

GENUINE GASTROINTESTINAL DISEASES UNDERDIAGNOSED IN PATIENTS WITH ASSUMED NAUSEA AND EMESIS IN PREGNANCY

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REZUMAT

Simptomele gastrointestinale precum greața, vărsăturile, arsurile și constipația sunt extrem de comune în sarcină. Deseori aceste simptome sunt considerate de obstetricieni și de gravide ca fiind intrinsec asociate cu sarcina și nu reprezentând o condiție patologică. În orice caz însă, cauzele organice ale acestor simptome trebuie excluse. Bolile gastrointestinale precum obstrucția intestinală, gastrita, cancerul gastric, bolile hepatice și biliare în sarcină sunt rare, dar dacă sunt suspectate, necesită diagnosticare și terapie urgentă. Întârzieri nejustificate sunt asociate cu morbiditate și rareori chiar cu mortalitate maternă.

Cuvinte cheie: Simptome gastrointestinale, sarcina, hiperemeza de sarcină, disgravidia, urgențe.

ABSTRACT

Cardiac anomalies are the most frequent congenital malformations and it has been shown that prenatal diagnosis has a major impact on the prenatal and postnatal management of affected pregnancies. Technical improvements and highly skilled operators, have demonstrated that early echocardiography, at 11-14 weeks scan, is feasible and a significant proportion of cardiac lesions present with abnormal ultrasound findings at this stage. Early evaluation is at this moment best reserved for cases at greater risk of cardiac defects (increased nuchal translucency and presence of extra cardiac lesions) but we proposed that it forms part of the early morphologic evaluation in low risk population where 80% of the cardiac anomalies happen. Second trimester fetal echocardiogram continually to be the gold standard and has to be performed for the ongoing pregnancies.

Key Words: First trimester; 11-14 weeks scan; Nuchal translucency; Cardiac defects; Fetal echocardiography; Prenatal diagnosis.

INTRODUCTION

Increased levels of female sex hormones cause alterations of gastrointestinal motility, and this fact explains, at least in part, why gastrointestinal symptoms such as nausea, vomiting, but also heartburn, and constipation are extremely common during pregnancy. In most instances, nausea and vomiting are considered by obstetricians but also by the pregnant women as being intrinsically associated with pregnancy and thus not a pathological condition. However, organic causes of these symptoms need to be appropriately excluded in severe cases, and in patients with alarm symptoms.

Serious gastrointestinal diseases such as intestinal obstruction, gastritis, gastric cancer, bile or liver diseases during pregnancy are rare, but if suspected, often warrant immediate confirmation and aggressive therapy. Unnecessary delays are associated with an increasing morbidity and, rarely, even mortality.

NAUSEA AND VOMITING DURING PREGNANCY

Up to 85% of all pregnant women experience some form of nausea and vomiting during their pregnancy.^{1,2} Nausea and vomiting during pregnancy, typically occur between the fourth and the 10th week of gestation, with resolution by 20 weeks of gestation.² A small percentage of women experience a severe form of nausea and vomiting known as hyperemesis gravidarum. Estimates of the incidence of hyperemesis vary from 0.3–1.5% of all live births.¹ Diagnosis is subjective, but the condition is usually described as intractable vomiting leading to fluid, electrolyte and acid base imbalance, nutritional deficiency and weight loss.¹

The etiology for nausea and vomiting during pregnancy is unknown, but there are several factors that can cause or contribute to these symptoms,

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including hormones, pregnancy-associated alterations to the vestibular system, taste and olfaction, and behavioral and/or psychological aspects.

The endocrine factor most commonly invoked is human chorionic gonadotropin hormone (HCG) on the basis of the observed temporal association, that incidence of hyperemesis is highest at the time that HCG production reaches its peak. In addition, hyperemesis is said to have a higher incidence in those conditions associated with elevated HCG concentrations such as twin and molar pregnancies.¹

Other etiological factors that have been proposed are oestrogen, placental serum markers, adrenocorticotrophic hormone (ACTH) and cortisol, growth hormone and prolactin. Severe nausea and vomiting is consistently associated with the presence of a female fetus, one study finding that women hospitalized for hyperemesis had a 50% increased chance of having a female fetus compared to controls.³ The usual explanation for this is higher oestrogen concentrations.

