

Nonobstetric surgical intervention in pregnancy

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Abstract. Nonobstetric surgery during pregnancy is relatively common. This review mainly focuses on common surgical diseases in pregnancy including appendicitis, biliary disease, bowel obstruction, trauma and relevant issues such as timing of surgery, the prevention of preterm labor and fetal monitorisation.

Key words: Pregnancy, tocolysis, appendicitis, trauma, bowel obstruction

1. Introduction

All gastrointestinal disorders can present during pregnancy and 0,5-1% of all pregnant women require surgery (1). The incidences of surgical diseases in pregnancy are outlined in table 1 (2). In general, the principles of diagnosing and treating the pregnant women with acute surgical abdominal problem remain the same as those governing the treatment of a nonpregnant patient (3). However, some important differences are present between a pregnant and nonpregnant patient and these may lead to some difficulties in the management of these patients for both an obstetrician and a surgeon. As a general rule, the condition of the mother should always take priority because proper treatment of surgical disease in the mother will usually benefit the fetus as well as the mother (3).

Acute abdomen in pregnancy due to nonobstetric causes is accompanied by a high incidence of poor fetal outcome and maternal morbidity (4,5). Delay in surgical intervention, together with the operative maneuvers may be the reason of poor outcome (6-8). Surgeons may

hesitate to interfere surgically with the fear of the complication of a negative laparotomy in a pregnant female and they may await clear-cut symptoms and signs of acute abdomen (7,9). Anatomic displacement of the intraperitoneal organs and decreased venous return due to pressure exerted on the inferior vena cava by the gravid uterus may alter the presentation of conditions that require surgery (10). Physiological changes of normal pregnancy, such as mild abdominal pain, increased cardiac output and heart rate, increased gastric acidity, physiologic anemia, leukocytosis and tachycardia, decreased gastric motility, increased ventilation and decreased functional residual capacity, constipation, nausea and vomiting may also blunt the symptoms and signs of the real pathology (10-12). Furthermore, enlarged uterus stretches the abdominal wall and compresses the viscera. This may result in a diminished response to peritoneal irritation and altered or referred pain perception and this makes localization of the pathology more difficult (10).

Prolonged delay carries a high risk to the mother and fetus (8). Although some surgeons advocate aggressive early surgical intervention in such patients (13,14), the others suggest an initial trial of conservative treatment and if it fails, then to intervene surgically (8,15). Good clinical insight, awareness of the physiologic changes of pregnancy as well as the most common gastrointestinal diseases affecting pregnant

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Table 1. Incidence of surgical diseases in pregnancy

Disease	Incidence
Appendicitis	1 in 1500-2000 pregnancies
Cholecystitis	1 in 1600-10,000 pregnancies
Bowel obstruction	1 in 3000 pregnancies
Cervical cancer	1 in 2000-2500 pregnancies
Breast cancer	1 in 3000 pregnancies
Melanoma	2,8 per 1000 births
Ovarian cancer	1 in 20,000-30,000 pregnancies

Adopted from Dietrich CS, 3rd, Hill CC, Hueman M. Surgical diseases presenting in pregnancy. Surg Clin North Am 2008;88:403-19, vii-viii (2).

women are required for proper management of the pregnant patient (10). Careful review of the history, a physical exam performed by keeping the gravid uterus in mind, and well judged use of radiologic studies are needed for a clear treatment plan without any delay (10).

If imaging is necessary, ultrasound is the most common and safest imaging technique and should be considered the first-line diagnostic test (16). Although there are theoretical risks associated with ionizing radiation, most diagnostic radiographic procedures are associated with minimal or no risk to the fetus with doses of 5 rads or less (16) and no single diagnostic study exceed this maximum (17).

For example, the amount of exposure to the fetus from a two-view chest x-ray of the mother is only 0.00007 rad (17). Such exposure is not an indication for pregnancy termination. The most sensitive time period for central nervous system teratogenesis is between 10 and 17 weeks of gestation and non-urgent radiologic testing should be avoided during this time (17). If there are good maternal indications, the benefits for the mother outweigh the small risks to the fetus (16). Judicious use with proper shielding and avoidance of repeat studies will minimize the radiation risk to the fetus (16).

