

Review

Acute Appendicitis and Pregnancy

Ioannis K. Thanasas*, Christina D. Tsiamanta and Achilleas A. Giannoulakos

Abstract

Department Obstetrics and
Gynecology, General Hospital of
Trikala, Trikala, Greece

*Corresponding Author's Email:
thanasasg@hotmail.com
Phone: 2431029103/6944766469

Acute appendicitis is the most common non-obstetric cause of diagnostic laparotomy in pregnancy. Diagnosis is not easy. It is usually a mild clinical picture that many times mimics the common discomforts during pregnancy and in particular the physiological changes in anatomical relationships caused by the gradual increase in the size of the uterus during pregnancy and it may delay the timely and correct diagnosis of the disease. The big dilemma in treating acute appendicitis in pregnancy is to take a timely and correct decision for surgical investigation of the disease (laparoscopy / laparotomy). The main concern of the modern obstetrician - gynecologist should be to be properly informed about the way the disease can affect or be influenced by pregnancy, but also his active participation in the diagnosis and treatment of the acute surgical problem in order to ensure better health for the mother and the fetus. In this article, based on current data, a brief literature review of acute appendicitis in pregnancy is attempted, particularly with regard to diagnosis, treatment and prognosis.

Keywords: Acute appendicitis, Pregnancy, Diagnosis, Treatment, Prognosis

INTRODUCTION

Gastrointestinal diseases which may be caused by pregnancy, or pre-exist or may appear randomly during this period, are of particular clinical interest. The anatomical, morphological, functional, metabolic, hemodynamic and biochemical changes experienced by the maternal body during the course of pregnancy, as well as the potential risks to the mother and fetus, affect to another extent the clinical manifestation, diagnosis, treatment and the prognosis of acute surgical conditions in pregnancy (Cunningham et al., 2005).

Acute appendicitis is the most common non-obstetric cause of diagnostic laparotomy in pregnancy (Segev et al., 2017). Acute appendicitis is the most common indication for surgical intervention in non-obstetric cases during pregnancy and occurs at approximately one per 500 to one per 635 to 2000 pregnancies (Walker et al., 2014; Franca Neto et al., 2015). The incidence of the disease appears to be the same for both pregnant and non-pregnant women. In general, the incidence of

appendicitis in pregnancy is estimated to be around 0.05% - 0.07% of all pregnancies (Machado and Grant, 2009). It is more common in the second trimester and accounts for approximately 27% - 60% of all cases. Less frequently, it may occur in the first and third trimesters of pregnancy with a frequency ranging from 19% to 36% and 15% to 33% respectively (Pastore et al., 2006). Although the incidence of the disease decreases in the last trimester of pregnancy, recent bibliographic data indicate an incidence of acute appendicitis in the third trimester, accounting for 59% of all cases (Zingone et al., 2015).

Diagnosis

Diagnosis of acute appendicitis in pregnancy is difficult. Diagnostic error rates remain high and appear to exceed 20% of cases (McGory et al., 2007). The difficulty of early

diagnosis of acute appendicitis during pregnancy also explains the high incidence of complicated appendicitis in pregnant women (Ghali et al., 2018). Clinical symptomatology of the disease and imaging workup remain vital in order to decide on the surgical treatment of the pregnant woman (Aggenbach et al., 2015). Abdominal pain is the predominant symptom and is observed in almost all cases. It is usually mild, dull and located along the right surface of the abdomen depending on the gestational age. Nausea, vomiting, anorexia and fever are frequent manifestations of the disease that accompany abdominal pain. Nausea is the most common accompanying symptom and is present in almost all cases. Vomiting and anorexia are observed in 2/3 and 1/3 - 2/3 of pregnant patients, respectively. Fever and tachycardia vary and are not a reliable clinical diagnostic criterion (Carol EH Scott - Conner and Robin Perry, 2006). High fever and an overall poor condition of the patient pose a suspicion of perforated appendicitis and generalized peritonitis. Rupture of the appendix is more common in pregnant women than in the general population and significantly increases maternal and perinatal morbidity and mortality (Somani et al., 2003). Maternal mortality is estimated to be between 0% and 2%. Fetal loss accounts for 1.5% - 9% of uncomplicated acute appendicitis cases, and in cases of a ruptured appendix, the fetal loss rate increases to 36%. The risk of premature birth is increased, especially during the first week postoperatively (Shahid et al., 2005).