Historically there was thought to be an association between hyperemesis and psychological conflicts in dealing with pregnancy. Studies of hyperemesis patients have found no difference in marital status, whether the infant was planned, or positive feelings about the pregnancy. More recent studies have suggested that psychological symptoms are the result of the stress and the burden of hyperemesis rather than the cause.¹ (Table 1)

GASTROINTESTINAL TRACT AND NAUSEA AND VOMITING DURING PREGNANCY

When limited to the gastrointestinal tract, gastric dysrhythmias — acute losses of the normal gastric slow wave frequency of three cycles per minute — are related to stomach dysfunction and nausea in pregnancy. Gastric dysrhythmias are probably caused by increased levels of female sex hormones, but raised levels of vasopressin might also have a role.⁴

These changes could explain how gastric contractility is reduced and consequently how gastric emptying is impaired. Recurrent abdominal pain can be caused by gastrointestinal dysmotility and can occur in patients with nausea and vomiting of pregnancy; however, such pain can also be a symptom of other genuine gastrointestinal diseases (e.g. GERD, ulcers, gastric cancer, cholecystitis, pancreatitis) that need to be excluded as appropriate, depending on the individual patient's presenting symptoms and signs.⁵

Table 1. Differential diagnosis of persistent nausea and vomiting in pregnancy.

Gastrointestinal disorders
Achalasia
GERD
Gastritis
Peptic ulcer disease
Gastroenteritis
Biliary tract disease
Cholelithiasis
Intestinal obstruction
Pancreatitis
Appendicitis
Genitourinary tract disorders
Pyelonephritis
Uremia
Degenerating uterine leiomyoma
Torsion
Kidney stones
Metabolic disorders
Diabetic ketoacidosis
Porphyria
Addison's disease
Hyperthyroidism
Neurologic disorders
Pseudotumor cerebri
Vestibular lesions
Migraine headaches
Central nervous system tumors
Pregnancy-related conditions
Nausea and vomiting of pregnancy
Hyperemesis gravidarum
Acute fatty liver of pregnancy
Preeclampsia
HELLP-Syndrom
Drug toxicity or intolerance

ACHALASIA

Achalasia is a motor disorder of the esophageal smooth muscle in which the lower esophageal sphincter does not relax normally with swallowing, and the esophageal body undergoes nonperistaltic contractions.

Achalasia has an incidence of one to two cases per 200 000 population per year. The disorder usually starts in the third to fifth decade and is often insidious.⁶ It is therefore not surprising to find that achalasia and pregnancy rarely coexist, and recent textbooks dealing with the complications of pregnancy give little or no information on the subject. The symptoms Achalasia presents with include dysphagia, chest pain, and regurgitation, but also nausea, vomiting, difficulty belching, pulmonary aspiration and respiratory distress, malnutrition, and weight loss.⁷ Although the largest study on the subject indicated that achalasia has no adverse effect on pregnancy or fetal outcome, there is a general paucity of data in the literature.⁸ Achalasia

might affect pregnancy outcomes through associated malnutrition and, in some cases, complications of therapy. In pregnancy in general, severe malnutrition has been associated with preterm delivery, as well as small-for-gestational-age infants and increased perinatal mortality.⁹

Recommendations for treating women with achalasia range from minimal concern to treatment before and during pregnancy to termination of pregnancy: Ideally, treatment of achalasia during pregnancy should be designed to reduce LES pressure and palliate maternal symptoms of functional obstruction without having any adverse effects on the fetus. Medical therapy (calcium-channel antagonists and nitrates-FDA Group C) for achalasia has resulted in suboptimal relief of dysphagia symptoms. On the other hand, surgical treatment such as esophagomyotomy carries a significant anesthetic and surgical risk if performed during pregnancy.

There are two case reports of successful and effective pneumatic dilation performed during the first and second trimesters of pregnancy, suggesting that this method should be preferred to surgical myotomy in pregnancy.⁷

GERD

Gastroesophageal reflux disease (GERD) is defined as a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications. GERD occurs at all ages from childhood to advanced age. Pregnancy has long been acknowledged as a condition that predisposes to GERD and heartburn as the predominant symptom is estimated to occur with a frequency of 30% to 50% in pregnant women.¹⁰ Most pregnant women show symptoms like nausea and vomiting and this can hide a gastroesophageal reflux disease.

