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Acute appendicitis in pregnancy

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ABSTRACT

Acute appendicitis is the most frequent non-obstetrical surgical emergency encountered in pregnancy with negative maternal and fetal outcomes, mostly attributed to appendicular perforation. The purpose of this article is to discuss the characteristics in diagnosing appendicitis in pregnancy, recommendations of management, as well as maternal and fetal outcomes. It is significantly challenging to diagnose appendicitis in pregnancy due to the anatomic displacement of the appendix caused by the enlargement of the uterus (which may cause uncommon symptomatology), the physiologic leukocytosis of pregnancy, the raised prevalence of abdominal discomfort along with the inability to perform computed tomography because of the radiation exposure of the fetus. These particularities may delay an accurate and timely diagnosis which is of utmost importance in order to avoid the significant complications associated with peritonitis. Rapid surgical intervention (especially laparoscopy) is recommended, nevertheless, the key in managing appendicitis in pregnant patients is finding a balance between the risk of delaying the diagnosis and consequent perforation against the risk associated with a negative appendectomy.

Keywords: pregnancy, appendicitis, non-obstetric surgery, laparoscopy, diagnosis, management

INTRODUCTION

During pregnancy 1-2% of women will develop a condition that requires a non-obstetrical surgical intervention [1]. Of these diseases, acute appendicitis is by far the most encountered in practice, appendectomies making up 25% of non-obstetrical abdominal surgeries [2], prevalence being estimated between 1:1,000 and 1:1,500 pregnancies [3-8]. The unique physiological changes that occur in pregnancy pose difficulties for the medical providers in terms of clinical assessment, surgical intervention and perioperative care, all of which will be discussed in further detail below, along with the specific maternal and fetal risks associated with appendicitis and its operative treatment.

MATERIALS AND METHODS

We conducted this review using data in published the literature in English language, identified through PubMed, which was searched for research articles, observational studies, meta-analyses, that assessed appendicitis in pregnancy. We also used recommendations from guidelines of the American College of Obstetricians and Gynecologists and the Society of American Gastrointestinal and Endoscopic Surgeons. Searched keywords were appendicitis, non-obstetric surgery, laparoscopy, pregnancy, diagnosis, management.

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CLINICAL PRESENTATION

The "classical" presentation of acute appendicitis begins with a colicky abdominal pain which initially is located periumbilical, then migrates to the right iliac fossa, at McBurney's point. Appendicular inflammation leads to irritation of the abdominal wall, rebound tenderness and guarding, being consequently found upon abdominal palpation [9]. Usually anorexia, nausea and vomiting are symptoms that follow the onset of pain. Fever (usually up to 38.3º C) may be fairly common in non-pregnant population and is among the last to appear, being however a rarer occurrence in pregnant women with appendicitis [8,10,11].

Clinical presentation is different in pregnant patients, particularly as they approach term. As the pregnancy advances the location of the appendix is displaced upwards in the abdomen, so in the third trimester the pain may often be localized in the right upper quadrant or right middle region of the abdomen, rather than the right lower quadrant [12,13]. Still, right lower quadrant pain remains the most frequent presenting symptom of appendicitis regardless of gestational age, being encountered in 69-86% of histopathologically confirmed appendicitis [8,14-16]. Moreover, the enlarged uterus lifting the abdominal wall and peritoneum away from the inflamed appendix, signs of muscular response like rebound tenderness and guarding will be less pronounced [9]. Another anatomical particularity presented in pregnancy is that the omentum and bowel are as well superiorly and laterally displaced in the abdomen, hence their contact with the inflamed appendix is prevented along with their usual ability to contain the infection, amplifying the chances of diffuse peritonitis [17,18].