Particularly characteristic clinical feature of appendicitis in pregnancy is the progressive displacement of the tenderness point (McBurney's point) to the right lateral abdominal wall. This displacement is due to progressive upward, right and back migration of the cecum and the appendix during pregnancy. Thus, in addition to atypical manifestations of the disease, first trimester pain is located in the right lower quadrant of the abdomen and can easily be attributed to the sensitivity of the round joints of the uterus (round ligament pain). In the second trimester the pain is located in the right lumbar region at the level of the umbilicus, while in the last trimester of pregnancy the pain may be diffused or located in the right upper quadrant of the abdomen (Carol EH Scott - Conner and Robin Perry, 2006) (Scheme 1). According to other authors, based on the latest data, the tenderness point does not migrate progressively with the increase in the gestational age, but in most cases it remains in the normal anatomical position (Ishaq et al., 2018). Rebound tenderness, Psoas sign, and Rovsing's sign are less common in pregnant than in non-pregnant women (Carol EH Scott - Conner and Robin Perry, 2006).

Leukocytosis, increased erythrocyte sedimentation rate (ESR) and C - reactive protein (CRP) should be evaluated with great caution, as they can also be observed in normal pregnancy. "Normal" leukocytosis during pregnancy of up to 16,000/ μ l makes it difficult to diagnose the disease early, given that the white blood

cell count does not exceed this limit in all cases of acute appendicitis. However, a left shift is seen in 75% of the patients and poses a serious suspicion of acute inflammation. Significant pyuria and macroscopic hematuria have to be differentiated from urinary tract disorders, especially from acute pyelonephritis, which is misdiagnosed instead as appendicitis more often than any other disease in pregnancy (Munoz and Usatine, 2005). Recently, Cinar and colleagues analyzing the results of their study showed that in pregnant women with acute appendicitis, white blood cell and neutrophils counts were significantly higher, while the number of lymphocytes was lower compared to healthy pregnant women (Çinar et al., 2018). Other important pathological conditions of obstetric / gynecological or other origin (Pastore et al., 2006) that require differential diagnosis from acute appendicitis in pregnancy are shown in the table below (Table 1).

Although pre - operatively, the diagnosis of appendicitis in pregnancy is mainly based on anamnesis and clinical examination, the use of imaging methods is not questioned (Brown et al., 2009; Di Saverio et al., 2016). Ultrasound imaging (US) using the real - time high - resolution sonography with graded compression technique, has a high specificity for diagnosis of the disease, provided the appendix is depicted without vague ultrasound findings. Ultrasound, although often used to diagnose acute appendicitis in women of reproductive age, has a hazy diagnostic value during pregnancy. Recently in 2016, Segev and colleagues analyzing the results of their own study showed that there was no statistically significant difference in the ability of ultrasounds to predict the diagnosis of acute appendicitis between pregnant women and non-pregnant women of reproductive age (Segev et al., 2016). However, ultrasound is recommended for all pregnant patients suspected of having appendicitis. Concern about the complications for the mother or fetus that may occur as a result of unnecessary surgery should not delay the surgical treatment required (Türkan et al., 2016).

