v22.0. Where applicable, statistical significance will be set at $P<0.05$. A sensitivity analysis will be performed by comparing data across these two five-year study time periods to ascertain if any major change in practice has occurred over time: 01.10.2013 to 30.09.2017 and 01.10.2017 to 30.09.2023. It is expected that the final sample size will be 300-500 patients.

4.4. Site recruitment

The study will be promoted through social media and through professional organisations. There will be no limit on the maximum number of sites that can contribute, and any NHS site in the UK can be included.

4.5. Team structure and responsibilities

Teams of collaborators at each participating site will consist of up to two juniors (ideally one trainee/junior doctor in General Surgery and one trainee in Obstetrics and Gynaecology, although a single trainee/junior doctor in either specialty is acceptable), supported by a senior collaborator (Consultant General Surgeon or Consultant in Obstetrics and Gynaecology).

One of the two junior collaborators will be the designated hospital lead for that participating site and will register the study with their local audit department. The junior collaborators are expected to be responsible for collecting data and uploading to REDCap. The overall responsibility of ensuring timely collection and submission of the data lies with the senior collaborator.

5. Data governance and local approvals

Although NHS Research Ethics Committee approval is not required for this service evaluation project (Appendix V), in accordance with the University of Sheffield policy, approval has been sought from the University Research Ethics Committee given our intention to publish our findings (ref 056754).

5.1. Data collection platform

All data will be collected and stored on the Research Electronic Data Capture (REDCap) web application hosted by the University of Sheffield. REDCap is a widely used and secure system in health research, which is encrypted and compliant with HIPAA-Security Guidelines. All electronic data will be held for up to five years, after which it will be permanently and safely removed according to local governance processes.

No patient identifiable information (such as hospital numbers) should be stored on REDCap. A unique 'REDCap ID' is generated for each patient, which can be used to upload data anonymously. It is advisable that the collaborators keep a local cross-reference of hospital numbers for local (re-)auditing purposes, but this should be stored securely according to local guidelines. For data security, only one REDCap login will be issued per team and will be issued to a nominated individual. Only this individual may use the login.

5.2. Local Registration and Caldicott Guardian approval

5.2.1. Registration

The project should be registered locally as a "clinical audit" or "service evaluation project" according to local guidelines. It is the responsibility of the local team to ensure this is managed correctly. Access to REDCap will not be granted until evidence of registration is sent to the Steering Committee.

5.2.2. Caldicott Guardian Approval

Collaborating teams must seek their NHS Trust's Caldicott Guardian's approval to submit anonymous patient data to the REDCap system. Evidence of approval must be sent to the steering committee prior to data collection. This will also be a prerequisite to issue REDCap logins. When seeking approval, the following points should guide the discussion:

- All data submitted to REDCap will be anonymous and stored securely.
- The project is a national service evaluation study.
- There will be with no changes to normal practice as part of the project and only routinely collected clinical data will be used.
- Data will be leaving the local Trust anonymously. REDCap is hosted by the University of Sheffield.
- Measures taken to ensure anonymity include:
    - An anonymised participant ID will denote each record.
    - Data will be collected on patient's age group and not specific age.
    - Data on the exact year of presentation and diagnosis will not be collected given that low numbers of patients are expected in some trusts. Data will be

collected on dates in the following format dd-mm, and on the year of presentation in a categorical format, i.e. option A: 01/10/2013-30/09/2017 and option B: 01/10/2017-20/09/2023 (wide time ranges chosen to minimise the risk of patient identification).

5.3. NHS National Data Opt-out

Eligible patients' opt-out choice should be checked before data collection and patients who have opted out of their data being used for audit and research purposes should be excluded from this study. The responsibility of checking patients' opt-out choices lies with the local collaborating team.

6. Authorship

All collaborators, including trainee hospital leads, senior hospital leads and the steering committee will be eligible for collaborative authorship on all project outputs. The corporate author title will be "MAMA (Management of acute appendicitis in pregnancy) group".

