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Acute Appendicitis During Pregnancy: Different from the Nonpregnant State?

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Abstract

Background Acute appendicitis is the most common nonobstetric indication for surgical intervention during pregnancy. However, the current literature is scarce and composed of relatively small case series. We aimed to compare the presentation, management, and surgical outcomes of presumed acute appendicitis between a contemporary cohort of pregnant women and nonpregnant women of reproductive age.

Methods The study group included 92 pregnant patients who underwent appendectomy for presumed acute appendicitis at a single tertiary medical center in 2000–2014. Preoperative, operative, and postoperative clinical data were derived from medical records and compared to data for 494 nonpregnant patients of reproductive age who underwent appendectomy in 2004–2007 at the same institution.

Results Median age was 28 years (range 25–33) in the study group and 26 years (range 20–34) in the control group ($P = 0.1$). There were no between-group differences in mean white blood cell count, patient interval, hospital interval, or operative time. Preoperative abdominal ultrasound was used in a significantly higher proportion of patients in the pregnant group than in the nonpregnant group (73 and 27 %, respectively, $P < 0.001$) and computed tomography, in a significantly lower proportion of patients (1 vs. 16 %, respectively, $P < 0.001$) . The two groups had similar rates of negative appendectomy (23 and 22 %, $P = 0.9$), complicated appendicitis (12 and 11 %, $P = 0.9$), and overall postoperative complications (15 and 12 %, $P = 0.3$).

Conclusions The clinical presentation and outcome of presumed acute appendicitis are similar in pregnant women and nonpregnant women of reproductive age. Therefore, similar perioperative management algorithms may be applied in both patient populations.

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Introduction

Acute appendicitis is the most common indication for nonobstetric surgical intervention during pregnancy [1–3]. However, it poses a challenging management dilemma for the treating physician. The diagnosis is based mainly on history and physical examination, which may be distorted in pregnancy when complaints of nonspecific abdominal pain increase and the patient undergoes anatomical changes due to the enlarging uterus. Furthermore, findings on auxiliary diagnostic laboratory tests may be misleading in the presence of physiological leukocytosis of pregnancy, and abdominal ultrasound scans may have a low yield due to air in the small bowel or overlying organs [4–6]. The use of computed tomography is relatively contraindicated in pregnancy, mainly in the period of organogenesis (weeks 8–15), owing to its ionizing radiation [7]. At the same time, prompt and accurate diagnosis is mandatory during pregnancy to avoid unnecessary abdominal surgery (i.e., negative appendectomy) which can increase the risk of an unfavorable obstetric outcome [8]. A delay in diagnosis can lead to a ruptured appendix, which is also associated with adverse outcomes [9].

The aim of the present study was to provide a descriptive analysis of the natural history of acute appendicitis in a large contemporary cohort of pregnant women with comparison to nonpregnant women of reproductive age.

Methods

Study design and population

A retrospective comparative study design was used. The study group consisted of all pregnant women who underwent appendectomy for presumed acute appendicitis in a single tertiary medical center in 2000–2014. The control group consisted of consecutive nonpregnant women of reproductive age who underwent appendectomy at the same institution in 2004–2007. Patients in both groups were identified from the hospital administrative archives using combinations of ICD-9 codes for appendicitis, appendectomy, and pregnancy. Preoperative, operative, and postoperative clinical data were extracted from the medical records and archives of all hospital departments/sites that provided care: emergency department, operating room, surgery department, and obstetrics and gynecology department, and clinics. Preoperative data included age, gestational age at surgery, body temperature, and white blood cell count (WBC) on admission, imaging findings, and patient and hospital intervals. Operative data included surgical approach, operative time, and operative complications. Postoperative data included length of hospital stay, postoperative complications, mortality, and pathology results. Before surgery, pregnant patients were assessed by an obstetrician to exclude the existence of any other pregnancy-related complications. Obstetric ultrasonography was performed in all patients to establish gestational age and to confirm fetal vitality. Ultrasonography was repeated after the operation and before patient's discharge from the hospital.

