



## Acute Appendicitis during Pregnancy; Results of a Cohort Study in a Single Iranian Center

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### ABSTRACT

**Objective:** To determine the effects of pregnancy on the presentation, management, surgical and obstetrics outcome of patients with acute appendicitis.

**Methods:** This prospective cohort study was conducted during a 2-year period from 2014 to 2016 in Shahid Faghihi hospital of Shiraz University of Medical Sciences. We enrolled all the pregnant individuals with acute appendicitis who required surgical appendectomy. We also enrolled age-matched controls of non-pregnant women undergoing open appendectomy during the study period. The presentation, clinical and laboratory characteristics, surgical and obstetrics outcomes were determined in both study groups and were further compared between them. In order to determine the determinants of outcome, we also ran a multivariate logistic regression model.

**Results:** Overall we included a total number of 584 patients with presumed appendicitis among whom there were 58 (9.94%) and 526 (90.06%) non-pregnant individuals. The pregnant patients had significantly longer duration of symptoms ( $p=0.038$ ), lower temperature ( $p=0.026$ ), longer duration of hospital stay ( $p=0.026$ ) and higher rate of hospital admission longer than 2 days ( $p=0.031$ ). The complications of the surgical procedure were comparable between the two study groups except for the pneumonia which was significantly higher in pregnant patient ( $p=0.041$ ). After adjusting for confounders such as age and ethnicity, pregnancy remained significantly associated with lower temperature ( $p=0.018$ ), longer symptom duration ( $p=0.042$ ) and higher rate of pneumonia ( $p=0.049$ ).

**Conclusion:** Acute appendicitis during the pregnancy was associated with longer duration of symptoms, lower body temperature and higher rate of pneumonia. The pregnancy and neonatal outcomes were comparable to the previously reported data.

**Keywords:** Acute appendicitis; Pregnancy; Open appendectomy; Outcome.

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## Introduction

Acute appendicitis is currently amongst the most common etiologies of non-obstetric abdominal surgery during the pregnancy [1-4]. The management and treatment of acute appendicitis poses a great challenge and is still considered a dilemma to the surgeons. The diagnosis of acute appendicitis is mainly based on history and physical examination which is less reliable in pregnant individuals [5-7]. In addition, the anatomical changes during the pregnancy causes the appendix to displace from its normal position due to the enlarged uterus [8, 9]. The supplementary diagnostic tools including the laboratory and ultrasonographic evaluation are less accurate during the pregnancy [10, 11]. Because of hemodilution during the gestations, the leukocytosis is less prominent and might be absent and due to enlarged uterus and presence of air in the bowel loops, the ultrasonography has less accuracy for detection of the appendicitis [11, 12]. The results magnetic resonance imaging (MRI) are of high accuracy; however the procedure is time-consuming and might not be available in all the centers [13, 14].

The prompt diagnosis and treatment of acute appendicitis during the pregnancy is important to avoid adverse maternal and neonatal outcomes [15, 16]. As demonstrated previously, acute appendicitis is associated with adverse maternal and pregnancy outcome and the condition worsen when rupture appendix and peritonitis occurs [1, 6]. Thus, conservative management is not recommended in the mothers with suspected acute appendicitis and surgery should be performed as soon as the diagnosis was made to avoid peritonitis and subsequent complications [1]. The knowledge of the presentation, management and the determinants of outcome will help the physicians to better manage and treat the acute appendicitis during the pregnancy. The aim of the current study was to determine the presentation pattern, management, surgical and pregnancy outcome of acute appendicitis in a cohort of Iranian women compared to non-pregnant individuals. We also determined the prognostic factors and the determinants of outcome in these series.

## Materials and Methods

### Study Population

This prospective cohort study was conducted during a 2-year period from March 2014 to March 2016 in Shahid Faghihi hospital, a tertiary healthcare center affiliated with Shiraz University of Medical Sciences located in southern Iran. We included all the pregnant women who underwent appendectomy with presumed acute appendicitis in our center during the study period (pregnant group). We also included age-matched women who underwent appendectomy with presumed acute appendicitis in our study during the study period who were not pregnant (non-pregnant).

We excluded pediatrics (<18 years), those with comorbidities and those who did not consent to be included in the study. The institutional review board (IRB) and medical ethics committee approved the study protocol. All the patients provided their informed written consents.

### Study Protocol

All the patients were visited in the emergency room by a general surgery resident and the findings were recorded in the data gathering forms. A complete history and physical examination was performed and the diagnosis was made based on Alvarado score [17] and results of ultrasonography. All the patients in both study groups underwent open appendectomy by the surgical team consisted of general surgery attending physician and the residents in our center. 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. We recorded the preoperative, operative, and postoperative clinical data. The 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. The obstetric outcome was recorded after the delivery and included the birthweight, Apgar at 1 and 5 minutes, low birth weight (less than 2500 grams), preterm birth, premature rupture of the membrane (less than 37 weeks of gestation), type of delivery and the neonatal intensive care unit (NICU) admission.