7. References

1. Tamir IL, Bongard FS, Klein SR. Acute appendicitis in the pregnant patient. Am J Surg. 1990;160(6):571-5; discussion 5-6.
2. Abbasi N, Patenaude V, Abenhaim HA. Management and outcomes of acute appendicitis in pregnancy-population-based study of over 7000 cases. Bjog. 2014;121(12):1509-14.
3. Mourad J, Elliott JP, Erickson L, Lisboa L. Appendicitis in pregnancy: new information that contradicts long-held clinical beliefs. Am J Obstet Gynecol. 2000;182(5):1027-9.
4. Oto A, Srinivasan PN, Ernst RD, Koroglu M, Cesani F, Nishino T, et al. Revisiting MRI for appendix location during pregnancy. AJR Am J Roentgenol. 2006;186(3):883-7.
5. Lurie S, Rahamim E, Piper I, Golan A, Sadan O. Total and differential leukocyte counts percentiles in normal pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2008;136(1):16-9.
6. Moghadam MN, Salarzaei M, Shahraki Z. Diagnostic accuracy of ultrasound in diagnosing acute appendicitis in pregnancy: a systematic review and meta-analysis. Emergency Radiology. 2022;29(3):437-48.
7. Duke E, Kalb B, Arif-Tiwari H, Daye ZJ, Gilbertson-Dahdal D, Keim SM, et al. A Systematic Review and Meta-Analysis of Diagnostic Performance of MRI for Evaluation of Acute Appendicitis. American Journal of Roentgenology. 2016;206(3):508-17.
8. Theilen LH, Mellnick VM, Longman RE, Tuuli MG, Odibo AO, Macones GA, et al. Utility of magnetic resonance imaging for suspected appendicitis in pregnant women. American Journal of Obstetrics and Gynecology. 2015;212(3):345.e1-.e6.
9. Ueberrueck T, Koch A, Meyer L, Hinkel M, Gastinger I. Ninety-four appendectomies for suspected acute appendicitis during pregnancy. World Journal of Surgery. 2004;28(5):508-11.
10. Kave M, Parooie F, Salarzaei M. Pregnancy and appendicitis: a systematic review and meta-analysis on the clinical use of MRI in diagnosis of appendicitis in pregnant women. World Journal of Emergency Surgery. 2019;14(1):37.
11. Hurwitz LM, Yoshizumi T, Reiman RE, Goodman PC, Paulson EK, Frush DP, et al. Radiation dose to the fetus from body MDCT during early gestation. AJR Am J Roentgenol. 2006;186(3):871-6.
12. Long SS, Long C, Lai H, Macura KJ. Imaging strategies for right lower quadrant pain in pregnancy. AJR Am J Roentgenol. 2011;196(1):4-12.
13. Cohen-Kerem R, Railton C, Oren D, Lishner M, Koren G. Pregnancy outcome following non-obstetric surgical intervention. The American Journal of Surgery. 2005;190(3):467-73.
14. Brown JJS, Wilson C, Coleman S, Joypaul BV. Appendicitis in pregnancy: an ongoing diagnostic dilemma. Colorectal Disease. 2009;11(2):116-22.
15. McGory ML, Zingmond DS, Tillou A, Hiatt JR, Ko CY, Cryer HM. Negative appendectomy in pregnant women is associated with a substantial risk of fetal loss. J Am Coll Surg. 2007;205(4):534-40.
16. Ball E, Waters N, Cooper N, Talati C, Mallick R, Rabas S, et al. Evidence-Based Guideline on Laparoscopy in Pregnancy: Commissioned by the British Society for Gynaecological Endoscopy (BSGE) Endorsed by the Royal College of Obstetricians & Gynaecologists (RCOG). Facts Views Vis Obgyn. 2019;11(1):5-25.
17. Cheng HT, Wang YC, Lo HC, Su LT, Soh KS, Tzeng CW, et al. Laparoscopic appendectomy versus open appendectomy in pregnancy: a population-based analysis of maternal outcome. Surg Endosc. 2015;29(6):1394-9.
18. Nakashima M, Takeuchi M, Kawakami K. Clinical Outcomes of Acute Appendicitis During Pregnancy: Conservative Management and Appendectomy. World J Surg. 2021;45(6):1717-24.
19. Yang J, Wen SW, Krewski D, Corsi DJ, Walker M, Mattison D, et al. Association of treatments for acute appendicitis with pregnancy outcomes in the United States from 2000 to 2016: Results from a multi-level analysis. PLOS ONE. 2021;16(12):e0260991.