Definitions

Reproductive age (control group) was defined as 15–49 years as stipulated by the World Health Organization (WHO) [10]. Three perioperative time intervals were calculated: patient interval, or time from onset of symptoms to admission to the emergency department, according to patient history; hospital interval, or time elapsed from emergency department admission to onset of surgery, determined from the electronic medical records; and operative time, or the actual length of surgery, determined from the operating room reports [11]. Abnormal WBC was defined as fewer than $3.5 \times 10^3/mm^3$ (leukopenia) or more than $11 \times 10^3/mm^3$ white blood cells (leukocytosis). Fever was defined as temperature above 37.8 °C. At our institution, the diagnosis of acute appendicitis requires neutrophilic infiltration of the muscularis propria [12]. Pathology results were divided into three categories: negative appendectomy, defined as no pathological signs of inflammation; simple appendicitis; and advanced appendicitis, including gangrenous appendicitis, perforated appendicitis, and periappendicular abscess. Postoperative complications were recorded and classified according to the Clavien–Dindo grading scale which is recognized worldwide [13]; major complications were defined as any complication of grade 3b and above.

The study was approved by the participating institutions' Independent Ethical Committee (IEC, Helsinki Committee).

Statistical analysis

Descriptive and comparative statistical analyses were performed using Statistical Software for the Social Sciences (SPSS) version 22. Continuous variables were compared between groups with Student's t test or Mann–Whitney test or analysis of variance, as appropriate by type of distribution. Categorical variables were compared with Chi-squared or Fisher's exact test, depending on the number of observations. A P value of <0.05 was considered significant. Variables that were significant on univariate analysis were entered into a multivariate analysis (unconditional logistic regression) model, where the outcome variable was advanced appendicitis.

Table 1 Preoperative characteristics of all patients who underwent appendectomy stratified by pregnancy status

Characteristic	Patients		P value
	Nonpregnant (n = 494)	Pregnant (n = 92)	
Age (yr)	26 (20–34)	28 (25–33)	0.1
Patient interval, h[a]			
Median (range)	24 (12–48)	24 (12–24)	0.3
Mean ± SD	34 ± 34	29 ± 30	
Hospital interval (h)[b]			
Median (range)	11 (8–16)	13 (8–17)	0.7
Mean ± SD	14 ± 8	13 ± 7	
Abnormal WBC[c]	351 (71 %)	72 (79 %)	0.1
WBC (/mm^3)			
Median (range)	14 (10.6–16.6)	13.4 (11.8–15.9)	0.4
Mean ± SD	13.9 ± 4.3	14.2 ± 3.8	
Fever[d]	100 (25 %)	12 (14 %)	0.02
Temperature (°C)			
Median (range)	36.6 (36.6–37.6)	36.6 (36.6–37.1)	0.001
Mean ± SD	37.1 ± 0.8	36.8 ± 0.6	
Neutrophilia[e]	319 (68 %)	75 (85 %)	0.001
Preoperative computed tomography	78 (16 %)	1 (1 %)	<0.001
Preoperative ultrasonography	133 (27 %)	67 (73 %)	<0.001
Preoperative MRI	0	2 (2 %)	0.02

Continuous variables are expressed as median (interquartile range); categorical variables are expressed as n (%)

MRI magnetic resonance imaging, *WBC* white blood cell count

[a] Time from onset of symptoms until emergency department admission

[b] Time from emergency department admission to start of surgery

[c] WBC less than 3.5×10^3/mm^3 or more than 11×10^3/mm^3

[d] Temperature above 37.8 °C

[e] More than 79 % neutrophils

Results

Demographics

Ninety-two pregnant women of median age 28 years met the study criteria. Their median gestational age at surgery was 19 weeks (IQR: 13–27). The control group included 494 nonpregnant women of median age 26 years (IQR 20–34, P = 0.1; Table 1).

Preoperative factors

A smaller proportion of the pregnant group presented to the emergency department with fever (14 vs. 25 %, respectively, P = 0.02). There were no significant between-group differences in patient or hospital interval or WBC on admission. Abdominal ultrasound was used in a significantly higher proportion of patients in the pregnant group than in the nonpregnant group (73 and 27 %, respectively, P < 0.001) and computed tomography, in a significantly lower proportion (1 and 16 %, respectively,

P < 0.001). Magnetic resonance imaging was performed in only 2 patients, both in the pregnant group (P = 0.02; Table 1).

Operative factors

The laparoscopic approach was applied in a significantly higher proportion of the nonpregnant than the pregnant group (81 vs. 54 %, respectively, P < 0.001). There was no significant difference between the groups in operative time (Table 2).

