AMERICAN COLLEGE OF GASTROENTEROLOGY

Pregnancy in Gastrointestinal Disorders

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Dedication

This second edition of the Monograph is dedicated to the memory of Radhika Srinivasan, M.D., MACG, past Chair of the American College of Gastroenterology Women in GI Committee and the driving force behind this revision of the first edition of this educational monograph.

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Constipation, Diarrhea, Hemorrhoids and Fecal Incontinence

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Pregnant women are susceptible to a host of bowel disturbances such as constipation, diarrhea, and fecal incontinence at rates similar to that of the general population. However, there is data to suggest that the pathophysiology of the alteration in bowel pattern may be specific to hormonal and structural changes that occur during pregnancy and as a result of delivery. In this section, we will discuss how the physiologic changes that occur during pregnancy may contribute to the development of specific bowel disturbances. In addition, we will address therapy for these conditions with special consideration for maternal and fetal safety.

Constipation

Constipation defined as 1) straining at defecation at more than 25% of bowel movements 2) hard stool at more than 25% of bowel movements, and 3) two or fewer movements a week is thought to occur in 1/3 of women in their third trimester.[1] However, in another study only 1.5 % of pregnant constipated women required laxatives.[2]

The etiology of constipation during pregnancy is multi-factorial (Table 1). The hormonal changes that occur during pregnancy, such as increased progesterone and estrogen, and decreased motilin have not been well studied in humans. However, pregnant rats were found to have prolonged colonic transit compared to nonpregnant or oviarectomy controls.[1] In dogs, progesterone has been shown to reduce the contractile force of both circular and longitudinally oriented strips of smooth muscle in vitro.[3] These effects were found to be mediated by cytoplasmic Ca^{2+} concentration. There are no studies on colonic transit in pregnant women. However, there are a few studies looking at the effect of sex hormones on colonic transit. Women were found to have slightly slower colonic transit than men, yet no significant difference was found. The effect of the menstrual cycle on colonic transit suggests that female sex hormones modestly affect colonic transit.[4]

The approach to management of constipation in pregnancy is similar to that of the general population. Commonly, constipation is managed primarily by dietary and behavioral modification. Dietary changes include increasing water (>8 glasses/day) and fiber intake (20-35 grams/day). Bulk laxatives, psyllium and methylcellulose, are safe and effective in pregnancy.[1] Osmotic laxatives such as polyethylene glycol (PEG) (8-25 gms/day) and lactulose (15-30 cc/day) stimulate fluid accumulation in the gut. Consequently, PEG has been found to

increase bowel frequency, accelerate colorectal transit times and improve defecation in patients with non-organic constipation refractory to dietary fiber and stimulant laxatives.[5] Although not FDA approved for use in pregnancy, PEG is inert and minimally absorbed, therefore toxicity is unlikely but does carry a pregnancy category C rating. A PEG solution, Miralax©, is now available over-the-counter.

The approach to management of constipation in pregnancy is similar to that of the general population.

Mineral oil has been found to be associated with decreased maternal absorption of fat soluble vitamins, neonatal hypoprothrombinemia, and hemorrhage, and therefore is not recommended in pregnancy.[1] Castor oil and saline hyperosmotic agents should be avoided during pregnancy because they may induce premature uterine contractions and salt and water retention, respectively.[1] Stimulant laxatives such the anthroquinones, senna and cascara, are safe in pregnancy if used intermittently, but are not recommended for regular use.[6] Docusate sodium reduces surface tension, thereby permitting intestinal fluids to penetrate into the fecal mass. However, there is no evidence-based data to support efficacy in constipation.[7]

Tegaserod, a 5-HT4 receptor agonist, was approved for chronic constipation in non-pregnant patients. However, tegaserod was suspended from the market in March 2007 and in July 2007 it was announced it will be available only on a restricted basis on an IND protocol. A newer agent approved for constipation is lubiprostone.7,8 However, this agent has not been studied in pregnant patients and is not recommended for general use during pregnancy. (Table 2)