20. Rottenstreich M, Tankel J, Vilk Ayalon N, Rotem R, Yellinek S, Khatib F, et al. Laparoscopic negative appendectomy during pregnancy is associated with adverse neonatal outcome. Surg Endosc. 2022;36(1):544-9.
21. Pearl JP, Price RR, Tonkin AE, Richardson WS, Stefanidis D. SAGES guidelines for the use of laparoscopy during pregnancy. Surg Endosc. 2017;31(10):3767-82.
22. Di Saverio S, Podda M, De Simone B, Ceresoli M, Augustin G, Gori A, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. World Journal of Emergency Surgery. 2020;15(1):27.
23. Wilasrusmee C, Sukrat B, McEvoy M, Attia J, Thakkinstian A. Systematic review and meta-analysis of safety of laparoscopic versus open appendicectomy for suspected appendicitis in pregnancy. Br J Surg. 2012;99(11):1470-8.
24. Balinskaite V, Bottle A, Sodhi V, Rivers A, Bennett PR, Brett SJ, et al. The Risk of Adverse Pregnancy Outcomes Following Nonobstetric Surgery During Pregnancy: Estimates From a Retrospective Cohort Study of 6.5 Million Pregnancies. Annals of Surgery. 2017;266(2).
25. HRA. Defining Research Table: Health Research Authority; 2022 [Available from: https://www.hra-decisiontools.org.uk/research/docs/DefiningResearchTable_Oct2022.pdf.
26. Intergrowth-21st. Intergrowth-21st Manual Entry: Oxford University; 2024 [Available from: http://intergrowth21.ndog.ox.ac.uk/en/ManualEntry.

Appendix I: Site resource profile questionnaire

	Questions	Responses	Notes
1.	Please enter the name of your trust.		This is so we can monitor which participating centres have completed this questionnaire.
2.	Please enter the name of your hospital.		This is so we can monitor which participating centres have completed this questionnaire.
3.	Does your trust have a defined pathway for managing pregnant patients with appendicitis?	Yes; No	
4.	Does your trust have a defined pathway for managing pregnant patients with other intra-abdominal surgical conditions?	Yes; No	
5.	Does your trust have a defined pathway for imaging pregnant patients with acute abdominal pain?	Yes; No	
6.	Are there facilities in place to allow ultrasound scans to be performed to investigate acute abdominal pain in pregnant patients at your site: Monday-Friday, daytime (08:00-17:00) Monday-Friday, in the evening (17:00-21:00) Monday to Friday, overnight (21:00-08:00) Over the weekend, daytime (08:00-17:00) Over the weekend, in the evening (17:00-21:00) Over the weekend, overnight (21:00-08:00)	 Yes; No; In exceptional circumstances Yes; No; In exceptional circumstances Yes; No; In exceptional circumstances Yes; No; In exceptional circumstances Yes; No; In exceptional circumstances Yes; No; In exceptional circumstances	Examples of "exceptional circumstances": calling in an off-site specialist radiographer to perform the scan, prior arrangement for a specialist radiographer to be present outwith their regular schedule, or discussion/arrangement between patient's consultant and consultant radiologist, etc. You may need to consult a radiology colleague to answer this question.
7.	Are there facilities in place to allow MRI scans to be performed to investigate acute abdominal pain in pregnant patients at your site: Monday-Friday, daytime (08:00-17:00) Monday-Friday, in the evening (17:00-21:00) Monday to Friday, overnight (21:00-08:00) Over the weekend, daytime (08:00-17:00) Over the weekend, in the evening (17:00-21:00) Over the weekend, overnight (21:00-08:00)	 Yes; No; In exceptional circumstances Yes; No; In exceptional circumstances Yes; No; In exceptional circumstances Yes; No; In exceptional circumstances Yes; No; In exceptional circumstances Yes; No; In exceptional circumstances	Examples of "exceptional circumstances": calling in an off-site specialist radiographer to perform the scan, prior arrangement for a specialist radiographer to be present outwith their regular schedule, or discussion/arrangement between patient's consultant and consultant radiologist, etc. You may need to consult a radiology colleague to answer this question.

