

IS PERFORATION OF THE APPENDIX A RISK FACTOR FOR TUBAL INFERTILITY AND ECTOPIC PREGNANCY? AN APPRAISAL OF THE EVIDENCE

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OBJECTIVE: To critically assess the evidence that appendiceal perforation is a risk factor for subsequent tubal infertility or ectopic pregnancy.

DATA SOURCES: Epidemiologic studies investigating the relationship between appendectomy and infertility or ectopic pregnancy were identified by searching the MEDLINE database from 1966 to 1997. Appropriate citations were also extracted from a manual search of the bibliographies of selected papers.

STUDY SELECTION: Twenty-three articles were retrieved. Only 4 presented original data including comparisons to a nonexposed control group and they form the basis for this study.

DATA EXTRACTION: Because the raw data or specific techniques of data analysis were not always explicitly described, indices of risk for exposure were extracted from the data as presented and were analysed without attempting to convert them to a common measure.

DATA SYNTHESIS: Articles were assessed according to the criteria of the Evidence-Based Medicine Working Group for evaluating articles on harm. Review of the literature yielded estimates of the risk of adverse fertility outcomes ranging from 1.6 (95% confidence interval [CI] 1.1 to 2.5) for ectopic pregnancy after an appendectomy to 4.8 (95% CI 1.5 to 14.9) for tubal infertility from perforation of the appendix. Recall bias, and poor adjustment for confounding variables in some reports, weakened the validity of the studies.

CONCLUSIONS: The methodologic weaknesses of the studies do not permit acceptance of increased risk of tubal pregnancy or infertility as a consequence of perforation of the appendix, so a causal relationship cannot be supported by the data currently available. Only a well-designed case-control study with unbiased ascertainment of exposure and adjustment for confounding variables will provide a definitive answer.

OBJECTIF : Évaluer de façon critique les données probantes selon lesquelles une perforation de l'appendice constitue un facteur de risque de stérilité tubaire ou de grossesse ectopique subséquentes.

SOURCES DE DONNÉES : On a repéré des études épidémiologiques portant sur le lien entre l'appendicectomie et la stérilité ou la grossesse ectopique en effectuant une recherche dans la base de données MEDLINE de 1966 à 1997. On a aussi extrait des citations pertinentes à la suite d'une recherche manuelle effectuée dans les bibliographies de certaines communications.

SÉLECTION D'ÉTUDES : On a extrait 23 articles dont 4 seulement présentaient des données originales, y compris des comparaisons avec un groupe témoin non exposé. Ces articles constituent la base de la présente étude.

EXTRACTION DE DONNÉES : Parce que les données brutes ou les techniques précises d'analyse des données n'étaient pas toujours décrites explicitement, on a extrait des données présentées des indices de risque d'exposition, que l'on a analysés sans essayer de les convertir en mesure commune.

SYNTHÈSE DES DONNÉES : On a évalué les articles en fonction des critères d'évaluation des articles sur le

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préjudice du Groupe de travail sur la médecine fondée sur des données probantes. Une recension des écrits a produit des estimations du risque de résultats indésirables sur la fécondité variant de 1,6 (intervalle de confiance [IC] à 95 %, 1,1 à 2,5) dans le cas de la grossesse ectopique après une appendicectomie à 4,8 (IC à 95 %, 1,5 à 14,9) dans celui de la stérilité tubaire à la suite d'une perforation de l'appendice. Le biais lié au rappel et le rajustement médiocre en fonction des variables confusionnelles contenues dans certains rapports ont affaibli la validité des études.

CONCLUSIONS : Les faiblesses méthodologiques des études ne permettent pas d'accepter le risque accru de grossesse ectopique ou de stérilité tubaire à la suite d'une perforation de l'appendice et les données actuellement disponibles ne peuvent donc appuyer un lien de cause à effet. Seule une étude cas témoin bien conçue comportant une évaluation non biaisée du risque et un rajustement en fonction des variables confusionnelles produira une réponse définitive.