However, the sensitivity of ultrasound is not as high as that of CT, which however has the disadvantage of using ionizing radiation that can cause harm to the fetus. In any case of suspected acute inflammation, a nonvisualized appendix using ultrasound imaging should give rise to a dilemma between deciding to perform diagnostic laparotomy based on clinical criteria only and investigating the disease further with CT imaging (Williams and Shaw, 2007). Recently, Terasawa and his colleagues found that CT's diagnostic value was greater than that of the US. In particular, the sensitivity, specificity, positive predictive value and negative predictive value of US and CT were 0.86 / 0.94, 0.81 / 0.95, 5.8 / 13.3, and 0.19 / 0.09, respectively (Terasawa et al., 2004). Also, low dose CT is extremely effective in diagnosing acute appendicitis and can be considered a valid, alternative first line imaging test that reduces the

potential risk of exposure to ionizing radiation (Yun et al., 2017; Zinsser et al., 2019).

MRI is an excellent method for diagnosing acute appendicitis in pregnancy (Patel et al., 2017). MRI is currently considered to be of great diagnostic value and can reliably exclude those cases where the appendix isn't portrayed sufficiently or in those cases where there is absence of inflammatory elements of the appendix while providing alternative diagnoses to guide further disease management (Theilen et al., 2015; Tsai et al., 2017). Pedrosa and colleagues argued that Magnetic Resonance Imaging (MRI) is expected to contribute significantly in the diagnosis of acute abdomen in pregnancy in the future and to replace the "harmful" for the embryo CT. In their study of 51 pregnant women with appendicitis that were MRI and US evaluated, they found sensitivity, specificity, positive predictive value, negative predictive value and accuracy 100%, 93.6%, 1.4%, 100%, and 94%, respectively (Pedrosa et al., 2006). Recently, Israel and his colleagues reported that when appendicitis is depicted in MRI, sensitivity, specificity, positive predictive value and negative predictive value for the diagnosis of acute appendicitis are 100% for all parameters. On the contrary, sensitivity and negative predictive value of ultrasound imaging of the appendix fall to 50% and 66%, respectively (Israel et al., 2008). More recently, in 2015, Burke and his colleagues, analyzing the results of a large multinational study, concluded that MRI is useful and reproducible in the diagnosis of acute appendicitis during pregnancy. 9.3% (66/709) of the evaluated cases had MRI findings for acute appendicitis. Sensitivity, specificity, accuracy, positive predictive value and negative predictive values were 96.8%, 99.2%, 99.0%, 92.4% and 99.7%, respectively (Burke et al., 2015).

Treatment

The treatment of acute appendicitis is always surgical. Compared to non-pregnant women, in pregnancy, acute appendicitis has higher rates of undesirable complications. Conservative treatment should be avoided given the serious risk of undesirable complications during pregnancy (Abbasi et al., 2014). Prophylactic administration of antibiotics during surgery and postoperatively is indicated in almost every case, particularly in complicated situations, such as after ruptured appendix, peritonitis or gangrenous form of appendicitis. First-line treatment is ampicillin or second-generation cephalosporins in combination with metronidazole depending on the severity of the disease (Stone, 2002; Niebyl, 2003). Concerning the prophylactic use of various tocolytic drugs, opinions differ in the international literature. It appears to be unnecessary in non-complicated appendicitis but may be necessary

when the disease is advanced (Hee and Viktrup, 1999).

The big dilemma in treating appendicitis in pregnancy is to take a timely and correct decision for the surgical investigation of the disease. It is estimated that to ensure better maternal and fetal health the period from the onset of symptoms to surgery should not exceed 20 hours (Yilmaz et al., 2007). In addition, increased diagnostic error rates ranging from 25% to 50% and according to other researchers up to 75%, make it even more difficult to take the decision to operate (laparoscopy or laparotomy) given the risk of possible complications during pregnancy (Barclay and Nghiem, 2007).

The type of laparotomy depends on various factors, such as uterine size, gestational age, type of abdominal pain, the location of abdominal pain, and peritonitis. Both the type of laparotomy and the intraoperative manipulations are facilitated by a certain lateral position of the patient at the surgical table, especially when it comes to obese individuals. The location of the incision usually refers to the point of maximum tenderness in relation to the gestational age and the presence or absence of complications. In the last trimester of pregnancy, as well as in cases of a ruptured appendix and diffuse peritonitis, the right paramedian incision provides the best intraoperative visual field and the mildest surgical manipulations (Chawla et al., 2003).