Postoperative outcomes

The pregnant group was hospitalized for a significantly longer time than the nonpregnant group (3 vs. 2 days, respectively; P = 0.001). No significant between-group differences were found in overall rate of postoperative complications or rate of major postoperative complications. However, the prevalence of wound infection was significantly higher in the pregnant patients (5 vs. 1 %, P = 0.01;

Table 2 Operative characteristics of all patients who underwent appendectomy stratified by pregnancy status

Characteristic	Patients		P value
	Nonpregnant ($n = 494$)	Pregnant ($n = 92$)	
Duration of surgery (min)	61 (50–80)	60 (45–75)	0.9
Operative time >60 min	248 (50 %)	34 (40 %)	0.08
Laparoscopic approach	401 (81 %)	50 (54 %)	<0.001
Conversion from laparoscopic to open approach	2 (0.5 %)	0	1

Continuous variables are expressed as median (interquartile range); categorical variables are expressed as n (%)

Table 3 Postoperative outcomes of all patients who underwent appendectomy stratified by pregnancy status

Characteristic	Patients		P value
	Nonpregnant ($n = 494$)	Pregnant ($n = 92$)	
Pathology			
Negative appendectomy	114 (23 %)	20 (22 %)	0.9
Simple appendicitis	327 (66 %)	59 (66 %)	
Advanced appendicitis[a]	53 (11 %)	11 (12 %)	
Length of hospital stay (days)	2 (2–3)	3 (2–5)	0.001
Length of hospital stay >2 days	169 (35 %)	62 (68 %)	<0.001
Wound infection	7 (1 %)	5 (5 %)	0.01
Intra-abdominal abscess	16 (3 %)	0	0.09
Any postoperative complication	58 (12 %)	14 (15 %)	0.3
Major postoperative complication[b]	9 (2 %)	3 (3 %)	0.4

Continuous variables are expressed as median (interquartile range); categorical variables are expressed as n (%)

[a] Pathological report of gangrenous appendicitis, perforated appendicitis, or periappendicular abscess

[b] Grade 3b or more according to the Clavien–Dindo classification[12]

Table 3). Of note, in the pregnant group, the postoperative contractions rate was 10 %, the median gestational age at delivery was 39 weeks (38–40), the median Apgar score was 9 at 1 min and 10 at 5 min, the median weight at delivery was 3.2 kg (IQR: 2.9–3.5), and 8 (12 %) patients experienced preterm delivery. There were four postoperative fetal losses (6 %), two in the open appendectomy group and two in the laparoscopic appendectomy group ($p = 0.7$). All 4 pregnancies were considered normal and nonhigh risk, and no other obvious reason was found for the fetal loss. The fetal losses in the open appendectomy group and laparoscopic appendectomy group occurred 1–3 days and 2–3 weeks after surgery, respectively. The corresponding gestational age was 9 weeks and 18–21 weeks, respectively. None of the fetal losses occurred in association with advanced appendicitis.

Pathology

There were no significant differences between the pregnant and nonpregnant groups in rates of negative appendectomy (22 and 23 %, respectively), simple appendicitis (66 % for

both), and advanced appendicitis (12 and 11 %, respectively, $P = 0.9$; Table 3).

Independent risk factors for advanced appendicitis

Univariate and multivariate analyses were performed to investigate the effect of previously established risk factors and of pregnancy on advanced appendicitis [14]. Three factors were found to be significant: fever, abnormal white blood cell count, and prolonged patient interval. Pregnancy status was not a risk factor for advanced appendicitis (Table 4). Table 5 details the inflammatory response markers in the pregnant and nonpregnant patients stratified by the grade of appendicitis.

Discussion

It has traditionally been accepted that acute appendicitis presents atypically during pregnancy [15, 16] and warrants an aggressive surgical approach to prevent delayed diagnosis and perforation and a consequent increased risk of

Table 4 Univariate and multivariate analyses of the risk factors for advanced appendicitis among all patients ($n = 586$)

Factors	Advanced appendicitis ($n = 64$)	Univariate P value, OR (95 %CI)	Multivariate P value, OR (95 %CI)
Pregnancy			
Yes	11 (17 %)	0.7; 1.2 (0.6–2.3)	NA
No	53 (83 %)		
Ages	–	0.05; 1.03 (1.01–1.06)	0.02; 1.04 (1.01–1.09)
Abnormal WBC[a]			
Yes	60 (94 %)	<0.001; 6.4 (2.3–18)	0.001; 6.3 (2.1–18.5)
No	4 (6 %)		
Fever ≥ 37.8 °C			
Yes	19 (38 %)	0.008; 2.3 (1.2–4.2)	0.049; 2.0 (1.01–3.9)
No	31 (62 %)		
Patient interval ≥ 1 day			
Yes	29 (51 %)	0.002; 2.4 (1.4–4.2)	<0.001; 3.3 (1.7–6.3)
No	28 (49 %)		
Hospital interval > 12 h			
Yes	24 (41 %)	0.4; 0.8 (0.4–1.3)	NA
No	35 (59 %)		