8.	Are there facilities in place to allow CT scans to be performed to investigate acute abdominal pain in pregnant patients at your site: Monday-Friday, daytime (08:00-17:00) Monday-Friday, in the evening (17:00-21:00) Monday to Friday, overnight (21:00-08:00) Over the weekend, daytime (08:00-17:00) Over the weekend, in the evening (17:00-21:00) Over the weekend, overnight (21:00-08:00)	 Yes; No; In exceptional circumstances Yes; No; In exceptional circumstances Yes; No; In exceptional circumstances Yes; No; In exceptional circumstances Yes; No; In exceptional circumstances Yes; No; In exceptional circumstances	Examples of "exceptional circumstances": calling in an off-site specialist radiographer to perform the scan, prior arrangement for a specialist radiographer to be present outwith their regular schedule, or discussion/arrangement between patient's consultant and consultant radiologist, etc. You may need to consult a radiology colleague to answer this question.
9.	Are the obstetrics & gynaecology and general surgery departments based at the same site within your trust?	Yes; No	
10.	Are the general surgery and neonatal services based at the same site within your trust?	Yes; No	
11.	If the general surgery and Obstetrics & Gynaecology/ Neonatal services are based at different sites, which of the following best describes <u>usual</u> practice when a pregnant patient requires emergency non-obstetric abdominal surgery (such as appendicectomy or laparotomy), after the age of foetal viability?	N/A (all services are based at the same site); The operation is performed at the site where specialist obstetric/neonatal facilities are available as far as possible; The operation is performed at the site where the General Surgery department is based; The operation is performed at the site where the General Surgery department is based, with an obstetrics specialist &/or neonatal specialist is readily available.	Take the age of foetal viability to mean >=22 weeks gestation
12.	Which of the following best describes <u>usual</u> anaesthetic practice in your trust for pregnant patients requiring emergency non-obstetric abdominal surgery (such as appendicectomy or laparotomy)?	This would be administered by the on-call anaesthetist, regardless of their sub-specialty; This would be administered by an anaesthetist with experience or expertise in obstetric anaesthesia.	You may need to consult an anaesthetic colleague to answer this question.
13.	What was/is the standard approach to an appendicectomy for acute appendicitis in the **non-pregnant** patient in your hospital: in 2013? In 2018?	 Laparoscopic; Open Laparoscopic; Open	Please take the "standard" approach to mean the approach that would be adopted as <u>first-line in the majority of patients by the majority of surgeons in your hospital</u>

	Currently (2023)?	Laparoscopic; Open	unless (relative) contraindications identified pre-operatively warranted a change in strategy.

Appendix II: Retrospective study data collection template

	Field	Responses	Notes
Patient characteristics			
1.	Study ID		
2.	Age at initial presentation (years)	18-25; 26-30; 31-35; 36 and above	
3.	Gestational age at presentation (weeks)	[value] weeks; [value] days	
4.	Parity	Primiparous; Multiparous	
5.	Co-morbidities Pre-pregnancy BMI Diabetes or gestational diabetes Smoker Immunosuppression Previous C-section Hypertension (pre-existing or gestational) Other cardiovascular comorbidity Previous presentation with acute appendicitis ASA	 [value] Y;N Y;N Y;N Y;N Y;N Y;N Y;N I II III IV V	
Details of initial presentation and admission with possible appendicitis			
6.	Date of initial presentation to hospital with suspected appendicitis	dd-mm	
7.	Year of initial presentation	01.10.2013 – 30.09.2017; 01.10.2017 – 30.09.2023	
8.	White cell count ($X10^9$/L) at initial hospital presentation	[value]	
9.	Neutrophil count ($X10^9$/L) at initial hospital presentation	[value]	
10.	CRP at initial hospital presentation (mg/L)	[value]	
11.	Was the patient already an inpatient at the time of symptom onset?	Yes; No	
12.	Which team did the patient initially present to with appendicitis in hospital?	Accident and Emergency; Obstetrics &/or gynaecology; General Surgery; Medicine; Other (specify)	Only if answer to question 11 is No
13.	Was the patient admitted to hospital at the time of presentation?	Yes; No	Only if answer to question 11 is No