2. Timing of surgery

In general, elective surgery should not be performed during pregnancy and if surgery is necessary, choice of timing is essentially a balance between maternal and fetal risks and the urgency of surgery (18). Since the theoretical risk of teratogenicity is increased during the period of organogenesis in the first trimester and the risk of preterm labor is higher during the third trimester, the second trimester is the optimal time to perform surgery (18). Because of physiological

changes of pregnancy, maternal risk is greatest during the third trimester.

However, the primary goal is to preserve the mother's life, and remote fetal risks associated with anesthesia and surgery are of secondary importance in the event of a serious maternal illness (18).

It has been reported that minimal risk of fetal wasting and teratogenicity is associated with gastrointestinal operations during pregnancy (19-21). Nonobstetric surgery may be necessary during any trimester of pregnancy (18). Details are given in Figure 1.

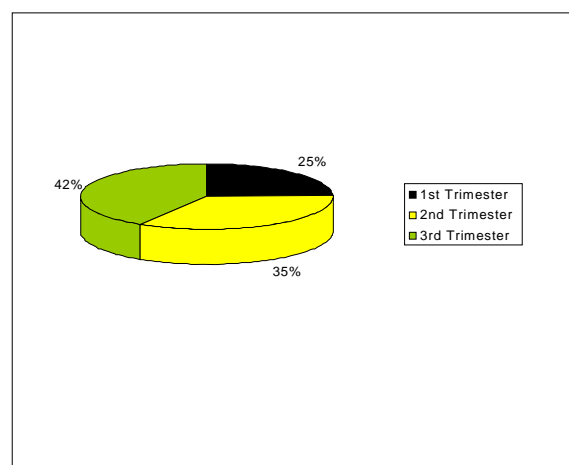


Fig. 1. Nonobstetric surgery during pregnancy according to the trimesters of pregnancy. Adopted from Mazze RI, Kallen B. Am J Obstet Gynecol 1989; 161: 1178-85 (22).

3. Fetal monitoring and tocolysis

For the viable-age fetus and for major surgical procedures, intermittent or continuous fetal heart rate (FHR) monitoring which is feasible from 18-22 weeks gestation may be considered (18).

However, the decision to use fetal monitoring should be individualized (23) and current clinical evidence does not confirm the need for obstetric personnel to monitor FHR changes during surgical procedures since no change in fetal outcome has been documented (24). In the United States, while nearly 60% of responding hospitals routinely used some form of fetal monitoring during maternal surgery, more than 40% did not use intraoperative fetal and uterine monitoring routinely during maternal surgery (25). Prophylactic tocolytics are not indicated unless uterine contractions are confirmed (26). There is no measurable benefit from the use of perioperative prophylactic tocolytics. Postoperatively, patients should be monitored and treated with tocolytic agents when appropriate (27).

4. General guidelines for surgery during pregnancy

Physiologic changes during pregnancy alter the maternal response to stress (10). Maintenance of adequate hydration, availability of blood for transfusion and maternal blood oxygenation and pH to avoid acidosis should be ensured, preoperatively (10). Deep venous thrombosis (DVT) prophylaxis should be employed with intermittent pneumatic compression devices and tocolytics should be administered only for documented or perceived contractions, not prophylactically (10). To prevent uterine compression of the vena cava and left iliac vein, the patient should be placed in the slight left lateral position intraoperatively (10). Especially in laparoscopic procedures, maternal blood gases should be monitored (28). The uterus should be manipulated as little as possible (10). If fetal monitoring is used, it should be continued also in the postoperative period (2,29). Ideally, surgery should be performed during the second trimester and whenever feasible, regional anesthesia should be used (29). Patients may receive acid aspiration prophylaxis in order to reduce gastric content and increase gastric pH (29).

5. Appendicitis

Appendicitis is the most common surgical emergency in a pregnant patient. It occurs once in every 1500-2000 pregnancies, with approximate equal frequency in each trimester (30). In gravid and in nongravid females of same age, acute appendicitis occurs with the same frequency. Suspected cases should be treated as if the patients were nonpregnant and operative exploration without any delay will prevent