Time-honoured surgical practice dictates that a physician entertaining a diagnosis of acute appendicitis in a young woman must be especially aware of the consequences of appendiceal perforation. It is thought that complications after acute appendicitis may result in damage to the fallopian tubes, with the attendant risk of tubal infertility or ectopic pregnancy subsequently, and although this dictum has been repeated in textbooks of surgery and gynecology,^{1,2} there have been few well-designed studies that specifically address the issue of this association.

There is good reason to establish whether appendiceal perforation is a true independent risk factor for subsequent disease of the fallopian tubes. The natural history of acute appendicitis is considered to follow a roughly sequential progression, usually beginning with appendiceal obstruction and luminal distension, followed by secondary bacterial infection, progressive inflammation and intramural ischemia,

with eventual transmural necrosis and perforation if left untreated.³ There is evidence that a well-timed appendectomy before appendiceal perforation can prevent this sequence of events, avoiding the morbidity and mortality associated with generalized peritonitis.⁴ However, any attempt to liberalize the indications for surgery in questionable cases will result in an increased rate of unnecessary appendectomies, and possible appendectomy-related complications.⁵⁻⁷ Surgeons are already aware of the significantly higher rate of unnecessary appendectomy (lower diagnostic accuracy) in young women due to the similar presentation of common obstetric and gynecologic diseases.^{5,8} Unfortunately, no laboratory test, imaging study or physical manoeuvre is sensitive and specific enough to differentiate among the possible diagnoses.⁹⁻¹³ Nevertheless, several authors have advocated early operation for possible appendicitis in young women to avoid the perceived risk of impaired fertility.¹⁴⁻¹⁷

This is not a trivial problem given the case-perforation rate of approximately 20%⁸ and the large numbers of young women who undergo appendectomy each year (94.1 per 100 000 women aged 20 to 34 years in Ontario, 1994/95).¹⁸ To resolve the uncertainty over whether appendiceal perforation does lead to poor fertility we conducted a systematic review of the literature.

METHODS

A computer search of the MEDLINE database for the period 1966 to 1997 was carried out using the MeSH heading "appendectomy" linked to "infertility" and "ectopic pregnancy." Titles and abstracts were scanned, and all English language papers reporting the results of controlled studies (i.e., case-control or cohort studies) were retained. A manual search of the bibliographies of selected papers was also conducted to identify any other appropriate citations.

Papers meeting our criteria (English language, controlled studies) were then appraised according to the guidelines of the Evidence-Based Medicine Working Group for evaluating the validity of an article about harm (Table I).¹⁹ We next graded the quality of the studies as "good," "adequate" or "poor," based on how well the 5 validity guides¹⁹ were fulfilled and whether the subjects' characteristics and analyses were described in sufficient detail to permit evaluation. Because raw data were omitted from

Table I

Validity Guides for an Article About Harm

Primary guides

1. Were there clearly identified comparison groups that were similar with respect to important determinants of outcome, other than the one of interest?
2. Were the outcomes and exposures measured in the same way in the groups being compared?
3. Was follow-up sufficiently long and complete?

Secondary guides

4. Is the temporal relationship correct?
5. Is there a dose-response gradient?

some studies it was not possible to pool the data to give an overall risk estimate. Also, we report measures of risk for exposures as in the original papers, with effects considered significant if the 95% confidence intervals (95% CI) did not include 1.0. Finally we used Sackett's modification of the Bradford Hill criteria²⁰ to determine if there was a sufficient causal relationship between appendiceal perforation and poor fertility outcomes.

RESULTS

Our search identified 23 articles addressing the title question. Of these, 11 reported original data: 7 were descriptive case series without an appropriate comparison group^{14-17,21-23} and were excluded, yielding 4 studies with an appropriate epidemiologic design. One case-control study looked specifically at the relationship between appendectomy and tubal infertility,²⁴ and 3 case-control studies examined appendectomy as a risk factor for ectopic pregnancy in combination with other exposures.²⁵⁻²⁷ The study designs, results and critical analysis, including quality grade, are summarized in Table II.