14.	Date of admission	dd-mm	Only if answer to question 11 is No
15.	Primary admitting team	Obstetrics &/or gynaecology; General Surgery; Medicine; Other (specify)	
16.	Date of review by General Surgery (if not admitted under General Surgery)	dd-mm; N/A (admitted under General Surgery)	Only if answer to question 15 is not General Surgery
17.	Was the patient's care transferred to General Surgery?	Yes; No	Only if answer to question 15 is not General Surgery
18.	Date of transfer to General Surgery (if not admitted under General Surgery)	dd-mm; N/A (admitted under General Surgery)	Only if answer to question 17 is Yes
Details of diagnosis			
19.	How was the diagnosis of appendicitis first confirmed?	Imaging; Intra-operative findings; Neither of the above - treated as appendicitis on the basis of clinical suspicion	Option 3 refers to instances where the patient was managed as having acute appendicitis even if not proven on imaging or intra-operatively
20.	Grade of senior-most member of General surgical team making or confirming the diagnosis of appendicitis	SHO or equivalent; SpR or equivalent; Consultant grade	
21.	Date of first imaging	dd-mm	
22.	Time of first imaging	Daytime (08:00-17:00); Evening (17:01 – 21:00); Night time (21:01-07:59)	
23.	Modality of first imaging and findings on first imaging	**Ultrasound** Appendix appearance: normal/ abnormal /not seen; Surrounding echogenic fat: Yes/No/Not reported; Free fluid: Yes/No/Not reported; Focal tenderness on compression: Yes/No/Not reported; Thickened/oedematous appendix wall: Yes/No/Not reported; Appendicolith: Yes/No/Not reported; Dilated appendix: Y/N/Not reported **MRI** Appendix visualised: Yes/No Dilated appendix: Y/N/Not reported Stranding or inflammatory change around appendix or caecum or in right iliac fossa Yes/No/Not reported Appendicolith: Yes/No/Not reported Perforation: Yes/No/Not reported Abscess or collection: Yes/No/Not reported	A dilated appendix is defined as one measuring >6mm in diameter Perforation – this may have been described indirectly without using the term "perforation" e.g. focal defect in appendiceal wall, appendicular abscess, extraluminar gas, extraluminal appendicolith. You may need to consult a surgical colleague to help with interpretation of the report.

		CT Appendix visualised: Yes/No Dilated appendix: Y/N/Not reported Stranding or inflammatory change around appendix or caecum or in right iliac fossa Yes/No/Not reported Appendicolith: Yes/No/Not reported Perforation Yes/No/Not reported Abscess or collection Yes/No/Not reported	
24.	Date of second imaging	N/A (no subsequent imaging); dd-mm	
25.	[If applicable] Time of second imaging	[same values as field no. 22]	
26.	[If applicable] Modality of second imaging and findings on second imaging	[same values as field no. 23]	
27.	Date of third imaging	N/A (no subsequent imaging); dd-mm	
28.	[If applicable] Time of third imaging	[same values as field no. 22]	
29.	[If applicable] Modality of third imaging and findings on third imaging	[same values as field no. 23]	
Details of treatment			
30.	How was this episode of appendicitis managed? Tick all that apply.	No treatment; Antibiotics; Radiological drain; Surgery	
31.	Date of initiation of antibiotics	dd-mm	If answer to Q30 includes “antibiotics”.
32.	Date of radiological aspiration or drain	dd-mm	If answer to Q30 includes “radiological drain”
33.	Date of operation for suspected/confirmed appendicitis	dd-mm	If answer to Q30 includes “surgery”
34.	Time of operation	Daytime (08:00-17:00); Evening (17:01 – 21:00); Night time (21:01-07:59)	If answer to Q30 includes “surgery”
35.	Anaesthesia	General; Regional	If answer to Q30 includes “surgery”
36.	Name of operation documented on operation note	Appendicectomy; Right hemicolectomy; Drainage of sepsis and/or washout only; Other – please specify	If answer to Q30 includes “surgery”
37.	How was the operation performed?	Open via right lower quadrant incision; Open via midline laparotomy; Laparoscopic; Laparoscopic converted to open via	If answer to Q30 includes “surgery”