Diarrhea

There are no recent studies that report on the prevalence of diarrhea in pregnancy. Nonetheless, the only physiologic alteration that may theoretically stimulate diarrhea in pregnancy is the increase in prostaglandins which induce smooth muscle contraction, resulting in enhanced propulsive forces.[9] In addition, as is seen with exogenous prostaglandins, such as misoprostol, the gut may be stimulated to secrete water and electrolytes.[10]

The etiology of diarrhea during pregnancy spans the spectrum of diagnosis similar to that of the nonpregnant individual. The most common causes of acute diarrhea in pregnancy are infectious viral agents such as rotavirus and Norwalk virus. Bacterial infections such as Campylobacter, Shigella, Escherichia coli, Yersinia, and Salmonella may also result in acute diarrhea. Noninfectious causes include medications, food intolerances, lactose, fructose, sorbitol and mannitol intolerance, inflammatory bowel disease, and irritable bowel syndrome.[1] (Table 1)

Table 1
Etiology of Constipation and Diarrhea during Pregnancy

Constipation	Diarrhea
Dehydration	Infection
Decreased physical activity	Viral
Slowed GI transit	Bacterial
Increased progesterone	Parasites
Increased estrogen	Inflammatory bowel disease
Decreased motilin	Accelerated GI transit
? Increased relaxin	Increased prostaglandins
Low fiber diet	Medications
Enlarged gravid uterus	Irritable bowel syndrome
Pelvic floor dysfunction	Food intolerances
Metabolic	Lactose
Thyroid disease	Fructose
Diabetes mellitus	Sorbitol
	Mannitol

The evaluation of acute diarrhea is warranted if the diarrhea is persistent or if alarm symptoms such as weight loss and malnutrition develop. The diagnostic

work-up should include collecting stool for bacterial culture, analysis for ova and parasites, fecal leukocytes, and stool assay for Clostridium difficile toxin.[9] Flexible sigmoidoscopy is safe in pregnancy when necessary. A multicenter study by Cappell and associates found that in 48 pregnant women, sigmoidoscopy was not associated with pre-term labor or fetal malformations.[10]

Typically, the treatment of acute diarrhea involves conservative management with oral rehydration, correction of potential electrolyte abnormalities with orange juice and bananas (K+ replacement), salted crackers and broth. Of the anti-diarrheals, loperamide is most often recommended. In a prospective case controlled study, loperamide use in the first trimester of pregnancy was not associated with a significant difference in the development of major fetal malformations between the treatment and control groups.[11] However, diphenoxylate with atropine has been found to be teratogenic in animals and humans in the second and third trimester of pregnancy, and therefore is not recommended in pregnancy.[1] Bismuth subsalicylate is not recommended in pregnancy because it has been found to be associated with decreased birth weight, neonatal hemorrhage, and increased perinatal mortality.[9] (Table 3)

Hemorrhoids

Hemorrhoids are a common complaint during pregnancy. They are even more common in the postpartum period. Symptomatic hemorrhoids manifested by pruritus, pain, and bleeding, develop during pregnancy in 1/3 of women. Increased abdominal pressure by the enlarging gravid uterus is thought to cause vascular engorgement and venous stasis.[12]

Additionally, straining on defecation in constipated patients and pressure from pushing during the second stage of labor may contribute to hemorrhoid development.

Symptomatic hemorrhoids in pregnant individuals should initially be treated conservatively with increasing dietary fiber and water intake as well as stool softeners.[12] Hydrocortisone suppositories may reduce swelling and pruritus. Witch hazel pads are safe and effective in relieving pruritus as well, but should be used judiciously as long-term use can lead to thinning of the perianal area.

Surgical hemorrhoidectomy is a safe option in pregnancy when medical therapy fails.