Several pathogenetic mechanisms have been suggested to contribute to the development of GERD during pregnancy. These include increasing intra-abdominal pressure resulting from the expansion of the uterus as well as gestational hormone changes. Hormonal changes in pregnancy were suggested to exert an effect on the lower esophageal sphincter (LES) pressure. Increased levels of sex hormones during pregnancy, like progesterone and estrogen, seem to induce a lowering effect on the pressure of the LES.¹¹

As in the non-pregnant patient, the initial diagnosis of GERD in pregnancy can reliably be made based on symptoms alone. Oesophageal manometry and pH studies are rarely necessary during pregnancy but

can be performed safely. Upper gastrointestinal (GI) endoscopy is the procedure of choice to evaluate intractable reflux symptoms or complications.⁵ GERD during pregnancy should be treated with a step-up algorithm beginning with lifestyle modifications and dietary changes.¹² Antacids or sucralfate are considered the first-line drug therapy. If symptoms persist, any of the histamine₂-receptor antagonists can be used. Proton pump inhibitors are reserved for women with intractable symptoms or complicated reflux disease.¹⁰ The diagnose of GERD in pregnancy is important because without a good therapeutic management the symptoms can persist and influence dramatically the quality of live and can also lead to complications like peptic ulcer.

GASTRIC OR DUODENAL ULCER

Peptic ulceration (mucosal erosion) is uncommonly associated with pregnancy and complications of peptic ulcer during pregnancy are extremely rare.¹³ Peptic ulcer symptoms as epigastric distress, heartburn, nausea, and vomiting are frequent complaints during normal pregnancy and therefore, often overlooked. Definitive diagnosis depends on endoscopy or x-ray confirmation which is considered hazardous and avoided during gestation. Eighty-eight per cent of women with known peptic ulcer disease prior to gestation experience amelioration of symptoms during pregnancy.¹⁴ Exacerbation of peptic ulcer symptoms might occur in the last trimester of pregnancy and the early postpartum period, and results in significant morbidity and mortality to mother and fetus. A small number of reports of perforation and hemorrhage from peptic ulcer in pregnant women resulting in maternal and fetal mortality have been published so far.¹⁵ The majorities of these instances were unrecognized during life and were necropsy findings. The association of acute peptic ulcer (stress ulcer) and preeclampsia has been well documented.¹⁶

Pregnant women with previous histories of peptic ulcer or of preeclampsia who complain of epigastric distress should be under strict medical management and be observed for complications of ulcer disease. Bleeding is less common than perforation.¹⁵ Severe ulcer complications in late pregnancy are shortly followed by premature labor and delivery. Uterine contraction is stimulated by laparotomy or the presence of peritonitis. Vaginal delivery should be permitted when obstetrically feasible, and caesarean section avoided despite easy access to the gravid uterus during operation for peptic ulcer complications. The present instance of massive hemorrhage from a

gastric ulcer in an anxious patient who had no previous symptoms of peptic ulcer, and who was toxemic in pregnancy strongly suggests a stress factor and acute ulcer formation. Persistent hemorrhage necessitates operation despite the risk of abortion or premature birth. Vagotomy, pyloroplasty, and deep suture ligation of the ulcer bed high in the cardia with survival of both the mother and fetus have been described.¹⁷

GASTRIC CANCER

Gastric cancer primarily occurs in patients over 50 years of age. The described proportion of young patients with gastric cancer varies from 2% to 15% depending on the age defined as young.¹⁸ Female patients have a relative dominance in this group and the incidence of gastric cancer is higher in women over the age of 30. The frequency of pregnancy has been increasing in these women and this may lead to a higher coincidence of pregnancy and gastric cancer.¹⁹ Pregnancy-associated gastric cancer is currently attributed to 0.1% of all cases. There is an increased risk of diffuse and scirrhous type carcinomas in this group of patients.²⁰ Common presenting signs and symptoms of gastric cancer include dyspepsia, epigastric pain, early satiety, nausea, vomiting, anemia, dysphagia, weight loss and melena. Except for weight loss and melena, all of these symptoms are common in pregnancy. Weight loss can be caused by hyperemesis gravidarum or compensated and masked by the weight gain in pregnancy and melena may be initially attributed to pregnancy-related hemorrhoids.²¹