The only epidemiologic study that assessed the risk of tubal infertility was one by Mueller and colleagues.²⁴ The quality grade of this study was "adequate." This report used material from a population-based database in King County, Wash., established to investigate factors associated with female infertility. "Cases" had evidence of tubal disease on laparotomy, laparoscopy or hysterosalpingography and had been unable to conceive for at least 12 months. One hundred and fifty-eight cases of primary infertility were compared with a group of 504 matched controls taken from a registry of women who gave birth in the year after a corresponding woman in the

study group began trying to conceive. A separate analysis was carried out for women with secondary infertility. Groups were similar with respect to age, race, education and annual income. "Cases" were more likely to smoke cigarettes, use an intrauterine contraceptive device (IUCD) and have a history of pelvic inflammatory disease (PID).

A structured interview was used to ascertain a history of appendectomy or appendiceal perforation. There was no attempt to validate exposure by confirmation of appendectomy on medical records. Subjects who reported that they had undergone appendectomy incidentally were excluded from the analysis.

Using a multivariate analysis to adjust for cigarette smoking, IUCD use and a history of PID, the authors calculated a relative risk of 1.9 (95% CI, 0.9 to 4.2) for any appendectomy and 4.8 (1.5 to 14.9) for perforation of the appendix in women with primary infertility compared with controls. The number of sexual partners and a history of septic abortion or pelvic surgery, all factors associated with tubal infertility,² were not evaluated. The increased risk of infertility with perforation as opposed to an uncomplicated appendectomy suggests a dose-response relationship between increasing severity of appendiceal disease and infertility. Interestingly, ruptured appendix was also found to be a risk factor for secondary infertility (adjusted relative risk 3.2 [95% CI 1.1 to 9.6]), even though nearly all ruptures occurred before a successful pregnancy in this group.

Coste and associates²⁵ reported the results of a case-control study investigating the role of several risk factors in ectopic pregnancy. The quality rating of this paper was "good." The 279 "cases" were defined as women who were found to have an ectopic preg-

nancy at laparoscopy or laparotomy, and probably comprise all of the clinically important events that occurred over the study period. Each case was compared 1-to-1 to a control who was defined as the next woman giving birth at the same maternity hospital and who agreed to participate in the study. There were many differences between groups: the "cases" were older, more likely to smoke cigarettes, use an IUCD or other form of contraception, have more sexual partners, and have a history of PID, tubal surgery, ectopic pregnancy and therapeutic abortion. Exposures (including appendectomy) were determined on the basis of a structured interview, without independent validation with surgical records.

The univariate analysis revealed an odds ratio of 2.2 (95% CI, 1.6 to 3.2) for the association between ectopic pregnancy and appendectomy with unruptured appendix, and 1.7 (95% CI, 0.6 to 51) for rupture. These data suggest a significant risk for appendectomy but not for appendiceal perforation (95% CIs include unity), a puzzling result that may be partially explained by low numbers of these events (6 perforations among controls and 8 among "cases"). Subsequently, a multivariate model that included all important prognostic variables determined a small but significant adjusted odds ratio of 1.6 (95% CI, 1.1 to 2.5) for any appendectomy.

Michalas and colleagues²⁶ published their case-control study on a number of risk factors for ectopic pregnancy among a homogeneous population of Greek women. The "case" group of 361 women with pathologic evidence of ectopic pregnancy was compared with 420 age-matched obstetric patients at term. Interestingly, the authors excluded all women with a history of PID and those who used an IUCD or oral con-

traceptive, resulting in groups that were quite similar with respect to important variables. The “case” group had a slightly higher rate of infertility, previous pelvic surgery and therapeutic abortion. The exposure of interest for this analysis was appendectomy. Perforation and negative appendec-

tomy rates were not evaluated, and the method of determining exposure status was not reported. A multivariate analysis incorporating all the measured exposures as well as age, parity and history of infertility resulted in an adjusted relative risk of 1.8 (95% CI, 1.3 to 2.5) for appendectomy. The

quality rating given to this study was “adequate.”