### Statistical Analysis

In order to have 80% power to detect a 5% difference in primary endpoint of the study, with an  $\alpha$  equal to the 0.01, at least 50 pregnant women were required in the study. In order to compensate for non-evaluable patients, we included 58 pregnant and 526 non-pregnant individuals (1:10 ratio). All the data were analyzed utilizing the statistical package for social sciences (SPSS Inc., Chicago, Illinois, USA) version 21.0. Data are presented as mean $\pm$ SD and proportions as appropriate. The parametric variables with normal distribution were compared using the independent t-test between the study groups. Parametric variables without normal distribution were compared using the Mann-Whitney U-test. The categorical variables were compared using the chi-square test. The odds ratio (OR) for each comparison was reported with 95% confidence interval (95% CI). We also ran a multivariate logistic regression model to eliminate the effects of confounders on the study outcomes.

## Results

Overall we included a total number of 584 patients with presumed appendicitis who underwent open appendectomy in our center during the study period. Among these there were 58 (9.94%) and 526 (90.06%) non-pregnant individuals. The mean age of the participants was  $27.6 \pm 5.6$  (ranging from 18 to 42) years. Most of the pregnant individuals were in the second trimester (62.1%). The baseline characteristics including the age and the ethnicity were comparable between the two study groups. The pregnant patients had significantly longer duration of symptoms when compared to the non-pregnant patients ( $3.38 \pm 1.66$  vs.  $2.15 \pm 0.96$ ;  $p=0.038$ ). However, the clinical characteristics of the patients including the Alvarado score ( $p=0.095$ ), generalized pain ( $p=0.783$ ), right lower quadrant tenderness ( $p=0.807$ ), and rebound tenderness ( $p=0.532$ ) were comparable between the two study groups. The pregnant patients had significantly lower temperature when compared to non-pregnant patients ( $p=0.026$ ) while the rate of fever ( $\geq 38.5^\circ\text{C}$ ) was comparable between the two study groups ( $p=0.953$ ). The results of the ultrasonography examination were also comparable between the two study groups ( $p=0.384$ ). The baseline characteristics of the patients and their clinical information is summarized in Table 1.

The operation duration was comparable between the two study groups ( $p=0.680$ ) and all the patients in both study groups underwent open appendectomy.

Regarding the histopathological examination, the gangrenous appendicitis was the most common diagnosis being reported in 320 (54.7%) patients. However, the histopathologic examination was comparable between the two study groups ( $p=0.859$ ). The length of hospital stay was significantly longer in the pregnant individuals when compared to the non-pregnant patients ( $p=0.026$ ). In the same way, acute appendicitis in pregnancy was associated with higher rate of hospital admission longer than 2 days ( $p=0.031$ ). The complications of the surgical procedure were comparable between the two study groups except for the pneumonia which was significantly higher in pregnant patient ( $p=0.041$ ). The intraoperative characteristics, postoperative complications, pregnancy and neonatal outcome of the patients are summarized in Table 2. We ran a logistic regression model to compensate for the confounders. We found that after adjusting for confounders such as age and ethnicity, pregnancy remained significantly associated with lower temperature ( $p=0.018$ ), longer symptom duration ( $p=0.042$ ) and higher rate of pneumonia ( $p=0.049$ ).

## Discussion

The results of this prospective cohort study revealed that pregnant patients with acute appendicitis is associated with longer duration of symptoms, lower body temperature and higher rate of postoperative pneumonia. The results of this study are comparable

**Table 1.** Baseline characteristics and clinical presentation of 58 pregnant and 526 age-matched non-pregnant women with acute appendicitis.