Maconi et al. reported a mean delay, from first symptoms to final diagnosis of 29.3 ± 9.9 weeks in young patients without alarm symptoms. The initial diagnosis of gastric carcinoma is often delayed because up to 80 percent of patients are asymptomatic during the early stages of gastric cancer.²² Hormonal stimulation and pregnancy in young women may accelerate the growth of gastric cancer. Gastric cancer should be included, therefore, in the differential diagnosis of unusual or prolonged gastrointestinal symptoms like nausea and vomiting after the first trimester of pregnancy and in women who have recently been pregnant.²³ Coexistent risk factors such as positive family history should trigger immediate further investigation through gastrointestinal endoscopy which is not contraindicated during pregnancy.

INTESTINAL OBSTRUCTION

Intestinal obstruction in pregnancy is a rare but serious complication with significant maternal and

fetal mortality, often due to delay in both diagnosis and treatment.²⁴ The incidence of intestinal obstruction in pregnancy cited in the published literature ranges from one in 1500 to one in 66,000 deliveries.²⁵ Adhesions are the primary cause of mechanical intestinal obstruction in pregnancy (58%) followed by volvulus (24%); other causes are intussusceptions, hernia and cancer.²⁶ Seventy-seven percent of the patients with obstruction due to adhesions have undergone previous abdominal or pelvic surgery.

Abdominal pain, distension, and absolute constipation are the clinical triad of intestinal obstruction, often associated with nausea and vomiting. However, the diagnosis of intestinal obstruction in pregnancy is often not easy. The abdomen of the pregnant woman is distended by the enlarged uterus, and pregnant women tend toward constipation. During gestation, it is believed that the risk is highest between 16 and 20 weeks when the uterus moves from the pelvis to the abdomen and at 36 weeks when the fetal head descends into the pelvis. In the puerperium, the sudden drop in uterine size can also lead to bowel obstruction if intraabdominal adhesions are present.²⁷ Therefore, when examining pregnant women complaining of abdominal pain with a history of abdominal or pelvic surgery we should suspect intestinal obstruction, even when the pain is accompanied with uterine contractions.

Abdominal ultrasound can show dilated loops or air-fluid levels. Magnetic resonance imaging provides excellent anatomic resolution and tissue characterization without ionizing radiation and MR diagnosis frequently requires no contrast administration.²⁸ The basis of therapy is timely surgery. Surgery should be performed via midline vertical incision. In the third trimester, if adequate intestinal exposure cannot be obtained, caesarean section must be performed since intra-abdominal surgery can lead to premature uterine contractions, tocolytic agents are prophylactically used.²⁵ Bowel viability should be assessed carefully and segmental resection with or without anastomosis is often necessary.

When intestinal obstruction complicates pregnancy, both mother and fetus are at risk. In one series of 66 pregnant patients with bowel obstruction the fetal death rate was 26% and four maternal deaths were reported.²⁹

CHOLECYSTITIS/CHOLELITHIASIS IN PREGNANCY

The incidence of biliary tract disease during pregnancy ranges from 0.05% to 0.3% and occurs

mainly during the last trimester.³⁰ Obstruction of the cystic duct can be caused by cholecystitis or gallstones (calculus cholecystitis). However, in some cases the obstruction may be acalculous or caused by sludge. Whether women who are pregnant or have multiple pregnancies are more likely to develop stones or whether they are simply more symptomatic with stones is unknown. Despite the rarity of the condition, complications of gallstones represent the second most common nongynecologic condition requiring surgery in pregnancy after appendicitis.³¹ The incidence of gallstones in pregnancy has been estimated to be between 2.5% and 4.2%.³² Pregnancy may accentuate gallbladder stone formation. Choledocholithiasis during pregnancy is a serious problem that may lead to cholangitis, gallstone pancreatitis, or both, with potentially life-threatening consequences for both mother and fetus.³³ A main symptom of gallstones is intense pain in the upper abdominal region, less common is pain in the back or the lower region of the abdomen. Also nausea and vomiting may occur.³³

ERCP (Endoscopic Retrograde Cholangiopancreatography) (sphincterotomy and stone removal) is an effective non-surgical treatment method for common bile duct stones and gallstone pancreatitis.³⁴ However, because ERCP is performed under fluoroscopic guidance, there is a widespread concern of radiation-induced damage to the fetus. Actually, the American College of Obstetricians and Gynecologists (ACOG) states that fetal risk of anomalies, growth restriction or abortions are not increased with radiation exposure of less than 5 rad, a level above the range of exposure for diagnostic procedures.