The study by Nordenskjold and Ahlgren²⁷ also examined the role of various exposures in the etiology of ectopic pregnancy. Every woman operated on for ectopic pregnancy in the authors’ facility over the study period

Table II

Epidemiologic Studies Examining the Relationship Between Appendectomy and Infertility or Ectopic Pregnancy

Data	Study			
	Mueller and colleagues, 1986 ²⁴	Coste and associates, 1991 ²⁵	Michalas and colleagues, 1992 ²⁶	Nordenskjold and Ahlgren, 1991 ²⁷
Outcome	Tubal infertility*	Ectopic pregnancy	Ectopic pregnancy	Ectopic pregnancy
Design	Case-control	Case-control	Case-control	Case-control
No. of cases	158	279	361	119
No. of controls	501 (obstetric pts)	279 (obstetric pts)	420 (obstetric pts)	357 (other intrauterine pregnancy outcomes)
Similar comparison groups (confounding variables between cases and controls)?	IUCD use, PID and smoking history more common in cases; higher annual income in controls	Previous PID, tubal surgery and ectopic pregnancy, IUCD use, smoking and older age more common in cases	Similar age, parity and rate of spontaneous abortion; “cases” were more likely to have had infertility, pelvic surgery or therapeutic abortion.	Insufficient information
Outcome/exposure assessment	Structured interview; potential recall bias in cases	Structured interview; some recall bias	Ascertainment of exposure not described	Ascertainment of exposure not described
Complete follow-up?	Yes	Yes	Yes	Yes
Temporal relation	Correct for primary infertility	Correct	Correct	Correct
Dose-response effect?	Yes	Not demonstrated	Not assessed	Not assessed
Quality grade	Adequate	Good	Adequate	Poor
Comments	Biased ascertainment of exposure probably more pronounced in cases; contamination by inclusion of secondary infertility with exposure predating first pregnancy	Bias due to choice of control group (term pregnant women); otherwise excellent design, multivariate analysis to account for possible confounding exposures	Bias due to choice of controls; patients with history of PID or use of IUCD or oral contraceptives excluded; multivariate analysis	Equivalence of groups not demonstrated; raw data not provided; poor correction for confounding exposures
Risk due to exposure (95% CI)				
Appendectomy	1.9† (0.9–4.2)	1.6‡ (1.1–2.5)	1.8† (1.3–2.5)	2.2¶ (1.5–3.1)
Perforation	4.8† (1.5–14.9)	1.7§ (0.6–5.1)	—	—

* Only primary infertility data were included.

† Adjusted relative risk

‡ Adjusted odds ratio

§ Crude odds ratio

¶ Crude observed:expected ratio

IUCD = intrauterine contraceptive device, PID = pelvic inflammatory disease.

was counted as a case. For each case, 3 age-matched controls were selected from hospital records. Three different control groups were included: women having an intrauterine pregnancy, a spontaneous abortion or a therapeutic abortion. Information about the demographic composition of the cases and controls and other data reflecting comparability were not provided. The 119 cases and 357 controls were assessed for a number of risk factors, but the paper does not describe how exposures were ascertained. These limitations decreased the quality score of the study to "poor."

The analysis did not involve the usual determination of risk such as odds ratios. Instead, exposure rates were calculated for each of the 3 control groups, and an aggregate expected frequency for each exposure within age-classed groups was determined from the proportion of the various pregnancy outcomes within groups of similar age in the general population. The frequencies of exposures observed were then compared with the expected frequencies within age classes and were summed to calculate an overall observed:expected ratio, the statistic used to indicate the risk of each exposure. The observed:expected ratio for women with appendectomy was 2.16 (95% CI, 1.52 to 3.06). When appendectomy cases with a history of PID or tubal surgery were excluded (a crude method of controlling for confounding exposures), the elevated risk persisted (2.19, 95% CI 1.42 to 3.39).

DISCUSSION

Methodologic weaknesses plague each of the 4 case-control studies. In the paper by Mueller and colleagues,²⁴ several problems were identified. The comparison groups were not entirely comparable, and some important de-

terminants of outcome were omitted from the analysis. Although patient self-report has been shown to be a valid measure of surgical, medical and pregnancy history (such as whether hospitalization occurred),²⁸⁻³⁰ it is not clear that this is generalizable to surgical pathologic findings (such as the presence or absence of appendiceal rupture).