NA not analyzed, WBC white blood cell count

[a] WBC less than $3.5 \times 10^3/\text{mm}^3$ or more than $11 \times 10^3/\text{mm}^3$

adverse pregnancy outcomes [17–19]. Therefore, a higher negative appendectomy rate (20–35 %) among pregnant compared to nonpregnant women was considered acceptable [3]. However, an increased risk of fetal loss and early delivery has also been observed in pregnant women with negative appendectomy [19, 20]. Recently, improvements in the accuracy of diagnostic imaging modalities and the efficacy of antibiotic treatment have called the traditional approach into question. Accordingly, we hypothesized that today, there is little difference between pregnant and age-matched nonpregnant women with acute appendicitis in terms of presentation, management, and postoperative course.

The present comparative study of a large contemporary cohort of pregnant women treated for presumed appendicitis yielded no significant differences from nonpregnant women of reproductive age in either patient or hospital interval. By contrast, previous studies reported a significantly shorter hospital interval for pregnant patients, which was explained by a possible priority given to pregnant women in emergency management and their more rapid referral for imaging [19]. This may be indicative of the traditional aggressive approach to appendicitis in pregnancy.

In healthy women, pregnancy is associated with leukocytosis, which is predominantly related to increased circulation of neutrophils. The neutrophil count begins to increase in the second month of pregnancy and plateaus in the second or third trimester, at which time the total white blood cell counts range from 9000 to 15,000 cells/microL [21]. Therefore, it was proposed that the inflammatory markers have lower diagnostic accuracy in pregnant patients with suspected appendicitis compared to healthy pregnant patients. The current study focused only on patients with suspected appendicitis. Healthy women with normal pregnancy were not evaluated. We noted, in agreement with others [22], no significant difference between the groups (i.e., pregnant with appendicitis vs. nonpregnant with appendicitis) in WBC on admission. It is noteworthy that neutrophilia was more common in the pregnant group. However, a smaller proportion of the pregnant group presented to the emergency department with fever, although the majority of patients in both groups were not febrile at presentation.

Also in concordance with the previous literature [23], ultrasound was the first and main imaging mode of choice in the pregnant patients (73 %). This was also true for the nonpregnant patients, although ultrasound was used in only 27 % of cases in that group. It is our institutional policy to avoid ionizing radiation when possible in women of reproductive age in general and pregnant women in particular. This explains why preoperative computed tomography was utilized in only 16 % of the control group and one patient in the study group. Imaging was used in the vast majority of the pregnant women but only in a minority of the nonpregnant women. This difference probably reflects our efforts to establish an accurate diagnosis preoperatively in order to spare them unnecessary surgery and its potentially adverse fetal effects [19]. The higher rates of preoperative imaging in the pregnant group may account for their similar negative appendectomy rate to the nonpregnant group (23 and 22 %, $P = 0.9$). Previous studies found that negative appendectomy rates in pregnant women dropped from 54 % without any imaging to 36 % using ultrasound and to 8 % using ultrasound followed by computed tomography [24]. These numbers are in line with the reported range of 13 to 50 % for negative appendectomy during pregnancy [8, 25–27]. The variability may be attributable to differences in the use of preoperative imaging among studies.

We did not find differences in the rate of advanced appendicitis between the pregnant and nonpregnant groups (12 and 11 %, $P = 0.9$). This contrasts with most earlier studies which reported higher rates of advanced appendicitis in pregnant women [9, 28]. The authors attributed the difference from nonpregnant women to delays in diagnosis and treatment. However, according to our results in a contemporary cohort, the natural history of acute appendicitis is no different between pregnant women and nonpregnant women of reproductive age. These findings are supported by a recent population-based study wherein rates of complicated appendicitis were similar in pregnant

Table 5 Inflammatory markers in the pregnant and nonpregnant patients stratified by the grade of appendicitis