		right sided incision; Laparoscopic converted to midline laparotomy	
38.	Operative findings –appendix Select all that apply.	Normal; Inflamed; Perforated; Gangrenous	If answer to Q30 includes "surgery"
39.	Operative findings- contamination	None; Localised; generalised Serous; Pus; Faecal matter	If answer to Q30 includes "surgery"
40.	Operative findings- associated abscess	Yes; No	If answer to Q30 includes "surgery"
41.	Histology	Normal; Acute appendicitis; Malignancy; Other – specify [value]	
42.	Post-operative antibiotics	Yes; No	
43.	Duration of post-operative antibiotics	[value] days	If answer to above is "Yes"
Outcomes			
44.	Date of discharge	dd-mm	
45.	Did the patient experience any complication within 30 days of initial admission (or initial presentation with appendicitis if the patient was already an inpatient at the time of presentation)? Select all that apply.	None; Wound infection (requiring abx); Wound infection (requiring drainage); intra-abdominal collection (requiring antibiotics); intra-abdominal collection (requiring drain); Ileus; hospital acquired pneumonia; DVT/PE; Return to theatre; Level 2/3 care; Death	
46.	30-day re-attendance with an **acute** presentation – date	dd-mm; N/A (did not reattend within 30 days)	Re-presentation for an acute problem within 30 days of initial admission (or initial presentation with appendicitis if the patient was already an inpatient at the time of presentation). Any planned follow-up such as obstetric scan should be disregarded
47.	30-day re-attendance reason (tick all that apply)	Repeat presentation with appendicitis/suspected appendicitis; Complication of appendicectomy; Pregnancy-related; Other – specify [value]	
48.	Re-attendance(s) with appendicitis during this pregnancy?	Yes; No	
49.	Date of first re-attendance with appendicitis during this pregnancy?	dd-mm	If answer to Q48 is "Yes"
50.	First re-attendance with appendicitis during this pregnancy – management	Antibiotics; Interventional radiology (drain); Operation – appendicectomy; Operation – other; please specify [value]	If answer to Q48 is "Yes"

51.	Any further re-attendance(s) with appendicitis during this pregnancy?	Yes; No	If Q48-50 answered
52.	Date of second re-attendance with appendicitis during this pregnancy?	dd-mm	If Q48-50 answered
53.	Second re-attendance with appendicitis during this pregnancy – management	Antibiotics; Interventional radiology (drain); Operation – appendicectomy; Operation – other; please specify [value]	If Q48-50 answered
54.	How did the pregnancy end?	Livebirth; Stillbirth; Neonatal death; Termination of pregnancy (surgical/medical); Miscarriage	
55.	Mode of delivery	Vaginal (including assisted deliveries) C-section	If answer to Q54 is “livebirth” or “stillbirth”
56.	Date when pregnancy ended	dd-mm	
57.	Gestational age when pregnancy ended	[value] weeks; [value] days	
58.	Small for gestational age	Y; N	This is defined as a birth weight less than the 10th centile for gestational age. Use this calculator to work this out, by entering foetal sex, gestational age (weeks + days) and weight (kg): http://intergrowth21.ndog.ox.ac.uk/en/ManualEntry

Appendix III: Coding

The following search strategies are suggested:

1. ICD-10 diagnostic codes for ‘acute appendicitis, other appendicitis, unspecified appendicitis, or other diseases of appendix’ **AND** ICD-10 diagnostic codes for ‘pregnancy’, or ‘diseases of the digestive system complicating pregnancy, childbirth and the puerperium’

2. ICD-10 diagnostic codes for ‘pregnancy’, or ‘diseases of the digestive system complicating pregnancy, childbirth and the puerperium’ **AND** OPCS procedure codes for any ‘excision of appendix’

3. In addition, it may be helpful to find all patients who have a recorded diagnosis of appendicitis or appendicectomy that coincides with the period of time when they have a registered pregnancy (pregnancy registration date – pregnancy end date).