appendiceal rupture and its resultant terrible maternal and fetal consequences (31). The incidence of perforated appendicitis in pregnant woman is 43%, which is greater than 4% to 19% seen in the nonobstetric population (32,33). This increased incidence may be due to an unwillingness to operate on a pregnant woman and a delay in diagnosis (2). Maternal and fetal morbidity and mortality correlate with perforation, which usually results from delayed diagnosis, and its associated complications (34). Uncomplicated appendicitis has a 3% to 5% fetal loss rate with negligible maternal mortality in contrast to appendiceal perforation which is associated with a 20% to 35% fetal loss rate and a 4% rate of maternal mortality (30,35,36). Although preterm contractions caused by uterine irritation from peritonitis occur in up to 83% of the cases, preterm labor and delivery occur in only 5% to 14% of the cases. However, up to 50% of the patients in the third trimester deliver preterm (37). Open procedures and laparoscopy do not differ with respect to the incidence of preterm delivery and other complications (19). Fetal loss rate for patients undergoing appendectomy is significantly greater than the fetal loss rate for patients undergoing other surgical procedures during pregnancy (2). It was concluded that the effects of appendicitis and surgery differed from other acute surgical conditions of pregnancy and somehow were more severe. However, it was not associated with any increased risk for major birth defects over that of the general obstetric population (2).

The diagnosis of appendicitis in the first two trimesters is essentially the same as in nonpregnant women. The signs and symptoms of acute appendicitis are similar to those in nonpregnant patients and include anorexia, nausea, vomiting and periumbilical pain migrating to the location of the appendix (38). Peritoneal irritation develops in the right lower quadrant in early pregnancy, but the appendiceal position and the site of pain is shifted superiorly above the right iliac crest and the appendix tip is rotated medially by the gravid uterus after the fifth month of gestation (10). As distention of the abdomen lifts the peritoneum away from the inflamed appendix and cecum, the tenderness also becomes less localized (5). Right sided abdominal pain develops in nearly all patients with appendicitis, and tenderness is still the most important clinical finding (10). As it is normal in pregnancy, leukocytosis is difficult to interpret and fever is less common (25% of patients) (10). The most reliable diagnostic tool is physical exam on presentation. However, radiologic

studies are sometimes needed to rule out ovarian torsion and cysts, degenerating uterine myomas, biliary tract disease, urolithiasis, pyelonephritis or pancreatitis (10). Ultrasound is a safe, reliable imaging method, especially early in pregnancy (2). Its diagnostic accuracy is highest in the first and second trimesters and decreases in the third trimester due to the displacement of the appendix (2). A ruptured appendix is identified less clearly on ultrasound (39). Magnetic resonance imaging (MRI) which is considered safe in pregnancy may be performed if the appendix is not identified, or the study is equivocal (40). MRI avoids exposing the fetus to the ionizing radiation which is associated with computerized tomography (CT) and CT should be used only when ultrasound and MRI imaging are nondiagnostic or unavailable (2).

Surgical procedure is chosen according to the uterine size and experience of the operator (2). Before 20 weeks of gestation, diagnostic and operative laparoscopy is reasonable and is as safe as laparotomy (19,35,36). When peritonitis is present, laparoscopy is contraindicated due to its high complications rate (41). Beyond the later second trimester, laparotomy may be preferred instead of laparoscopy (2). Only for the usual obstetric indications or if there is appendiceal rupture, cesarean delivery is indicated (1).

6. Biliary tract disease

Biliary tract disease is the second most common nonobstetric gastrointestinal disorder requiring surgery during pregnancy (36,42). It affects 1 in 1600 to 10000 pregnancies (35). Pregnancy is a predisposing factor for gallstone formation and they occur in approximately 7% of nulliparous women but 19% of women with two or more pregnancies (43). Biliary stasis, increased cholesterol saturation of bile and prolonged intestinal transit may cause gallstones and sludge (10). One to eight of 10000 pregnant women will suffer from acute cholecystitis (37). When elective operations are done in the second trimester, maternal and fetal complications are uncommon and likelihood of fetal demise or preterm delivery is minimized (10). Inappropriate delays, gallbladder rupture, infection or pancreatitis can lead to increased rates of fetal mortality (44). The clinical presentation of acute cholecystitis in pregnancy mirrors the presentation in the nonpregnant patient (2). Nausea and vomiting, intolerance of fatty foods, anorexia, dyspepsia, and midepigastic or right upper quadrant pain are common symptoms (2). In pregnant patients, Murphy's sign may be elicited less frequently (45). The differential

diagnosis for cholecystitis includes pyelonephritis, appendicitis, the syndrome of hepatitis, right lower lobe pneumonia, peptic ulcer disease, acute fatty liver, HELLP syndrome (hemolytic anemia/elevated liver enzymes/low platelet count), pancreatitis, myocardial infarction, and herpes zoster (10,45,46). Since it is noninvasive and quickly obtained, the pregnant patient who has right upper quadrant tenderness should undergo ultrasound evaluation first (2). If extrahepatic ductal stones are suspected but not demonstrated on ultrasound, MR cholangiography can be performed safely during pregnancy (10).