	Pregnant (n=58)	Non-pregnant (n=526)	OR (95% CI)	p value
<b>Age (years)</b>	28.1±5.8	27.6±5.6	1.21 (0.77-1.34)	0.475
<b>Ethnicity</b>				
Iranian (%)	49 (84.5%)	449 (85.6%)	0.87 (0.21-0.98)	0.926
Afghan (%)	9 (15.5%)	77 (14.4%)		
<b>Gestational Age (weeks)</b>	24.8±4.9	-	-	-
1 <sup>st</sup> trimester (%)	14 (24.1%)	-	-	-
2 <sup>nd</sup> trimester (%)	36 (62.1%)	-	-	-
3 <sup>rd</sup> trimester (%)	8 (13.8%)	-	-	-
<b>Symptom duration (days)</b>	3.38±1.66	2.15±0.96	1.48 (1.12-2.24)	0.038
<b>Alvarado Score</b>	7.13±1.07	7.89±1.22	0.57 (0.12-2.13)	0.095
<b>Generalized pain (%)</b>	27 (9.6%)	253 (48.8%)	0.91 (0.53-1.57)	0.783
<b>RLQ tenderness (%)</b>	57 (98.3%)	519 (98.7%)	0.77 (0.09-6.36)	0.807
<b>Rebound tenderness (%)</b>	41 (70.7%)	391 (74.3%)	0.83 (0.45-1.51)	0.532
<b>Pain migration (%)</b>	38 (65.5%)	370 (70.3%)	0.801 (0.45-1.42)	0.453
<b>Guarding (%)</b>	12 (20.7%)	116 (22.1%)	0.922 (0.47-1.79)	0.812
<b>Temperature (°C)</b>	36.9±1.01	37.6±0.98	1.39 (1.02-1.68)	0.026
<b>Fever <math>\geq 38.5^\circ\text{C}</math> (%)</b>	12 (20.7%)	91 (20.4%)	1.021 (0.51-2.06)	0.953
<b>Anorexia (%)</b>	31 (53.4%)	305 (58.0%)	0.832 (0.48-1.43)	0.507
<b>Nausea (%)</b>	44 (75.9%)	412 (78.3%)	0.870 (0.46-1.64)	0.738
<b>Vomiting (%)</b>	34 (58.6%)	310 (58.9%)	0.987 (0.56-1.71)	0.963
<b>Leukocytosis (%)</b>	42 (72.4%)	414 (78.7%)	0.71 (0.38-1.31)	0.315
<b>Ultrasonography</b>				
Normal (%)	9 (15.5%)	61 (11.5%)	-	0.384
Suspicious (%)	36 (62.1%)	296 (56.2%)	-	
Appendicitis (%)	13 (22.4%)	169 (32.3%)	-	

**Table 2.** The intraoperative characteristics, postoperative complication, pregnancy and neonatal outcome of 58 pregnant and 526 age-matched non-pregnant women with acute appendicitis.

	Pregnant (n=58)	Non-pregnant (n=526)	OR (95% CI)	p value
<b>Operation duration (min)</b>	51.98±5.37	51.68±5.24	0.28 (0.08-1.57)	0.680
<b>Pathology</b>				
Normal (%)	7 (12.1%)	49 (9.3%)	-	0.859
Inflamed (%)	18 (31.0%)	142 (27.0%)	-	
Gangrenous (%)	28 (48.3%)	292 (55.5%)	-	
Perforated (%)	5 (8.6%)	43 (8.2%)	-	
<b>Hospital LOS<sup>c</sup> (days)</b>	3.31±1.22	1.78±0.87	1.72 (1.22-4.29)	0.026
<b>LOS ≥ 2 days</b>	39 (67.2%)	128 (24.3%)	1.86 (1.22-3.84)	0.031
<b>Complications</b>				
Wound infection (%)	6 (10.3%)	26 (4.9%)	0.98 (0.17-1.58)	0.072
Abdominal abscess (%)	1 (1.72%)	12 (2.2%)	0.41 (0.11-1.47)	0.253
Pneumonia (%)	3 (5.2%)	9 (1.7%)	1.37 (1.01-2.65)	0.041
DVT <sup>a</sup> (%)	2 (3.44%)	6 (1.14%)	0.89 (0.28-1.78)	0.068
<b>Delivery type</b>				
NVD <sup>e</sup> (%)	36 (62.1%)	-	-	-
Cesarean section (%)	22 (37.9%)	-	-	-
<b>Pregnancy outcome</b>				
LBW <sup>b</sup> (%)	5 (8.62%)	-	-	-
PROM <sup>f</sup> (%)	8 (13.7%)	-	-	-
Premature labor (%)	6 (10.3%)	-	-	-
Preeclampsia (%)	1 (1.7%)	-	-	-
<b>Neonatal outcome</b>				
APGAR at 1 min	8.91±1.2	-	-	-
APGAR at 5 min	9.35±1.3	-	-	-
Meconium aspiration (%)	6 (10.3%)	-	-	-
Sepsis (%)	8 (13.7%)	-	-	-
Jaundice (%)	16 (27.5%)	-	-	-
NICU <sup>d</sup> admission	9 (15.5%)	-	-	-

<sup>a</sup>DVT: Deep venous thrombosis; <sup>b</sup>LBW: Low birth weight; <sup>c</sup>LOS: Length of stay; <sup>d</sup>NICU: Neonatal Intensive Care Unit; <sup>e</sup>NVD: Normal vaginal delivery; <sup>f</sup>PROM: Premature rupture of membrane

with previous studies [1, 6, 10, 16]. It has been previously believed that acute appendicitis during pregnancy is associated with atypical presentation and should be treated as soon as possible surgically [18] being associated with higher rates of negative appendectomy during pregnancy [19]. The surgeries of the abdomen are also associated with adverse pregnancy outcome [20]. However, the results of the current study demonstrate that acute appendicitis in pregnancy shares similar presentation characteristics when compared to non-pregnant women. This was reflected in comparable rates of clinical symptoms and Alvarado score.