If conservative therapy is unsuccessful, surgical or endoscopic therapy may be indicated. Internal hemorrhoids can safely be treated with endoscopic band ligation, injection sclerotherapy, and infrared coagulation.[1] Surgical hemorrhoidectomy is a safe option in pregnancy when medical therapy fails.[13]

Fecal Incontinence

Fecal incontinence (FI) is an embarrassing and socially-limiting problem. Many patients do not volunteer this symptom to their physician and it is not always part of the physician's repertoire in eliciting a review of systems. In a U.S. household survey by Drossman et al., the prevalence of this condition was found to be 7.4% in the overall population.[14] A community-based survey from Wisconsin reported a general prevalence of 2.2%.[15] Interestingly, anal incontinence has been found to be prevalent before, during, and three months after pregnancy in 1.4%, 7.0%, and 8.7% of women, respectively.[16]

Normal continence depends on several factors: stool volume and consistency, anal sphincter and pelvic floor function, neurological integrity, rectal sensation, storage capacity, and psychological motivation. During pregnancy, laxity of the pelvic floor may occur as a result of increased pelvic floor pressure from the gravid uterus. Furthermore, there appears to be two additional causes of incontinence related to childbirth:

traumatic disruption of the sphincter muscles resulting in fecal incontinence immediately after delivery and pudendal neuropathy causing late manifestations of incontinence. However, in a recent systemic review, cesarean section was not associated with a decrease incidence of FI.[17] Therefore, aside from childbirth trauma, laxity of the pelvic floor during pregnancy seems to be the most important risk factor for FI in pregnant women.

It is imperative that we have a good understanding of the pathophysiology of the bowel disturbance and the appropriate therapy for our pregnant patients.

Anorectal physiologic tests include anorectal manometry, electromyography (EMG), pudendal nerve conduction studies, defecography, anal endosonography, and functional magnetic resonance imaging. The evaluation of fecal incontinence may include all of the above tests. However, defecography is not helpful in detecting sphincter or nerve defects associated with childbirth. The evaluation of fecal incontinence may include all of the above tests, however, should be reserved for patients six months postpartum who suffer with fecal incontinence. Currently, pelvic MRI is investigational and is not recommended for routine use.

Sultan et al reported in the *New England Journal of Medicine* that vaginal delivery may be associated with mechanical disruption of both the internal and external anal sphincter. Anal endosonography revealed sphincter damage in 35% of primiparous women and 44% of multiparous women six weeks after delivery. Sphincter injury was associated with a decrease in maximal resting anal pressure. Anal endosonography and manometry evaluation in these women did not change six months postpartum and there was a strong association between symptoms and sphincter defects.[18]

Treatment for incontinence may include dietary modification, fiber supplementation, and pharmacologic intervention with agents such as loperamide. Biofeedback and surgical techniques such as creating a neosphincter have also been shown to be effective. Newer therapies such as sacral nerve stimulation and implantable artificial sphincter devices show promise for patients suffering with fecal incontinence. It is important to clarify the etiology of fecal incontinence and thus to tailor therapy accordingly.

In conclusion, disturbances in bowel function are common in pregnancy. These disturbances are frequently responsive to conservative medical therapy. However, even some medical therapies are contraindicated in pregnancy due to the risk of fetal and maternal complications they may incur. Therefore, it is imperative that we have a good understanding of the pathophysiology of the bowel disturbance and the appropriate therapy for our pregnant patients.

Table 2 FDA Classification of Drugs Used for Constipation in Pregnancy

Drug	FDA Class	Comments*
Bulk Laxatives		
Psyllium	None	Considered safe
Methlycellulose	None	Considered safe
Osmotic Agents		
Polyethylene glycol (PEG)	C	Inert, minimally absorbed, limited data, considered safe
Lactulose	B	Limited by bloating
Stimulants		
Senna	C	Safe in pregnancy
Bisacodyl	B	Limited by cramping
Emolients/Lubricants		
Ducosate Sodium	C	Safe, but questionable efficacy
Mineral Oil	X	Decrease absorption of fat soluble vitamins
Castor Oil	X	Premature uterine contractions
Prokinetics		
Tegaserod	B	Limited data in pregnancy, no teratogenic effects in rats; Suspended from the market in March 2007 with restricted availability as of July 2007
Lubiprostone (chloride channel activator)	C	No data in pregnant humans, no teratogenic effects in rabbits or rats