Under appropriate circumstances, laparoscopic appendectomy may be as safe as the open surgery, except that it cannot be performed in the last trimester of pregnancy. There were no statistical differences between the two methods in regards to the duration of pregnancy, Apgar score and birth weight of the newborns. Some concerns about the increased intra – abdominal pressure and the use of carbon dioxide for the formation of pneumoperitoneum, have not been confirmed. The main advantage of the laparoscopic method is the use of milder medications for anesthesia, resulting in reduced risk of fetal distress. In addition, shorter hospital stay, milder post-operative pain, better intraoperative visual field, and faster return of bowel function and early postoperative mobilization, are key advantages of the laparoscopic approach versus open laparotomy (Guttman et al., 2004). Recently in 2017, Maiamati and colleagues analyzing the results of their study showed that the laparoscopic approach for the treatment of acute appendicitis in pregnancy may be considered the preferred approach. The laparoscopic surgery performed by experienced physicians is currently considered not to increase morbidity and mortality and to reduce the risk of complications (Maimaiti et al., 2017).

Instead, Walsh and colleagues after analyzing the results of their study, which included 637 cases of laparoscopic appendectomy during pregnancy for a period of 27 years (1980-2007), published that open appendectomy may be safer for pregnant women who have indication for surgical treatment. More specifically,

Table 1. Pathologic conditions of obstetric / gynecological and other origin that require differential diagnosis from acute appendicitis in pregnancy.

• Obstetric / gynecological conditions	• Non-obstetric / gynecological conditions
- ovarian cyst	- gastroenteritis
- adnexal torsion	- urinary tract disorders
- salpingitis	- pyelonephritis
- corpus luteal cyst ruptured	- cholecystitis
- degenerated uterine myoma	- cholelithiasis
- ectopic pregnancy	- pancreatitis
- placental abruption	- nephrolithiasis
- chorioamnionitis	- mesenteric adenitis
- preeclampsia	- colorectal diverticulitis
- premature labor	- pulmonary embolism
- hyperemesis gravidarum	- pneumonia

they showed that although the laparoscopic approach during pregnancy is associated with low rates of surgical complications in all quarters and the incidence of premature labor is the same or even lower in the laparoscopic method, the frequency of embryonic loss was significantly increased compared to open laparotomy (Walsh et al., 2008). On the contrary, Yau and colleagues, in their study which included 1133 cases of operated pregnant women for acute appendicitis, comparing laparoscopic with open surgery, found that laparoscopic appendectomy is safe even for complicated forms of the disease. In particular, laparoscopic surgery versus open is associated with a significant reduction in the duration of the operation (55 minutes versus 70 minutes), with a lower risk of infection (0.6% versus 10%) and a reduction in patient hospital stay (5 days versus 6 days in open laparotomy) (Yau et al., 2007).

Similarly, Cheng and his colleagues have shown that laparoscopic appendectomy can be safely performed in pregnant women without causing additional complications for the mother compared to open surgery. In particular, analyzing the results of their study involving a total of 859 pregnant women with acute appendicitis from 2005 to 2010, the authors showed that the patients who underwent laparoscopic appendectomy did not present with an increased risk of maternal complications compared to the group of patients who underwent open surgery. Additionally, atrial fibrillation patients had shorter hospital stays than pregnant women treated with open surgery (Cheng et al., 2015).

On the contrary, Winter and his colleagues more recently in 2017 have shown that open appendectomy appears to be a safer method for the treatment of pregnant women with suspected acute appendicitis. In particular, analyzing the data of 218 patients from seven hospitals (125 went under laparoscopic surgery and 93 open surgery) there were 7 fetal losses in the laparoscopic surgery group (5.6%), 6 of which were in the first trimester, and no embryo loss in the group of

pregnant women exposed to open appendectomy. Premature labor rates (6.8% laparoscopic surgery versus 8.6% open-surgery group, CI: -12.6%, 5.3%) and length of hospital stay (3.7 days laparoscopic surgery vs. 4.5 days open-surgery group, CI: -1.3, 0.2 days) were similar (Winter et al., 2017).