Leukocytosis is the most important laboratory finding in diagnosing appendicitis, most of non-pregnant patients having a mild leukocytosis (over 10 x109/l) with a left shift in the differential. In pregnant patients the physiological leukocytosis with a slight left shift (with values up to 16.9 x109/l in the third trimester rising to 29 x109/l in labor) makes WBC interpretation difficult and unreliable. A helpful indicator of whether leukocytosis is caused by inflammation is a high level of C reactive protein (CRP). The usefulness of this marker is limited as it is a very non-specific marker for inflammation and may be identified in only 50% of cases [9,13,15,19]. Albeit its modest predictive value, it has been demonstrated that a WBC count over 18 x109/l makes the diagnosis of appendicitis in pregnancy more probably [14].

A challenge in diagnosing acute appendicitis amongst pregnant patients comes from the fact that many of the classical symptoms of this condition are considered to be fairly "normal" in pregnancy and thus disregarded upon presentation. Nausea, vomiting, and malaise are common in the first trimester, as well as right lower quadrant pain (due to round ligament syndrome), but they are not associated with each other and the pain is not progressive [9,10,13].

The differential diagnosis should be made with other pathologies unique to pregnancy. In early pregnancy, ectopic pregnancy should be excluded as a cause of right lower quadrant pain by correlating ultrasound images with human chorionic gonadotropin dynamics [9,10]. Microscopic hematuria and leukocyturia may be present in urinalysis when the inflamed appendix is in proximity of the bladder or urethra. However, pyelonephritis is a more frequent condition in the pregnant population, and it is also associated with pain on the right side of the abdomen, leukocytosis and leukocyturia. Patients may be often treated for pyelonephritis, the diagnosis of appendicitis being overlooked, thus delaying adequate intervention [9,10,15]. After 20 weeks gestation, and especially in the third trimester, preeclampsia and its more severe complication, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) may cause symptoms such as nausea, vomiting and abdominal pain. However, pain is usually located in the upper right quadrant or epigastric region of the abdomen, hypertension is present in most of the cases and leukocytosis is not prevalent [9,10]. Other obstetrical conditions associated with abdominal pain are uterine rupture and premature detachment of the placenta. In contrast to appendicitis, both of the above conditions usually present with vaginal bleeding, fetal distress (FHR abnormalities on ultrasound or cardiotocography) and increased uterine tonus [9,10].

Diagnosing appendicitis in labor is extremely difficult and may be often impossible until after delivery. Pain may be more lateralized on the right, fever is present in cases of chorioamnionitis, WBC counts may be extremely high and vomiting is a symptom commonly experienced in labor [9,10].

IMAGING

When clinical findings are not sufficiently diagnostic, further imaging studies may be performed to increase diagnostic accuracy. Graded compression ultrasonography is the first method of choice due to its large availability, low costs and waiting times. Ultrasound may identify an enlarged appendix viewed as a noncompressible, blind-ended, fluid-filled tubular structure in the right iliac fossa, greater than 6 mm diameter [4,15]. It may as well identify other causes of abdominal pain, such as ovarian cysts, ovarian torsion, uterine fibroids, or gallbladder disease [9]. Ultrasonography (US) has a

low accuracy (between 20 and 50%) [15,16,20], its sensitivity being 48%, while specificity 100% [15]. Its reliability further decreases as gestational age increases (especially in the third trimester) due to the enlarged uterus which obstructs the visualization of the appendix [4,8].

When clinical and US findings are inconclusive in diagnosing acute appendicitis in pregnant patients, MRI is the next imaging technique of choice. The main advantages of MRI are not being operator dependent and offering more accurate images, having a superior sensitivity (91.8%) and specificity (97.9%) over US. In addition, it does not expose the mother, nor the fetus to ionizing radiation (as opposed to computed tomography) [4,5]. Nonetheless, its real usage in common practice is considerably limited due to its elevated costs and general low availability (along with high waiting times which may lead to appendiceal perforation and subsequent increase in morbidity and mortality). It is advisable to avoid the use of gadolinium, the contrast agent that is most used in MRI studies, as it has been proven to cross the placenta into the fetal circulation and amniotic fluid, limited studies implying greater risk of rare infiltrative skin conditions, stillbirth, or neonatal death. Favorably, in most cases it is not needed, native MRI being capable of properly visualizing the appendix in pregnant patients [4].

