EAES Rapid Guideline: Systematic review, meta-analysis, GRADE assessment and evidence-informed European recommendations on appendicitis in pregnancy

PROTOCOL

Introduction

Background

Acute appendicitis complicates about 1 out of 1000 pregnancies, with an estimate of 6.3 per 1000 patient years. Management of the disease in this population varies, depending on the stage of pregnancy, the severity of the disease, patient preferences, surgical expertise and anesthesiological considerations.

A survey of European surgeons by the EAES Research Committee/Guideline Subcommittee prioritized non-obstetric operations in pregnancy as a candidate topic to be addressed by a clinical practice guideline (33% among responders).

Objective

The objective of this rapid guideline is to provide transparently developed, reliable, and evidence-informed recommendations on the management of suspected acute appendicitis in pregnancy.

Methods

The present protocol adheres to AGREE and PRISMA-P reporting standards [28][29]. It will be available on the EAES website for access by healthcare professionals, and EAES members will be asked to comment on the content. Relevant comments will be considered by the steering group.

Funding

The project is funded by the European Association for Endoscopic Surgery. The funding body will not have any influence on the guideline development process.

Steering group

The steering group consists of a member of the EAES Education & Training Committee and a certified guideline methodologist, chair of the EAES Guidelines Subcommittee.

Guideline methodologist

The senior author is a certified guideline methodologist (INGUIDE certificate number 2021-L2-V1-00001), has participated in the development of more than 15 clinical practice guidelines and will serve as a guideline methodologist in this guideline.

Guideline panel and external advisors

The guideline panel will consist of 4 general surgeons, 2 obstetricians/gynecologists, 1 midwife, 1 anesthesiologist and 2 patient representatives. Management of conflicts will comply with Guidelines International Network guidelines.

Guideline questions

Two PICO question will address the management of suspected appendicitis in pregnancy and subgroup analyses will address the 1st, 2nd and 3rd trimester of pregnancy:

1. Should surgery versus conservative management be preferred for suspected acute appendicitis in pregnancy?
2. Should laparoscopic versus open appendectomy be preferred for suspected acute appendicitis in pregnancy?

Guideline development methodology

The guideline development process will adhere to GRADE and AGREE-II guideline development standards, and methodology parameters of rapid recommendations. The guideline panel and external advisors will comment on the protocol, they will vote on thresholds for minimal important differences in the form of absolute effect differences for each outcome, and they will rate the importance of outcomes on a 9-point scale as per GRADE. Any additional outcomes proposed by the panel will be considered for inclusion. Their responses will be summarized and they will direct the decision about the selection of outcomes and thresholds for minimal importance differences.

The literature search strategy will be developed by the guideline methodologist, who has vast experience in evidence outreach and synthesis. PubMed and OpenGrey will be interrogated with no language, publication type or other limits.

A scoping search of PubMed has identified only observational studies addressing the clinical questions of this guideline. Risk of bias of eligible studies will be assessed using ROBINS-I for cohort studies [6]. Study selection, risk of bias assessment and data extraction will be performed by one investigator and independently cross-checked by the guideline methodologist. Statistical analyses will be performed independently by the statisticians' group using the methodology reported below.

GRADE summary of findings tables will be constructed and discussed in a consensus meeting of the guideline development group. In this consensus meeting, draft recommendation(s) will be formulated, and direction/strength of recommendations will be defined within a GRADE evidence-to-decision framework using a fully contextualized approach and refined/validated through an online anonymous Delphi process. Comments by the Delphi panel must be in accordance with the GRADE methodology in order to be considered. Formulation of recommendations will be informed by GRADE and AGREE-REX.

Evidence synthesis methodology

A random effects meta-analysis model will be applied as we expect variation in the PICO criteria among trials. Random effects models are used to incorporate heterogeneity in meta-analyses. For dichotomous outcomes, we will use Mantel-Haenszel pooled odds ratios as effect size, while for continuous outcomes we will calculate standardized mean differences. In all cases, the summary effects will be accompanied by their corresponding 95% confidence intervals and 95% prediction intervals. The latter show the plausible values for the effect of future trials and is a useful way to incorporate statistical heterogeneity and infer on the conclusiveness of results.

Between-study heterogeneity will be statistically assessed by Cochran's Q test; heterogeneity will be quantified using the I^2 statistic and characterized as not important, substantial, moderate or considerable according to Cochrane Handbook. The estimated heterogeneity variance will be also compared to its empirical distribution as estimated by empirical studies.

We will explore for small-study effects both visually (funnel plots) and statistically (e.g. Egger's test), provided that there are at least 10 studies included per outcome.

For completion, we will perform a fixed-effect meta-analysis as a sensitivity analysis. Statistical analyses will be performed using the meta and metafor libraries in R. In all analyses we will use a significance level of 5% with the exception of Egger's and chi-square statistic for which we will use a 10% significance level.

Target users

This guideline is intended to be used by general surgeons, multidisciplinary team members, hospital administrators, policy makers, and patients. The guideline publication will contain a short abstract in plain language to be used by patients.

Publication and dissemination strategy

As a EAES Research Committee/Guideline Subcommittee project, this guideline will be submitted for publication in Surgical Endoscopy, official journal of the Association.

Feedback

The steering group will consider constructive feedback received during the conduct of the project via various routes and sources such as letters to the editor and social media. Such feedback will be taken into account in the guideline development process or a future update of the guideline.

Monitoring, update and future steps

Use of the guideline by EAES members will be monitored through an online survey 2 years after publication. The timing of the update of the guideline will be decided by the steering group on the basis of new research data on this topic.

Discussion

Implications for practice and research

Stringent criteria defined by GRADE and AGREE II will be applied to collate, appraise and analyze the available evidence. The guideline is expected to inform decision making, and guide clinical practice and health policy. Guidance will be provided on direction and implications for future research in light of identified evidence gaps.

Strengths and limitations

The strengths and limitations of rapid guidelines have been previously reported. The merits of rapid guidelines, including trustworthiness, credibility, and time efficiency have to outweigh the shortcomings, such as the narrow scope and possible missing of resources due to the rapid review process.

Research ethics

Conflicts of interest statements will be collected by all participants before and upon completion of the project. Participants with substantial conflicts will be either re-assigned functions or replaced as per Guidelines International Network recommendations. Authors of studies considered for development of evidence summaries will not be involved in risk of bias appraisal of these studies and discussion of the relevant evidence to decision framework.

Conclusion

This rapid guideline will address the management of suspected appendicitis during pregnancy and aspires to constitute a useful information source for key stakeholders.