On the other hand, according to ACOG, during pregnancy, other imaging procedures such as ultrasonography and magnetic resonance imaging (MRI) not associated with ionizing radiation should be considered instead of X-rays when possible. The latter recommendation reveals that although these procedures carry minimal risk, they should not be undervalued.

ACUTE PANCREATITIS

Nearly 25% of acute pancreatitis attacks in pregnancy are severe, leading to complications, and the mortality rate from over 15 pooled series approached 10% in a recent review.³⁵ Acute pancreatitis is a rare complication of pregnancy. Its incidence has been cited to range from 1 in 1000 to 1 in 3333 pregnancies in more recent reports.³⁵ Most cases of pancreatitis in pregnancy are associated with biliary tract disease.

Although gallstones and gallbladder disease are the most frequent causes of acute pancreatitis in pregnant patients, with an incidence of 68% reported by Ramin et al, a number of cases of hyperlipidemia-induced pancreatitis in pregnancy have also been reported.^{35,36} In spite of its rarity, it remains an important clinical entity because of increased rates of maternal and perinatal morbidity and mortality.³⁷ Also the incidence of preterm delivery and perinatal death is high compared with the general obstetric population.

Prompt recognition and hospitalization of pregnant women with acute pancreatitis has been associated with a decline in both maternal and perinatal morbidity and mortality, which include operative intervention for the disease itself and surgical treatment of associated biliary tract disease once acute inflammation subsides.

Exploratory laparotomy is indicated in women with unremitting (duodenal pseudocysts or infected peripancreatic abscess) disease and in those in whom the diagnosis is uncertain. The differential diagnosis for those requiring surgical exploration includes mesenteric infarction, gangrenous cholecystitis, or other intraabdominal pathologic mechanisms.

Baillie et al. reported the use of endoscopy and sphincterotomy in four pregnant women with acute cholangitis and one with gallstone pancreatitis. They concluded that such an approach is safe and effective during pregnancy but that definitive cholecystectomy should be performed post partum.³⁸

HELLP SYNDROME

HELLP syndrome is characterized by hemolysis, elevated levels of liver enzymes and low platelet numbers. HELLP syndrome occurs in approximately 1 per 1000 pregnancies. The majority of cases are diagnosed between 28 and 36 weeks of gestation.³⁹ The disease presents prior to delivery in 70%, postpartum in 30% of cases, usually within 48 h, but occasionally as long as 7 days after delivery. HELLP syndrome is a multisystemic disorder that involves changes in the immunologic fetal–maternal balance, platelet aggregation, activation of complement and coagulation cascades, and endothelial dysfunction.⁴⁰ Liver injury is caused by intravascular fibrin deposition, hypovolemia and increased sinusoidal pressure, and is sometimes complicated by subcapsular hematoma or hepatic rupture. The clinical presentation of HELLP syndrome varies. Although some patients have no symptoms, most complain of abdominal pain and tenderness.³⁹ The pain is located in the midepigastrium, right upper quadrant, or below the sternum. Many patients also have nausea, vomiting,

and malaise. Disseminated intravascular coagulation or renal failure can complicate the situation. The only definitive therapy for HELLP syndrome is induction of delivery.⁴¹ In women with early-onset HELLP syndrome (before week 34), corticosteroids have been recommended to stabilize the maternal abnormalities and allow maturation of the fetus.⁴² HELLP syndrome is associated with maternal mortality of 1–3.5%.⁵ Fetal outcome is more strongly determined by the gestational age at the time of delivery than by the severity of HELLP syndrome in the mother.⁴²

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy (AFLP) is a rare, but very serious disease of the last trimester of pregnancy (1 case per 10,000–15,000 pregnancies).⁴¹