Appendix IV: Checklist for successful inclusion of your centre

☐ A list of participating hospitals can be found here: https://docs.google.com/spreadsheets/d/1FDdsetOOkZwd-NkRRH_mp-VdnO-qg8r1fxf4fnr_zRw/edit#gid=0. If your hospital is not listed, please contact the steering committee for further information and to consider joining the study as a Hospital Lead: mama.study2024@gmail.com. If your hospital is already a participating centre but has no representative from your specialty, please email the steering committee so we can put you in touch with your Hospital Lead.

☐ Teams should ideally consist of a trainee in General Surgery +/- a trainee in obstetrics and gynaecology and a senior collaborator (either a consultant in General Surgery or a consultant in Obstetrics and Gynaecology).

☐ Obtain approval from your hospital audit department (or equivalent) according to local processes. The hospital lead should send evidence of registration to the steering committee (insert email).

☐ Confirm your NHS Trust's Caldicott Guardian's approval to upload data to REDcap. This involves contacting the information governance team in your trust and sending them the study protocol for review. Please send evidence of your Caldicott Guardian's approval to the steering committee.

 It is important that you begin approval processes immediately as they can take time. Please liaise with your local **Hospital Lead** 

☐ Once the project is approved, and the hospital lead has forwarded the required evidence to the steering committee, one nominated member of your team will be provided with login details for the REDCap data collection system.

☐ Your audit department should be able to assist in pulling records for patients eligible for this study (suggested search strategy in Appendix III). Please carefully consider the eligibility criteria at this stage.

 Patients are eligible if they were diagnosed with acute appendicitis (clinically, radiologically, histologically or intra-operatively) whilst pregnant. Pregnant patients who had an appendicectomy for suspected appendicitis (regardless of whether histological examination subsequently revealed a normal appendix) are also eligible for inclusion. 

 It is likely that a combination of electronic and paper records will need to be accessed to obtain the required data for each patient. 

☐ Contact your information governance team with the list of patients eligible for the study. Request them to check which (if any) of the patients have opted out of their data being used for audit and research purposes (NHS National Data Opt-Out). Any patient who

has opted out should be excluded from the study and their data should not be uploaded to REDCap. If you have already collected data on a patient that has opted out, please ensure to delete their data when the opt-out choice is communicated to you.

Appendix V: Opinions from the Health Research Authority and an NHS Research & Development department

Re: Management of appendicitis in pregnancy (MAMA)

Queries <queries@hra.nhs.uk>
Wed 06/12/2023 13:06
To:HUSNOO, Nilofer (SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST) <nilofer.husnoo@nhs.net>

You don't often get email from queries@hra.nhs.uk. Learn why this is important

This message originated outside of NHSmail from a securely accredited DCB1596 domain. This can be considered a trusted and verified domain however use caution when opening email from an unrecognised sender.

ENQUIRY TO QUERIES LINE

Dear Nilofer,

Your query was reviewed by our Decision Panel Advisors. We apologise for the delay in responding.

RE: MAMA: Management of acute appendicitis in pregnancy

Thank you for your email seeking additional clarity on whether your project should be classified as research and whether it requires ethical review by an NHS Research Ethics Committee (REC).

You provided the following information:

- A protocol (version 1.0, dated 01/10/2023)
- One page proposal (version 1.1)
- A PDF / screenshot of the results page of the decision tool(s)
- A copy of any previous correspondence/advice, with the HRA or another organisation, in relation to this query

Based on the information you have provided, our decision is that the project is **not considered to be research and does not require review by an NHS Research Ethics Committee.**

This decision is based on the information provided. The advisors agreed that this project was not considered research and could be categorised as a service evaluation due to the following:

- Objectives and design consistent with a service evaluation

The advisors agreed that NHS REC review was not required as this project is not considered research

The advisors agreed that you should consult the relevant NHS R&D office, as NHS R&D permission would need to be sought as this project would be using NHS resources and data.

This decision is in line with:

- Governance Arrangements for Research Ethics Committees
- UK Policy Framework for Health and Social Care Research
- The Research Ethics Service (NRES) *Defining Research* table (linked to from the first page of the 'Is it research?' Decision Tool)
- Algorithm *Does my project require review by an NHS Research Ethics Committee?* (linked in the footer of the 'Do I need NHS REC review?' Decision Tool)

This decision should not be interpreted as giving a form of ethical approval or endorsement to your project on behalf of the HRA. However, it may be provided to a journal or other body as evidence if required.