Although in the general adult population computed tomography (CT) is the first-line imaging technique used, it implicates the use of ionizing radiation which is known to have carcinogenic effects as well as an increased risk of congenital defects, microcephaly, growth restriction, intellectual disability, and fetal loss. These risks are maximal if the fetus is exposed in the first trimester. Ionizing radiation has a dose-dependent effect and most modern imaging techniques use low doses that do not expose the fetus to a significantly high risk. Despite its safety, CT imaging in pregnancy remains controversial and a last resort, only when diagnostic imaging is of utmost necessity and there are no other available imaging options [4].

MANAGEMENT

The treatment of acute appendicitis in pregnancy is surgical [9]. Non-obstetric surgery is considered to be generally safe, pregnant and non-pregnant patients having similar major morbidity after appendectomy. However, surgery does increase the risk of adverse birth outcomes like premature labor, low birth weight and stillbirth, compared with pregnant women who did not have surgery [2,4,21,22].

Generally, in pregnancy, open appendectomy is the predominant surgical technique used over laparoscopy. Laparoscopic surgeries are by far more frequent in the first trimester, making up for most appendectomies, whereas in the second, and especially, the third trimester, the ratios are reversed, the open abdominal approach being preferred later in pregnancy. These differences are caused by a traditional reluctance to perform laparoscopy after 26-28 weeks of gestation because of surgeons' preconceptions about the risk of this procedure as the uterus increases in size, although it has been demonstrated that laparoscopy is generally safe and is strongly recommended to be performed in any trimester by the Society of American Gastrointestinal Endoscopic Surgeons [1,2,6,23].

When comparing negative outcomes, there is no significant difference in the risk of stillbirth or preterm delivery rate between women who underwent open versus laparoscopic surgery [2,24]. Laparoscopic approach has been recently more and more accepted due to its undisputable advantages over open appendectomy [1,4,25]. Its main benefits consist of a better visualization of the abdominal cavity, less post-operative pain, reduced postoperative ileus, significantly reduced hospital stays (with an average hospitalisation of 3.8 days versus 5.5 days in cases of open appendectomies), and an earlier return to daily activities [4,23-25]. Laparoscopy is not only a therapeutic tool. In cases when the diagnosis is doubted and imaging studies are either inaccessible or inconclusive, a diagnostic laparoscopy may be performed to avert extensive delays in determining the underlying condition, therefore decreasing poor fetal and maternal outcomes [23,25]. If a macroscopically normal appendix is to be found during surgery, it is still advisable for it to be removed as inflammation may be found upon histological examination and excision avoids future interventions [9].

One factor that has limited the use of laparoscopy in pregnant patients in the past was the concern regarding the effect of high intraabdominal pressure caused by pneumoperitoneum on the mother's already altered pulmonary physiology. However, recent guidelines state that CO2 insufflation up to 15 mmHg may be safely used without adverse outcomes [4,20]. Another problem that has been raised in laparoscopy is the risk of trocar injury to the gravid uterus. During pregnancy the increased uterine blood flow may cause acute and endangering blood loss even in cases of superficial serosal lacerations. In order to avoid accidental injury, the open Hasson peritoneal entry technique is preferred [4]. In regard to general anesthesia required for laparoscopy, there is no evidence for any of the commonly used anesthetic drugs to have teratogenic effects at any gestational age [26-28]. All things considered, the choice of approach (laparotomy vs. laparoscopy) should be based on the surgeon's ex-

perience level, on the available equipment and resources, the patient's clinical status and preference and gestational age [9].