Pregnant women are less likely to have a classic presentation of appendicitis than non-pregnant women, especially in late pregnancy. The most common symptom of appendicitis, ie, right lower quadrant pain, occurs close to McBurney's point in the majority of pregnant women, regardless of the stage of pregnancy [9, 21, 22]; however, the location of the appendix migrates a few centimeters cephalad with the enlarging uterus, so in the third trimester, pain may localize to the mid or even the upper right side of the abdomen [21, 23]. Recently, Segev *et al.*, [6] in a comparative study of a large contemporary cohort of pregnant women treated for presumed

appendicitis yielded no significant differences from non-pregnant women of reproductive age in either patient or hospital interval and clinical characteristics. 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. However, in our study, it was demonstrated that those with acute appendicitis have longer duration of symptoms which might be due to vague presentation of the abdominal pain and the more conservative approach toward the management of acute appendicitis.

In a large historical cohort study, Abbasi *et al.*, [1] demonstrated that among 7 million maternities, there were 1,203 women with appendicitis who delivered in the same admission. Pregnant women with appendicitis were more likely to deliver preterm OR 2.68 (95 % CI 2.31-3.11) and had an increased risk in abruptio. Among the 27% of patients with peritonitis, the rate of preterm birth was fourfold higher, and the caesarean section rate was almost doubled [1]. In another study, the same study group demonstrated that there was an overall incidence of

101.1 cases of appendicitis per 100,000 births [24]. Peritonitis occurred in 20.3% of pregnant women with appendicitis, with an adjusted OR of 1.3 (95% CI 1.2-1.4) when compared with non-pregnant women with appendicitis. In pregnancy, there was an almost two-fold increase in sepsis and septic shock, transfusion, pneumonia, bowel obstruction, postoperative infection and length of stay >3 days [24]. We also demonstrated that the pregnancy was associated with increased risk of pneumonia and longer hospital stay in pregnant patients, however, the rate of other postoperative complications such as deep vein thrombosis, intra-abdominal abscess formation and transfusion were comparable between the two study groups. In addition, Silvestri *et al.* found an increase in preoperative systemic infection in pregnant women with appendicitis, but did not find any difference in composite 30-day major morbidity or individual morbidities, including transfusion, infection, thrombosis, sepsis or septic shock rates except pneumonia [25].

In the current study all the appendectomies were performed in an open manner. This is because the facilities of elective laparoscopic surgeries are not available in emergency setting and also all the appendectomies are performed by general surgery residents and they do not have enough skill to work with laparoscopic instruments. Peled *et al.*, [26] compared open appendectomies during pregnancy versus laparoscopic ones. The surgical approach was decided by the operating surgeon and as expected the mean gestational age at operation was earlier in the laparoscopic appendectomy group compared to the open appendectomy group. This difference can be attributed to the preference of the surgeon to perform laparoscopic appendectomy at earlier stage of pregnancy when the uterus is relatively small and insertion of intra-abdominal devices is safer [26]. At more advanced gestational age, the surgeon might prefer the traditional approach (open appendectomy) due to uterine size in order to avoid unintentional harm to the uterus. Another explanation can be the

non “anatomic position” of the appendix during advance pregnancy that may cause difficulty in identifying and manipulating it while operating in pregnancy with enlarged uterus [27, 28].

We note some limitations to our study. First we included a limited number of the patients in this cohort. However, the study had a power of 85% to detect at least 5% difference between the main study variable. The point that this was a prospective cohort study should be mentioned and this made it hard to increase the sample size. We are currently running larger studies accordingly. The second limitation was that we included a group of pregnant patients with acute appendicitis and a group of non-pregnant patients with acute appendicitis and thus we cannot comment on the pregnancy outcome compared to the normal pregnancies not complicated with acute appendicitis. We recommend further study including pregnant patients with and without acute appendicitis to be able to comment on the outcome of pregnancies complicated with acute appendicitis. This is among the only prospective cohort studies in Iranian patients addressing the clinical and characteristics of acute appendicitis in pregnant patients.

In conclusion, acute appendicitis during the pregnancy was associated with longer duration of symptoms, lower body temperature and higher rate of pneumonia. The pregnancy and neonatal outcomes were comparable to the previously reported data. Further studies with larger study populations including the normal pregnancies not complicated by acute appendicitis are recommended.

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