Please note that this decision was based on the information provided to us as listed above. If any changes are made to information you provided, this may alter the decision.

You should also be aware that:

- This response only covers whether your project is classified as research and whether it requires review by an NHS REC. You are strongly advised to consider other approvals that may be required for your project.
- All types of study involving human participants should be conducted in accordance with basic ethical principles, such as informed consent and respect for the confidentiality of participants. Also, in processing identifiable data there are legal requirements under the Data Protection Act (2018). When undertaking an audit or service/therapy evaluation, the investigator and his/her team are responsible for considering the ethics of their project with advice from within their organisation.

Regards,

Queries Line
REF 1361/134/122/81

The Queries Line is an email-based service that provides advice from HRA senior management, including operations managers based in our regional offices throughout England. Providing your query in an email helps us to quickly direct your enquiry to the most appropriate member of our team who can provide you with an accurate written response. It also enables us to monitor the quality and timeliness of the advice given by the HRA to ensure we can give you the best service possible, as well as use queries to continue to improve and to develop our processes.

Health Research Authority
2 Redman Place | Stratford | London | E20 1JQ
E. queries@hra.nhs.uk
W. www.hra.nhs.uk

CRIO Review of Protocol V1.0 dated 01.10.2023 - The MAMA study

HARRIS, Modhumita (SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST)
<modhumita.harris@nhs.net>

Mon 06/11/2023 14:18

To:HUSNOO, Nilofer (SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST) <nilofer.husnoo@nhs.net>

Dear Nilofer,

RE: CRIO Review of Protocol V1.0 dated 01.10.2023 - Management of Acute Appendicitis in Pregnancy: The MAMA study

Following my review of the updated Protocol (v1.0 dated 01.10.2023 for the MAMA study), I am happy to re-confirm that this still does not require Research Governance, REC or HRA approval to go ahead at our Trust.

If you require any further information, please do not hesitate to get in touch.

Thanks and BW, from Mod

Dr Mod Harris

Research Coordinator for Academic Radiology & MIMP, Laboratory Medicine, Pharmacy, General Surgery & ENT

Clinical Research & Innovation Office
Sheffield Teaching Hospitals NHS Foundation Trust
Room D49, D Floor, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF
Tel. 0114 2713570
Email: modhumita.harris@nhs.net
Website: http://www.sheffieldclinicalresearch.org
Twitter: @Shef_Research

Please note, I work Mondays – Thursdays 9-3pm

Appendix VI: University of Sheffield Research Ethics Committee Approval Letter

The University Of Sheffield.

Downloaded: 06/12/2023
Approved: 28/11/2023

Nilofer Husnoo
Oncology

Dear Nilofer

PROJECT TITLE: Management of appendicitis in pregnancy (MAMA)
APPLICATION: Reference Number 056754

On behalf of the University ethics reviewers who reviewed your project, I am pleased to inform you that on 28/11/2023 the above-named project was **approved** on ethics grounds, on the basis that you will adhere to the following documentation that you submitted for ethics review:

- University research ethics application form 056754 (form submission date: 27/11/2023); (expected project end date: 31/08/2024).

If during the course of the project you need to deviate significantly from the above-approved documentation please inform me since written approval will be required.

Your responsibilities in delivering this research project are set out at the end of this letter.

Yours sincerely

Cecilia Bolchini
Ethics Administrator
Medical School

Please note the following responsibilities of the researcher in delivering the research project:

- The project must abide by the University's Research Ethics Policy: https://www.sheffield.ac.uk/research-services/ethics-integrity/policy
- The project must abide by the University's Good Research & Innovation Practices Policy: https://www.sheffield.ac.uk/polopoly_fs/1.671066!/file/GRIPPolicy.pdf
- The researcher must inform their supervisor (in the case of a student) or Ethics Administrator (in the case of a member of staff) of any significant changes to the project or the approved documentation.
- The researcher must comply with the requirements of the law and relevant guidelines relating to security and confidentiality of personal data.
- The researcher is responsible for effectively managing the data collected both during and after the end of the project in line with best practice, and any relevant legislative, regulatory or contractual requirements.