Inflammatory marker	Nonpregnant group ($n = 327$)	Pregnant group ($n = 59$)	p value
Simple appendicitis			
WBC (/mm3)			0.7
Median (IQR)	14 (11–17)	14 (12–17)	
Mean ± SD	14.2 ± 4.1	14.4 ± 4.1	
Abnormal WBC[1]	244 (75%)	47 (80%)	0.4
Neutrophilia[2]	238 (73%)	50 (88%)	0.02
Fever[3]	54 (21%)	8 (14%)	0.3

Inflammatory marker	Nonpregnant group ($n = 53$)	Pregnant group ($n = 11$)	p value
Advanced appendicitis			
WBC (/mm3)			0.2
Median (IQR)	15 (13–17)	13 (12–16)	
Mean ± SD	16 ± 4.1	14.4 ± 3.4	
Abnormal WBC[1]	50 (94%)	10 (91%)	0.5
Neutrophilia[2]	47 (89%)	11 (100%)	0.6
Fever[3]	19 (48%)	0	0.008

Continuous variables are expressed as median (interquartile range); categorical variables are expressed as n (%)

[1] WBC less than $3.5 \times 10^3/\text{mm}^3$ or more than $11 \times 10^3/\text{mm}^3$

[2] More than 79 % neutrophils

[3] Temperature above 37.8 °C

and nonpregnant women [19]. Given the risk of appendiceal perforation during treatment of patients with acute appendicitis, and specifically women of reproductive age, we performed univariate and multivariate analyses to investigate potential factors of advanced appendicitis, including pregnancy. The factors identified were fever, abnormal white blood cell count, and prolonged patient interval. Pregnancy per se was not associated with an increased risk of complicated appendicitis in our cohort.

Our results showed that the laparoscopic approach was applied more often in the nonpregnant than in the pregnant group, similar to other studies [22]. The tendency of physicians to avoid laparoscopy during pregnancy may be explained by the gradually enlarging uterus and the technical difficulty involved, especially in the third trimester. The higher rate of laparoscopic appendectomy in the nonpregnant group could account, in part, for their shorter hospital stay relative to the pregnant patients. The higher rate of open appendectomy in the pregnant group could account for their higher rate of wound infection. Otherwise, there were no between-group differences in the rates of either overall postoperative complications or major complications. The present fetal loss rate is in line with a population-based study that reported a 4 % fetal loss rate after surgery [19]. However, it is noteworthy that the rate in pregnant women with appendicitis is substantially higher compared to 5.96 fetal deaths per 1000 births in the general population of pregnant women [29]. Of note, our preterm

delivery rate in pregnant patients with appendicitis (12 %) is comparable to the preterm delivery rate in the general population of pregnant women (11.4 %) [30].

To our knowledge, this study is the most comprehensive single-institution attempt to represent the clinical dilemma faced by physicians treating pregnant women with presumed appendicitis. Nevertheless, it has several limitations. Because of the retrospective design, we could not rule out a selection bias. For example, antibiotic treatment was initiated without an exact timing protocol and might have halted pathological progression. Furthermore, the restriction of the cohort to a single institution limits the generalizability of the findings. There may also have been a temporal bias, as the pregnant and nonpregnant groups were selected within two different time frames: 2000–2014 for the pregnant group and 2004–2007 for the nonpregnant group. Owing to the relatively small numbers, we did not stratify the pregnant patients according to weeks of gestation, which may have an impact on clinical presentation and patient management. Furthermore, our patient selection process did not include patients who were taken to the operating room for suspected acute appendicitis but whose appendix was not removed. Other surgical series have struggled with the selection bias related to the relatively narrow denominator of surgical cohorts, which is a consequence of the administrative surgical databases that are limited to patients who were operated on. Therefore, prospective studies are needed to determine the effect of a

larger cohort denominator that includes patients who were not operated on. The major strengths of this study are the descriptive and comparative analyses of the natural history of acute appendicitis in the largest contemporary cohort of pregnant women undergoing appendectomy reported to date. We assessed in greater detail than prior analyses the prehospital and intra-hospital time variables associated with delay in care. In addition, other than patient interval, data for all parameters were collected from objective sources.

In conclusion, our results suggest that, in contemporary cohorts, pregnant women and nonpregnant, reproductive age women with presumed acute appendicitis behave similarly in terms of clinical presentation and outcomes are not different. We believe that similar perioperative management algorithms for acute appendicitis may be used in both pregnant women and nonpregnant women of reproductive age.

Compliance with ethical standards

Conflict of interest None.

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