As any abdominal surgery comes with a risk of premature labor, any patient of viable gestational age who undergoes surgery should be admitted in a multi-disciplinary hospital with neonatology services adequate for the fetus' gestational age and an obstetrician should be available to perform cesarean delivery if needed. An obstetrical care provider is also required for fetal monitoring pre- and postoperatively, guidelines strongly recommending it [4,26]. If the fetus is not yet considered viable, documenting fetal heart rate by Doppler is enough. For viable pregnancies, cardiotocography is the current standard, being indicated before and after surgery to determine fetal well-being and the presence or absence of contractions. Intraoperative electronic fetal monitoring is recommended when it is possible to perform. However, in the case of appendectomy, it can be rather difficultly applicable, its necessity and utility are inconclusive considering all anesthetic drugs cross the placenta affecting normal FHR patterns [23,26,28,29].

Further considering the potential risk of premature delivery associated with surgery, corticosteroid therapy for fetal lung maturation may be taken into consideration for gestational ages between 24 and 34 weeks. One dose may be given preoperatively, but surgery should not be delayed for the second dose which can be given postoperatively. Nevertheless, its utility in acute appendicitis should be discussed. On the one hand, glucocorticoids' maximal effect for the fetus is at a minimum of 24 hours after the first dose, while surgery for appendicitis should be performed promptly after diagnosis, making these waiting times threatening for both mother and fetus. On the other hand, emergent delivery at the same times of appendectomy is a rare occurrence. Lastly, steroids should be given with caution to the patient, especially in cases of severe infection, being known that this class of drugs may impact with the immune system's ability to fight off infection [4,9].

An important aspect to be considered perioperatively is the adequate oxygenation of the fetus. In general, after 20 weeks gestational age left lateral decubitus is recommended to reduce inferior vena cava compression syndrome, thus improving venous return and cardiac output and consequently placental perfusion [4,23].

Perioperative thromboprophylaxis is indicated taking into consideration that pregnancy, as well as surgery, are independent risk factors for venous thromboembolism. Methods of prophylaxis are usage of pneumatic compression devices (intra- and postoperatively), early postoperative ambulation or pharmacological prophylaxis. The decision to use the latter should be individualized according to each patient's risk factors for venous thrombosis [4,23,30].

Conservative approach of acute appendicitis in pregnancy should be avoided due to high risk of adverse outcomes. Cases managed conservatively have a significantly higher risk of peritonitis, septic shock, and venous thromboembolism, as opposed to surgically managed cases [31]. Furthermore, patients receiving antibiotic-only treatment have been proven to experience increased rates of abortion and preterm labor [25].

MATERNAL AND FETAL OUTCOMES

The most important predictive factor associated with high maternal and fetal morbidity and mortality is appendiceal perforation [2,6,15,31,32]. The rate of complications in patients with a perforated appendix and a non-perforated one is significantly different (52% versus 17%) [15]. The risk of sepsis and septic shock is considerably increased, as well as the rates of prolonged hospitalization. While pneumonia and transfusions are up to four times more likely to occur in perforated appendicitis, postoperative infection rates have an eight-fold increase [31]. Maternal mortality was mostly absent in the studied cases and, if present, it was an isolated occurrence related to severe sepsis and extensively delayed intervention. [15,16,31]. In a study of 63,145 pregnant patients with appendicitis the mortality rate was 0.1% [33].

Adverse pregnancy outcomes that are associated with acute appendicitis and its surgical treatment include low birth weight, premature delivery, and fetal loss [2,6,14,15,34,35]. The risk of miscarriage is higher within the first week following appendectomy, approaching that of general population two weeks postoperatively [22]. Cohen-Kerem et al. found a fetal loss rate of 2.6% following appendectomy, which rose to 10.9% in presence of peritonitis [36]. Fetal mortality is mostly associated with preterm birth. One element implicated in initiating contractions prematurely could be the irritation of the uterine muscle by the inflammatory process located in its proximity [35]. One study has shown that a vast majority (83%) of pregnant patients with gestational age > 24 weeks had contractions at the time of surgery, while only 13% had preterm labor with evident cervical changes [8]. Guidelines do not recommend routine prophylactic tocolysis in patients undergoing surgery, unless there are signs of premature labor, as there is no evidence in literature to support it [23].