A conservative approach is often the initial step in the management of symptomatic cholelithiasis (2). This treatment includes discontinuing oral intake, providing antibiotics and analgesia as well as adequate hydration (10). Those who have repeated bouts of biliary colic requiring hospitalization or fail to respond to medical therapy should undergo an operation (10). Recently, earlier surgical intervention for biliary tract disease in pregnancy has been advocated (14,45,47,48). Open cholecystectomy with choledocotomy or a laparoscopic approach constitutes the surgical approaches (10). Laparoscopic approach is suggested as a safe, and perhaps a safer procedure than open cholecystectomy with a growing body of evidence (20,49,50).

7. Intestinal obstruction in pregnancy

Bowel obstruction complicates 1 in 3000 pregnancies and is the third most common reason for a nonobstetric surgery (10,45,46,51). Approximately 60% to 70% of the cases are caused by adhesions, while 25% are the result of volvulus (2). Only 3% to 5% of obstructions are caused by volvulus in nonpregnant patient (45). Maternal mortality and fetal loss rates in bowel obstruction have been reported as 6% and 26%, respectively (52). The diagnosis of intestinal obstruction may be delayed as a result of the typical pregnancy symptoms (2). In case of severe or persistent vomiting, the consulting physician should look for other etiologies, including obstruction (2). Typical air-fluid levels and dilated bowel loops may be seen on plain abdominal films in 82% of cases (46). The sensitivity of plain-film radiographs for volvulus is 95% (45). Contrast studies should be obtained if plain-film radiographs are normal and obstruction is still suspected by keeping in mind that high risk of fetal death is associated with delayed treatment (2). The management of bowel obstruction in pregnancy is essentially no

Table 2. Indications for an emergency cesarean delivery in a pregnant trauma patient

Traumatic uterine rupture
 Stable mother with viable fetus that is in distress
 A unsalvageable mother who still has a viable fetus
 A gravid uterus that is interfering with intraoperative surgical repair

Adopted from Carvalho B. Nonobstetric surgery during pregnancy. IARS 2006 review course lectures 2006, pp 23-30 (18).

different from treatment of nonpregnant patients and includes decompression, intravenous hydration, and timely surgery (53-57).

8. Trauma during pregnancy

Trauma is one of the leading nonobstetric causes of morbidity and mortality and the primary management goals are similar to the care of nonpregnant trauma cases (18). For maintenance of uteroplacental perfusion and fetal well-being, avoidance of hypoxia, hypotension, acidosis and hypothermia are important (18). Trauma may result in placental abruption and fetal loss (18). The primary aim should be optimization of the mother, and the obstetric management can be planned at a later point (18). An early ultrasound in the emergency room is recommended to determine fetal viability after initial resuscitation and trauma surveys are complete (18). Table 2 outlines the indications for an emergency or urgent cesarean delivery. Although ultrasound and MRI do not utilize ionizing radiation and are preferable, whenever possible, the uterus should be shielded during radiation procedures and no radiological or invasive tests should be withheld because of fetal concerns (18).