Maternal and fetal defects of fatty acid metabolism, particularly deficiency of the enzyme long-chain 3-hydroxyacyl-coenzyme A dehydrogenase, are thought to cause increased accumulation of long-chain fatty acids, first in the fetal liver and then, via the circulation, in the maternal liver, which results in hepatotoxicity.⁴¹ Symptoms vary from nausea and/ or vomiting, upper abdominal pain and upper gastrointestinal hemorrhage to acute liver failure with hepatic coagulopathy, encephalopathy, renal failure and multiorgan failure. NSAID use can increase the risk of developing acute fatty liver of pregnancy, and this disease is more common in patients with pre-eclampsia.⁵ If recognized early and treated by induction of delivery, maternal mortality is less than 5%.⁴¹ Nevertheless, liver transplantation has been performed in women with AFLP, and 23–60% of babies born to women with AFLP die.⁴³

Women at risk of AFLP are those with a history of AFLP and those with children who have a disorder of fatty-acid oxidation or children who died of Reye syndrome. These women should be monitored closely, and must maintain a low-fat, high-carbohydrate diet and avoid fasting.^{41,43} Nausea and vomiting during pregnancy have to be taken serious because AFLP can be unsigned and these symptoms can be the only sign of this severe disease.

APPENDICITIS

Appendicitis is the most common non-obstetric surgical diagnosis during pregnancy and in consequence the most frequent reason for emergency general surgical intervention.^{44,45}

The incidence is reported to be between 1 case per 1250 and 1 case per 1500 pregnancies with 50%

of cases occurring in the second trimester. Accurate diagnosis is difficult with the typical clinical picture being present in only 50-60% of cases.^{44,46} Anatomical changes related to the gravid uterus, gestational symptoms, the physiological inflammatory response (elevated white cell count and left shift in neutrophils) and a wider differential diagnosis in pregnant women result in poor diagnostic accuracy, reported to range from 36 to 86%.⁴⁷

The symptom/sign complex does not sufficiently diverge from other causes of abdominal pain during pregnancy.

Nausea and vomiting are common in the obstetric population especially in early pregnancy when they may represent gestational symptoms. However, after the first trimester, their presence must be fully investigated as they remain the most consistent symptoms reported in patients with appendicitis.⁴⁴

Compression ultrasound in first and second trimester pregnancies has been shown to have good diagnostic sensitivity for appendicitis in pregnancy.⁴⁸ It has the advantage of being cheap, readily available and safe and as such remains the gold standard imaging modality.⁴⁸ CT has been used to diagnose appendicitis in pregnancy, however, concern remains as to the potential risk of the ionising radiation to the fetus.⁴⁹ MRI has also been used as a diagnostic modality. In the largest study to date (n=12), Cobben, reported high sensitivity, specificity and diagnostic accuracy.⁵⁰ The SMRI safety committee was more conservative and suggested that MRI should be avoided in the first trimester and that all mothers should be informed of potential risks.⁴⁴

Laparoscopic surgery is increasingly used in both the diagnosis and management of pregnant patients with suspicion of appendicitis. Present consensus is that the difficulties become increasingly acute with advancing gestational age (size of the uterus) and therefore local expertise will guide management. The negative laparotomy rate for suspected appendicitis in obstetric cases is 25% - 50% compared to 15% - 35% in general surgical cases.⁵¹

In the obstetric cases the consequence of unnecessary surgery include increased rates of miscarriage, premature labour (15-45%) and fetal loss.⁵¹ However, delay to surgery is equally risky with rates of fetal loss reported to be 1.5-4% in 'uncomplicated appendicitis' compared to 21-35% in the presence of 'ruptured appendicitis'.⁵²

Furthermore, increasing gestational age reduces diagnostic accuracy and is associated with increased rates of appendical perforation and hence complications.⁵²

CONCLUSIONS

Although rare, severe gastrointestinal diseases may occur during pregnancy. Nausea and vomiting during pregnancy should alert the physician to the presence of severe gastrointestinal diseases. Aggressive management and early medical or operative intervention when indicated is stressed.