Prognosis

The prognosis depends on the gestational age and the delay of diagnosis. Delayed diagnosis may lead to generalized peritonitis and septicemia due to periappendiceal abscess rupture and may increase maternal and perinatal morbidity and mortality significantly. Premature uterine contractions and premature labor (83% and 13% - 16%, respectively, in the last trimester) are the main complications of the disease (Guttman et al., 2004). Embryonic loss in localized uncomplicated acute inflammation ranges from 0% to 1.5%, and after appendix rupture and peritonitis occurring, rises to 20% - 35%. Maternal mortality today is extremely rare. Only in advanced pregnancy, but also in complicated forms of the disease, it can surpass 4% of all cases (Malangoni, 2003).

Thus the main concern of the modern obstetrician - gynecologist should be to be properly informed about the way the disease can affect or be influenced by pregnancy, but also his active participation in the diagnosis and treatment of the acute surgical problem, in order to ensure better health for the mother and the fetus - neonate. Appendicitis during the first trimester is estimated to be significantly associated with an abnormally progressing pregnancy (Theilen et al., 2017). Accurate diagnosis and direct surgical treatment of acute appendicitis in pregnancy is of primary importance in order to avoid complications and to ensure better health for both the mother and the fetus - neonate (Arer et al., 2016). (Table 1, Figure 1)

Schemes

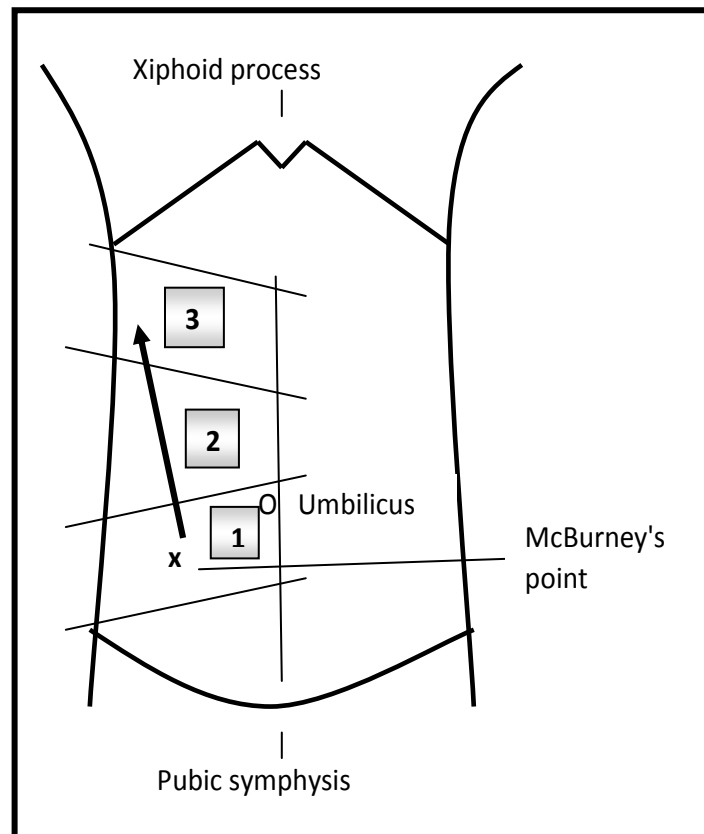


Figure 1. Schematic representation of the characteristic progressive migration of the cecum and the appendix upward, towards the right lateral abdominal wall during pregnancy, resulting in tenderness points being higher during palpation (black arrow). (1, 2 & 3: areas of localized tenderness that identify acute appendicitis in the first, second and third trimesters of pregnancy, respectively. X: McBurney's point – the point of tenderness during appendicitis in a non-pregnant woman located over the right side of the abdomen that is one-third of the distance from the anterior superior iliac spine to the umbilicus). (Our own figure).

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