References

1. Malangoni MA. Gastrointestinal surgery and pregnancy. *Gastroenterol Clin North Am* 2003; 32: 181-200.
2. Dietrich CS, Hill CC, Hueman M. Surgical diseases presenting in pregnancy. *Surg Clin North Am* 2008; 88: 403-419.
3. Parangi S, Pories S. Surgical problems in the pregnant patient. *Pregnancy in Gastrointestinal Diseases*. 2nd ed. Bethesda, MD: American College of Gastroenterology; 2007. pp 54-65.
4. Mazze RI, Kallen B. Appendectomy during pregnancy: a Swedish registry study of 778 cases. *Obstet Gynecol* 1991; 77: 835-840.
5. Weingold AB. Appendicitis in pregnancy. *Clin Obstet Gynecol* 1983; 26: 801-809.
6. Babaknia A, Parsa H, Woodruff JD. Appendicitis during pregnancy. *Obstet Gynecol* 1977; 50: 40-44.
7. Saunders P, Milton PJ. Laparotomy during pregnancy: an assessment of diagnostic accuracy and fetal wastage. *Br Med J* 1973; 3: 165-167.
8. Shnider SM, Webster GM. Maternal and fetal hazards of surgery during pregnancy. *Am J Obstet Gynecol* 1965; 92: 891-900.
9. Spitzer M, Kaiser IH. Perforative appendicitis in the third trimester of pregnancy. *N Y State J Med* 1984; 84: 132-133.
10. Parangi S, Levine D, Henry A, et al. Surgical gastrointestinal disorders during pregnancy. *Am J Surg* 2007; 193: 223-232.
11. Babler EA. Perforative appendicitis complicating pregnancy. *JAMA* 1908; 51: 1310-1314.
12. Cunningham FG, McCubbin JH. Appendicitis complicating pregnancy. *Obstet Gynecol* 1975; 45: 415-420.
13. Dixon NP, Faddis DM, Silberman H. Aggressive management of cholecystitis during pregnancy. *Am J Surg* 1987; 154: 292-294.
14. Swisher SG, Schmit PJ, Hunt KK, et al. Biliary disease during pregnancy. *Am J Surg* 1994; 168: 576-579.
15. Krejs GJ. Jaundice during pregnancy. *Semin Liver Dis* 1983; 3: 73-82.
16. DaSilva G. The acute abdomen during pregnancy. 2005, pp 258-262.
17. Toppenberg KS, Hill DA, Miller DP. Safety of radiographic imaging during pregnancy. *Am Fam Physician* 1999; 59: 1813-1818.
18. Carvalho B. Nonobstetric surgery during pregnancy. IARS 2006 review course lectures 2006, pp 23-30.
19. Affleck DG, Handrahan DL, Egger MJ, et al. The laparoscopic management of appendicitis and cholelithiasis during pregnancy. *Am J Surg* 1999; 178: 523-529.
20. Barone JE, Bears S, Chen S, et al. Outcome study of cholecystectomy during pregnancy. *Am J Surg* 1999; 177: 232-236.
21. Tracey M, Fletcher HS. Appendicitis in pregnancy. *Am Surg* 2000; 66: 555-559.
22. Mazze RI, Kallen B. Reproductive outcome after anesthesia and operation during pregnancy: a registry study of 5405 cases. *Am J Obstet Gynecol* 1989; 161: 1178-1185.
23. ACOG committee opinion. Nonobstetric surgery in pregnancy. Number 284, August 2003. *Int J Gynaecol Obstet* 2003; 83: 135.
24. Horrigan TJ, Villarreal R, Weinstein L. Are obstetrical personnel required for intraoperative fetal monitoring during nonobstetric surgery? *J Perinatol* 1999; 19: 124-126.
25. Kendrick JM, Woodard CB, Cross SB. Surveyed use of fetal and uterine monitoring during maternal surgery. *AORN J* 1995; 62: 386-389.