REFERENCES

1. Sheehan P. Hyperemesis gravidarum--assessment and management. *Aust Fam Physician* 2007;36(9):698-701.
2. Gadsby R, Barnie-Adshad AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. *Br J Gen Pract* 1993;43(371):245-8.
3. Schiff MA, Reed SD, Daling JR. The sex ratio of pregnancies complicated by hospitalisation for hyperemesis gravidarum. *Bjog* 2004;111(1):27-30.
4. Koch KL. Gastrointestinal factors in nausea and vomiting of pregnancy. *Am J Obstet Gynecol* 2002;186(5 Suppl Understanding):S198-203.
5. Keller J, Frederking D, Layer P. The spectrum and treatment of gastrointestinal disorders during pregnancy. *Nat Clin Pract Gastroenterol Hepatol* 2008;5(8):430-43.
6. Faloon T. Achalasia in pregnancy. A case of a rare coexistence. *Can Fam Physician* 1993;39:1182-4, 6.
7. Khudyak V, Lysy J, Mankuta D. Achalasia in pregnancy. *Obstet Gynecol Surv* 2006;61(3):207-11.
8. Clemendor A, Sall S, Harbilas E. Achalasia and nutritional deficiency during pregnancy. *Obstet Gynecol* 1969;33(1):106-13.
9. King JC. The risk of maternal nutritional depletion and poor outcomes increases in early or closely spaced pregnancies. *J Nutr* 2003;133(5 Suppl 2):1732S-6S.
10. Fill S, Malfertheiner M, Costa SD, et al. Handling of the gastroesophageal reflux disease (GERD) during pregnancy--a review. *Z Geburtshilfe Neonatol* 2007;211(6):215-23.
11. Fisher RS, Roberts GS, Grabowski CJ, et al. Altered lower esophageal sphincter function during early pregnancy. *Gastroenterology* 1978;74(6):1233-7.
12. Fill Malfertheiner S, Costa SD. Reflux in pregnancy - Secure and differential treatment *Gastroenterologie* 2008;4(3):303-8.
13. Grosfeld JL. Massive gastric hemorrhage in late pregnancy: survival of mother and offspring after vagotomy and pyloroplasty. *Ann Surg* 1968;168(6):971-3.
14. Clark DH. Peptic ulcer in women. *Br Med J* 1953;1(4822):1254-7.
15. Cappell MS. Gastric and duodenal ulcers during pregnancy. *Gastroenterol Clin North Am* 2003;32(1):263-308.
16. Langmade CF. Epigastric pain in pregnancy toxemias; a report of fatal peptic ulcers in toxemias. *West J Surg Obstet Gynecol* 1956;64(10):540-4.
17. Erez O, Maymon E, Mazor M. Acute gastric ulcer perforation in a 35 weeks' nulliparous patient with gastric banding. *Am J Obstet Gynecol* 2004;191(5):1721-2.
18. Kath R, Fiehler J, Schneider CP, et al. Gastric cancer in very young adults: apropos four patients and a review of the literature. *J Cancer Res Clin Oncol* 2000;126(4):233-7.
19. Ueo H, Matsuoka H, Tamura S, et al. Prognosis in gastric cancer associated with pregnancy. *World J Surg* 1991;15(2):293-7, discussion 8.
20. Khatib F, Shaya M, Samueloff A. Gastric carcinoma with metastasis to the placenta and amniotic fluid: case report and review of the literature. *Eur J Obstet Gynecol Reprod Biol* 2003;107(2):208-9.
21. Fill S, Taran A, Schulz HU, et al. Sister Mary Joseph's nodule as the first sign of pregnancy-associated gastric cancer: a case report. *World J Gastroenterol* 2008;14(6):951-3.
22. Maconi G, Kurihara H, Panizzo V, et al. Gastric cancer in young patients with no alarm symptoms: focus on delay in diagnosis, stage of neoplasm and survival. *Scand J Gastroenterol* 2003;38(12):1249-55.
23. Furukawa H, Iwanaga T, Hiratsuka M, et al. Gastric cancer in young adults: growth accelerating effect of pregnancy and delivery. *J Surg Oncol* 1994;55(1):3-6.
24. Kalu E, Sherriff E, Alsibai MA, et al. Gestational intestinal obstruction: a case report and review of literature. *Arch Gynecol Obstet* 2006;274(1):60-2.
25. Redlich A, Rickes S, Costa SD, et al. Small bowel obstruction in pregnancy. *Arch Gynecol Obstet* 2007;275(5):381-3.