A 2012 nationwide population study from Taiwan identified that acute appendicitis and surgery

for this condition were associated with several of the previously mentioned adverse pregnancy outcomes. In pregnant patients with appendicitis there was a significant higher prevalence of low birth weight infants (< 2,500 g) – (12% vs. 6.8%), fetal growth restriction (22.4% vs. 17.5%), premature delivery (11.6% vs. 7.3%). One interesting finding was the higher risk associated with appendicitis of major congenital anomalies such as anencephaly, microcephaly, hydrocephaly, encephalocele, spina bifida and myelomeningocele (1.4% vs. 0.7% in women without appendicitis). It should be noted that this latter risk was only seen in women who had appendicitis in the first trimester of pregnancy. Additionally, it has been demonstrated by this study that both low birth weight and fetal growth restriction risk was elevated when appendicitis happened in the first and second pregnancy trimester. Preterm labor was mostly associated with surgery for acute appendicitis in the third trimester, rather than the first two. There were no noteworthy discrepancies in the numbers of cases with Apgar scores lower than 7 at 5 min in pregnant women with or without appendicitis [34].

A retrospective study on more than 1,000 pregnant patients that underwent appendectomy further shows that fetal loss and early delivery are undoubtedly more likely to occur in complicated appendicitis (6% and respectively 11%) as opposed to simple appendicitis (2% and 4%). The negative appendectomy rate was relatively higher in pregnant patients (23%) than non-pregnant patients (18%). In addition, the number of pregnant patients with ruptured appendicitis was by far lower than in non-pregnant patients [37]. This shows a tendency towards prompt surgical treatment of pregnant women at the expense of a higher negative appendectomy rate compared to the non-obstetrical patient, which, historically, was generally accepted and justified to avoid progression to appendiceal perforation, with numbers largely varying from study to study, being up to 42% [8,14,20,32,35]. Still, it should be noted that negative appendectomies are associated with risks of their own [16,32]. Aggenbach et al. found a 4% rate of fetal loss and 10% rate of premature delivery in pregnant women who underwent a negative appendectomy [16]. Similarly, Ito et al. have proven that pregnant women undergoing negative appendectomies and those with confirmed appendicitis had similar obstetrical outcomes [32]. This furthermore shows the importance of balancing risk of delaying the diagnosis and consequent perforation against the risks associated with a negative appendectomy. To avoid the negative outcomes associated with both of these situations it is considered that, when the diagnosis is uncertain, an observation period of 6 to 10 hours is generally safe, with no raise in the number of appendiceal perforations and with a reduction in the number of negative appendectomies. Some authors state that this period can be lengthen and that it should be individualized taking into account physical examination and duration of symptomatology, nonetheless without, exceeding 20 hours between symptom onset and surgery [15].

In the articles studied, there was no (or only a minor) difference in the percentages of cesarean deliveries performed in patients with appendicitis versus the control groups, which shows that the general "rule" of only performing cesarean sections for obstetrical indications is respected [6,20,34]. Notably, in a study of 1,203 women with appendicitis who delivered in the same admission, Abbasi et al. found that the rate of cesarean section was almost two times higher in patients with associated peritonitis [6]. Cesarean delivery is not commonly justified at the same time as the appendectomy and it should be noted that performing a hysterotomy when the abdominal cavity is affected by peritonitis poses a substantial risk of intrauterine infection and adhesions [9].

CONCLUSIONS

Acute appendicitis, especially in association with peritonitis, carries a considerable risk for negative maternal and fetal outcomes. The physiological anatomic changes seen in pregnancy may pose an impediment in making an accurate diagnosis. Magnetic resonance imaging can be of great help in the assessment of this pathology. However, it may cause excessive delays in surgical intervention which should be avoided. Prompt surgery is desired, but, at the same time, the risks of a negative appendectomy should not be disregarded.

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