*** See text for References**

Table 3 FDA Classification of Drugs Used for Diarrhea in Pregnancy

Drugs FDA Class	Comments*
Antidiarrheals	
Loperamide	B	Considered safe
Diphenoxylate with atropine	C	Not recommended in pregnancy
Bismuth subsalicylate	D	Decreased birth weight, neonatal hemorrhage, and increased perinatal mortality
Cholestyramine	C	May cause malabsorption of fat soluble vitamins, not recommended

*** See text for References**

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Endoscopy in Pregnancy

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The spectrum of gastrointestinal diseases in the pregnant patient is virtually identical to that in nonpregnant women. The location of symptoms may be atypical but the differential diagnosis remains unchanged. Options for evaluating pregnant patients are limited since barium studies and other radiographic techniques subject the fetus to the risk of radiation. Although studies such as ultrasound are safe and often diagnostic, more invasive therapeutic maneuvers are often necessary. Recently, endoscopy has played a crucial role in the diagnosis and treatment of various disorders in the pregnant patient. A guideline to endoscopy during pregnancy was published by the American Society for Gastrointestinal Endoscopy (ASGE) and is a good resource on this topic.[1]

The first systematic attempt to collect information on the performance of endoscopic procedures during pregnancy was a survey of 3300 members of the American Society for Gastrointestinal Endoscopy (ASGE) by Rustgi, Cooper and Colcher in 1985.[2] The questionnaire asked about the age of the mother and fetus, indication for the procedure, the type of medication used for sedation, complication rate and usefulness of the procedure. Most respondents to the survey had no experience with endoscopy during pregnancy. The information gathered included only 110 procedures, including 73 upper endoscopies, 11 rigid sigmoidoscopies, 13 flexible sigmoidoscopies and 13 colonoscopies. No endoscopic retrograde cholangiopancreatographies (ERCPs) were reported.

This mail survey has since received several criticisms. For one, a mail survey relies on the voluntary reporting of procedure complications and is subject to a reporting bias. Second, the number of endoscopies performed by this group likely underrepresents the true number performed by this group of gastroenterologists. In fact, the number of endoscopies performed on pregnant women by this group is approximately 1% of the number of endoscopies performed on pregnant women by a similar group of physicians in a recent retrospective study.[3] In the past, much of our data concerning endoscopy in pregnancy revolved around this original mail survey. However, within the last 10 years, both single and multicenter studies have been published on endoscopy in pregnancy.

Upper Endoscopy

Upper endoscopy plays an important role in pregnant patients presenting with upper gastrointestinal tract bleeding as well as various gastrointestinal complaints. In the US alone, over 12,000

pregnant women a year will present with complaints that have an indication for upper endoscopy. Other diagnostic modalities, such as barium studies, are seldom chosen because of the radiation risk to the fetus.

In the US alone, over 12,000 pregnant women a year will present with complaints that have an indication for upper endoscopy.

Indications for upper endoscopy have only been addressed in a few large studies. The mailed ASGE survey of 73 endoscopies performed in pregnant patients found that the most common indication for upper endoscopy was nausea and vomiting in 41 of 73 patients (56%). Interestingly, only 10 of the patients with nausea and vomiting had these symptoms as their sole indication. Other indications included epigastric or abdominal pain in 24 (33%), upper gastrointestinal bleeding in 21 (29%) and esophageal symptoms in 6 (8%).[2]

The most common endoscopic finding in these patients was esophagitis in 25 (34%), which was the sole finding in 20 patients. Gastritis was found in 25% of patients and was the only abnormality in 15 patients. Nine ulcers were found of which four were in the duodenum, 3 in the stomach, 1 in the pyloric channel and 1 in the esophagus. Of the patients who presented with upper gastrointestinal bleeding the most common findings were esophagitis in 7, Mallory-Weiss tear in 6 and ulcers of various locations in 6 patients.