Women seeking treatment for infertility often undergo a prolonged and expensive therapeutic process, during which they may be repeatedly questioned about their surgical history.² In observational studies, case subjects are more likely than controls to report a true exposure, thus inflating the estimate of treatment effect.³¹ They are also prone to seeking an explanation for their disease and may exaggerate the severity of past exposures.³² This effect, termed "recall bias," may account for a proportion of the more frequent recall of a history of appendiceal perforation by women with tubal infertility.

The strength of the association in the study of Mueller and colleagues was further weakened by the finding that women with secondary infertility also reported an increased rate of appendiceal perforation, but the events usually preceded 1 or more pregnancies. Thus, some of these "cases" might equally have served as controls if they were assessed after a pregnancy but before a subsequent unsuccessful attempt at conception. Similarly, the control group of "fertile" women is undoubtedly contaminated with women who will eventually be unable to get pregnant, and might be more appropriately allocated to the group of secondarily infertile cases. Therefore, although this study concluded that appendiceal perforation is a cause of infertility, the recognized methodologic shortcomings suggest that the magnitude of any true effect is smaller than that reported.

The study by Coste and associates,²⁵ although well designed, also presents some difficulties, many of which are unavoidable. The between-group differences were marked, but the difficulty of identifying a control group of obstetric patients similar to those with ectopic pregnancy with respect to age, contraceptive use and PID is prohibitive and would probably only be possible at the risk of overmatching. Self-report of appendectomy history, although prone to some recall bias, poses less difficulty for ectopic pregnancy than infertility because the acuity of the event probably allows for less introspection. The choice of using obstetric patients as controls in a case-control study introduces bias in the investigation of some risk factors for ectopic pregnancy, such as a type of contraception. Many women who become pregnant while using the index contraceptive may choose to terminate their pregnancy and therefore would never appear as putative controls if the sampling frame used is the time of delivery. This would decrease the rate of contraceptive use reported among controls and falsely increase its associated risk. Coste and associates investigated this phenomenon by conducting a separate analysis including only case women who were planning to complete their pregnancy. They found no change in the results. In any event, this choice of control group should not significantly bias the investigation of appendectomy exposure, since women who become pregnant would be equally likely to want to continue a pregnancy, whether or not they had had their appendix removed.

Accepting a history of appendectomy without consideration of whether appendicitis was actually present is problematic, since some of these events will represent negative appendectomies. Case patients may be

more likely to undergo an appendectomy and have a nonappendiceal condition such as salpingitis, which would result in a falsely elevated risk. The overall risk of appendicitis in this study is rather small, is not demonstrable for perforation and may be attributed in large part to confounding factors.

In the study of Michalas and colleagues,²⁶ exclusion from the analysis of women with a history of PID, and IUCD and oral contraceptive use facilitates the use of term pregnant women as controls, since it minimizes the ability of pregnancy termination and risk factors for infertility to systematically alter the control group. The resulting comparability of cases and controls is impressive. Unfortunately, the validity of the study suffers from the omission of the methodology used to determine exposure. As well, the use of appendectomy history as the determinant of exposure provides little information on the effect of appendicitis or appendiceal perforation. From this study, one can conclude that there is a small but significant association of ectopic pregnancy with previous appendectomy, but the relative contribution of appendiceal inflammation or perforation may be more or less than this.

Because Nordenskojold and Ahlgren²⁷ reported on only a history of appendectomy, their study does not permit an evaluation of appendicitis and appendiceal perforation per se as risk factors. The validity of the study is suspect from a number of validity guide points,¹⁹ the most condemning of which are the lack of demonstrated comparability of groups and inexplicit measurement of exposure. The risk attributed to appendicitis in this study, albeit small, cannot be accepted because of these limitations.

To assess if there is a causal relation between appendiceal perforation and poor fertility outcomes, Sackett's modification of the Bradford-Hill criteria²⁰ were applied to the results of the systematic review. These criteria, and an assessment of whether they are adequately fulfilled, are summarized in Table III.

Although a randomized controlled trial offers the strongest evidence for causation, such methodology is irrelevant when the exposure under consideration is appendicitis. A prospective cohort study, although possible, is impractical due to the enormous sample sizes and prolonged follow-up that would be required. Therefore, a case-control design is the most practical

epidemiologic study for investigating the risk of a harmful exposure, such as perforation of the appendix. Nonetheless, because of the inherent weakness of the case-control study design, any increased risk must be interpreted with caution. Similarly, any risk associated with a history of appendectomy without consideration of whether appendicitis or perforation was in fact present, weakens any insight into the strength of association.