26. Sharp HT. The acute abdomen during pregnancy. *Clin Obstet Gynecol* 2002;45(2):405-13.
27. Connolly MM, Unti JA, Nora PF. Bowel obstruction in pregnancy. *Surg Clin North Am* 1995;75(1):101-13.
28. Brown MA, Birchard KR, Semelka RC. Magnetic resonance evaluation of pregnant patients with acute abdominal pain. *Semin Ultrasound CT MR* 2005;26(4):206-11.
29. Perdue PW, Johnson HW, Jr., Stafford PW. Intestinal obstruction complicating pregnancy. *Am J Surg* 1992;164(4):384-8.
30. Lu EJ, Curet MJ, El-Sayed YY, et al. Medical versus surgical management of biliary tract disease in pregnancy. *Am J Surg* 2004;188(6):755-9.
31. Printen KJ, Ott RA. Cholecystectomy during pregnancy. *Am Surg* 1978;44(7):432-4.
32. Stauffer RA, Adams A, Wygal J, et al. Gallbladder disease in pregnancy. *Am J Obstet Gynecol* 1982;144(6):661-4.
33. Bagci S, Tuzun A, Erdil A, et al. Treatment of choledocholithiasis in pregnancy: a case report. *Arch Gynecol Obstet* 2003;267(4):239-41.
34. Nesbitt TH, Kay HH, McCoy MC, et al. Endoscopic management of biliary disease during pregnancy. *Obstet Gynecol* 1996;87(5 Pt 2):806-9.
35. Ramin KD, Ramin SM, Richey SD, et al. Acute pancreatitis in pregnancy. *Am J Obstet Gynecol* 1995;173(1):187-91.
36. Roberts IM. Hyperlipidemic gestational pancreatitis. *Gastroenterology* 1993;104(5):1560-2.
37. Crisan LS, Steidl ET, Rivera-Alsina ME. Acute hyperlipidemic pancreatitis in pregnancy. *Am J Obstet Gynecol* 2008;198(5):e57-9.
38. Baillie J, Cairns SR, Putman WS, et al. Endoscopic management of choledocholithiasis during pregnancy. *Surg Gynecol Obstet* 1990;171(1):1-4.
39. Sibai BM, Ramadan MK, Usta I, et al. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). *Am J Obstet Gynecol* 1993;169(4):1000-6.
40. Kondrackiene J, Kupcinskas L. Liver diseases unique to pregnancy. *Medicina (Kaunas)* 2008;44(5):337-45.
41. Schutt VA, Minuk GY. Liver diseases unique to pregnancy. *Best Pract Res Clin Gastroenterol* 2007;21(5):771-92.
42. Martin JN, Jr., Rose CH, Briery CM. Understanding and managing HELLP syndrome: the integral role of aggressive glucocorticoids for mother and child. *Am J Obstet Gynecol* 2006;195(4):914-34.
43. Ibdah JA. Acute fatty liver of pregnancy: an update on pathogenesis and clinical implications. *World J Gastroenterol* 2006;12(46):7397-404.
44. Brown JJ, Wilson C, Coleman S, et al. Appendicitis in pregnancy: an ongoing diagnostic dilemma. *Colorectal Dis* 2008.
45. Tracey M, Fletcher HS. Appendicitis in pregnancy. *Am Surg* 2000;66(6):555-9; discussion 9-60.
46. Eryilmaz R, Sahin M, Bas G, et al. Acute appendicitis during pregnancy. *Dig Surg* 2002;19(1):40-4.
47. Yilmaz HG, Akgun Y, Bac B, et al. Acute appendicitis in pregnancy--risk factors associated with principal outcomes: a case control study. *Int J Surg* 2007;5(3):192-7.
48. Lim HK, Bae SH, Seo GS. Diagnosis of acute appendicitis in pregnant women: value of sonography. *AJR Am J Roentgenol* 1992;159(3):539-42.
49. Wallace CA, Petrov MS, Soybel DI, et al. Influence of imaging on the negative appendectomy rate in pregnancy. *J Gastrointest Surg* 2008;12(1):46-50.

50. Cobben LP, Groot I, Haans L, et al. MRI for clinically suspected appendicitis during pregnancy. *AJR Am J Roentgenol* 2004;183(3):671-5.
51. McGory ML, Zingmond DS, Tillou A, et al. Negative appendectomy in pregnant women is associated with a substantial risk of fetal loss. *J Am Coll Surg* 2007;205(4):534-40.
52. Hee P, Viktrup L. The diagnosis of appendicitis during pregnancy and maternal and fetal outcome after appendectomy. *Int J Gynaecol Obstet* 1999;65(2):129-35.