26. Bani Hani MN. Laparoscopic surgery for symptomatic cholelithiasis during pregnancy. *Surg Laparosc Endosc Percutan Tech* 2007; 17: 482-486.
27. Kort B, Katz VL, Watson WJ. The effect of nonobstetric operation during pregnancy. *Surg Gynecol Obstet* 1993; 177: 371-376.
28. Schirmer B, Kouretas PC. Gallstone pancreatitis. In: Cameron J, editor. *Current Surgical Therapy*. 7th ed. Philadelphia: Mosby; 2001. pp 528-33.
29. Van De Velde M, De Buck F. Anesthesia for non-obstetric surgery in the pregnant patient. *Minerva Anesthesiol* 2007; 73: 235-240.
30. Al-Mulhim AA. Acute appendicitis in pregnancy. A review of 52 cases. *Int Surg* 1996; 81: 295-297.
31. The Pregnant patient and non-obstetrical emergency surgery. In *Emergency general surgery* <<http://www.mc.vanderbilt.edu/surgery/trauma/Protocols/PregnancyNonObstet.pdf>>. Accessed 2004.
32. Hale DA, Molloy M, Pearl RH, et al. Appendectomy: a contemporary appraisal. *Ann Surg* 1997; 225: 252-261.
33. Tamir IL, Bongard FS, Klein SR. Acute appendicitis in the pregnant patient. *Am J Surg* 1990; 160: 571-575.
34. Epstein FB. Acute abdominal pain in pregnancy. *Emerg Med Clin North Am* 1994; 12: 151-165.
35. Firstenberg MS, Malangoni MA. Gastrointestinal surgery during pregnancy. *Gastroenterol Clin North Am* 1998; 27: 73-88.
36. Visser BC, Glasgow RE, Mulvihill KK, et al. Safety and timing of nonobstetric abdominal surgery in pregnancy. *Dig Surg* 2001; 18: 409-417.
37. Kammerer WS. Nonobstetric surgery during pregnancy. *Med Clin North Am* 1979; 63: 1157-1164.
38. Mourad J, Elliott JP, Erickson L, et al. Appendicitis in pregnancy: new information that contradicts long-held clinical beliefs. *Am J Obstet Gynecol* 2000; 182: 1027-1029.
39. Poortman P, Lohle PN, Schoemaker CM, et al. Comparison of CT and sonography in the diagnosis of acute appendicitis: a blinded prospective study. *AJR Am J Roentgenol* 2003; 181: 1355-1359.
40. Shellock FG, Crues JV. MR procedures: biologic effects, safety, and patient care. *Radiology* 2004; 232: 635-652.
41. Paik PS, Towson JA, Anthon GJ, et al. Intra-abdominal abscesses following laparoscopic and open appendectomies. *J Gastrointest Surg* 1997; 1: 188-192.
42. McKellar DP, Anderson CT, Boynton CJ, et al. Cholecystectomy during pregnancy without fetal loss. *Surg Gynecol Obstet* 1992; 174: 465-468.
43. Gilat T, Konikoff F. Pregnancy and the biliary tract. *Can J Gastroenterol* 2000; 14 Suppl D: 55D-59D.
44. Curet MJ, Allen D, Josloff RK, et al. Laparoscopy during pregnancy. *Arch Surg* 1996; 131: 546-550.
45. Augustin G, Majerovic M. Non-obstetrical acute abdomen during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2007; 131: 4-12.
46. Coleman MT, Trianfo VA, Rund DA. Nonobstetric emergencies in pregnancy: trauma and surgical conditions. *Am J Obstet Gynecol* 1997; 177: 497-502.
47. Cosenza CA, Saffari B, Jabbour N, et al. Surgical management of biliary gallstone disease during pregnancy. *Am J Surg* 1999; 178: 545-548.
48. Lu EJ, Curet MJ, El-Sayed YY, et al. Medical versus surgical management of biliary tract disease in pregnancy. *Am J Surg* 2004; 188: 755-759.
49. Bisharah M, Tulandi T. Laparoscopic surgery in pregnancy. *Clin Obstet Gynecol* 2003; 46: 92-97.
50. Cohen-Kerem R, Railton C, Oren D, et al. Pregnancy outcome following non-obstetric surgical intervention. *Am J Surg* 2005; 190: 467-473.
51. Kilpatrick CC, Monga M. Approach to the acute abdomen in pregnancy. *Obstet Gynecol Clin North Am* 2007; 34: 389-402.
52. Perdue PW, Johnson HW, Jr., Stafford PW. Intestinal obstruction complicating pregnancy. *Am J Surg* 1992; 164: 384-388.
53. Gangi S, Sparacino T, Furci M, et al. Hernia of the posterior lamina of the rectus abdominis muscle sheath: report of a case. *Ann Ital Chir* 2002; 73: 335-337.
54. John H, Gyr T, Giudici G, et al. Cecal volvulus in pregnancy. Case report and review of literature. *Arch Gynecol Obstet* 1996; 258: 161-164.
55. Joshi MA, Balsarkar D, Avasare N, et al. Gangrenous sigmoid volvulus in a pregnant woman. *Trop Gastroenterol* 1999; 20: 141-142.
56. Sato N, Miki T, Toyonaga T, et al. A case of herniation through a defect in the falciform ligament at late pregnancy. *Nippon Geka Gakkai Zasshi* 1996; 97: 787-790, (in Japanese).
57. Samara Ch, Tsikini A, Antoniou S, Polyzos D, Varras M. Ultrasonographic and computed tomography manifestations of intussusception secondary to primary non-Hodgkin's lymphoma diagnosed in puerperium: report of a case and review of the literature. *Eur J Gynaecol Oncol* 2002; 23: 569-572.