Reviewing the criteria, we found that the strength of association for perforation of the appendix ranged from a high of 4.8 for tubal infertility, reported by Mueller and colleagues,²⁴ to an insignificant association for ectopic pregnancy (Coste and associates²⁵). Studies reviewed were consistent in demonstrating a modest increase in risk, with all results in the same direction of increased risk. The temporal relation between exposure and outcome was correct in most studies, which is important given the clinical impression that ectopic pregnancy may result in some episodes of appendicitis.³³ A dose-response relation was demonstrated by Mueller and colleagues,²⁴ who found the risk of perforation to be higher than appendectomy alone, but not by Coste and associates.²⁵

A causal association does not entirely make "epidemiologic sense," since the incidence of appendicitis has been declining in recent decades with a stable number of perforations,³⁴ whereas ectopic pregnancy and, to a lesser extent, infertility have become more prevalent.^{2,27} Similarly, although the effect of appendiceal perforation on tubal dysfunction seems biologically plausible (no doubt reinforced by the finding, on countless laparoscopies for infertility evaluation, of dense peritubal adhesions under the appendectomy scar^{14,22}), there is no increase in the rate of right-sided ectopic

Table III

Nine Diagnostic Tests for Causation

Criterion	Present?*
Is there evidence from true experiments in humans?	No
Is the association strong?	Yes
Is the association consistent from study to study?	Yes
Is the temporal relationship correct	Partially
Is there a dose-response gradient?	Partially
Does the association make epidemiologic sense?	No
Does the association make biologic sense?	Partially
Is the association specific?	No
Is the association analogous to a previously proven causal association?	Yes

*See text for discussion.

pregnancies in patients with a history of perforated appendicitis^{27,35} even though, overall, most ectopic pregnancies occur on the right side.²⁷

The association is decidedly non-specific, since many other exposures are more strongly related to infertility and ectopic pregnancy than appendicitis.^{2,14,24-27} The putative association may be analogous to the relationship of other infections, such as PID, to tubal disease. Analogy, however, is the least important test of causation.

Given the results of the literature review and the analysis of the causal criteria, a global consideration of all the data does not permit us to accept a true risk of tubal infertility or ectopic pregnancy as a consequence of appendiceal perforation. Of course, the evidence does not preclude the existence of this risk, but a causal relation cannot be supported from the data currently available. A more definitive conclusion will need to be discovered through a large, well-designed case-control study that ascertains a valid appendicitis history from medical records, and adequately controls for confounding exposures.

However, assuming that a risk *does* exist, one can calculate the etiologic fraction (extra cases due to exposure as a proportion of total cases) for tubal infertility. Assuming an overall population prevalence of 2% for perforated appendicitis and a relative risk of 4.8 (the risk proposed by Mueller and colleagues²⁴), the etiologic fraction is 0.07. This means that appendiceal perforation would be responsible for about 7% of all tubal infertility. The implications for health resource management are considerable; recent developments in the diagnosis and management of appendicitis, especially the growing use of ultrasonography and laparoscopy, can improve the accuracy of surgeons treating this disease.^{9-12,36} Perhaps it is crucial that every young

woman presenting with suspected appendicitis should be offered access to these diagnostic modalities if the risk of later infertility could be avoided. Given the considerable costs associated with these diagnostic tests and the uncertainty of the importance of such an association, it behooves us to know if we are spending our health care dollars in a cost-effective manner.

In the absence of more conclusive data, the following general guidelines may be applied to the management of young women with suspected appendicitis: Although a period of observation of patients with uncertain findings of appendicitis appears to be safe,^{37,38} optimal evaluation should probably include early laparoscopy for diagnostic, if not also therapeutic, purposes.^{37,39,40} This strategy should prevent any cases of appendicitis from progressing to perforation once a surgeon has become involved and will minimize any effect on subsequent fertility that may exist.

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