A more recent retrospectively study assessed 83 consecutive pregnant patients who underwent upper endoscopy in 8 university hospitals within a 14-year period.[3] Controls included 48 pregnant patients with similar indications for upper endoscopy who did not undergo any endoscopic procedure and 83 nonpregant patients undergoing upper endoscopy for reasons similar to the study patients.

Over the study period, 83 of 121,800 (0.06%) pregnant patients underwent upper endoscopy. The average age of the patients was 28.7 years. Twenty-seven patients were in the first trimester, 33 were in the second trimester and 23 were in the third trimester when the upper endoscopy was performed. The most common indication was gastrointestinal bleeding in 37 patients, followed by nausea and vomiting and abdominal pain. Pregnant patients who underwent endoscopy had more prolonged, severe symptoms than their matched pregnant control patients who did not undergo endoscopy. Upper endoscopy was diagnostic in 65 patients of which the most common finding was esophagitis.

There were no endoscopic complications in any of the study groups. Of the 74 known fetal outcomes, 95% were healthy. There was no significant difference in outcome of the fetuses born to women who had undergone endoscopic procedures and fetuses born to women who had not. In addition, there were no congenital anomalies identified in any study group. There were no significant differences between number of premature deliveries, low birth weight babies and apgar scores between any of the groups. Therefore, upper endoscopy is a relatively safe procedure during pregnant patients and should be performed in pregnant patients who have appropriate indications.

Lower Endoscopy

The ASGE survey of lower endoscopy in pregnancy compiled information on the symptoms and endoscopic findings in 37 patients. The indication for endoscopic evaluation was rectal bleeding in 19, bloody diarrhea in 8, worsening or suspected inflammatory bowel disease in 8 and fecal incontinence in 2 patients. Overall, the finding in 28 patients (76%) was inflammatory bowel disease, while the second most common finding was hemorrhoidal bleeding. Four patients with rectal bleeding had normal examinations, and were presumed to have an upper gastrointestinal source.[2]

Cappell et al conducted a more recent multicenter retrospective study of 140,050 pregnant patients.[3] Overall, 48 (0.03%) of the patients underwent sigmoidoscopy and 8 (0.01%) underwent colonoscopy, while 150 (0.11%) of the patients did not undergo any endoscopic evaluation despite having appropriate indications. Similar to the previous ASGE survey, the most common indication for endoscopic evaluation was hematochezia in 28 patients. The remainder of the patients underwent lower endoscopy for diarrhea (10), abdominal pain (4) and other unspecified reasons (3).

Of the patients who underwent sigmoidoscopy, 27 had a lesion diagnosed by lower endoscopy. The indication with the highest yield was hematochezia. The most common diagnosis was reactivated or newly diagnosed inflammatory bowel disease in 15 patients who underwent sigmoidoscopy for hematochezia. Interestingly, the pregnant patients who underwent lower endoscopy for hematochezia had more severe bleeding than non-pregnant patients with the same indication. There was no difference in diagnostic yield between pregnant and nonpregnant patients who underwent lower endoscopy for similar indications. The rate of congenital defects, premature delivery or adverse events was similar in study and control groups.

Of the 8 patients who underwent colonoscopy, the most common indications were abdominal pain and bloody diarrhea. In 6 patients, a diagnostic lesion was identified although cecal intubation was only achieved in three patients. The most common endoscopic findings were features consistent with inflammatory bowel disease. No explanation was given to explain why these 8 patients underwent colonoscopy instead of sigmoidoscopy. Only 1 unplanned adverse event occurred, which was a miscarriage 4 months after the colonoscopy. The miscarriage was not felt to be related to the endoscopic procedure.

The results of this study suggest that lower endoscopy, specifically sigmoidoscopy, can be safely performed in pregnant patients. Performance of sigmoidoscopy should be limited to patients with appropriate indications such as hematochezia or significant diarrhea or abdominal pain. Elective indications such as change in bowel habits or colorectal cancer screening should be deferred until the postpartum period. Whether colonoscopy should ever be considered the initial procedure of choice in this patient population has not been clearly studied.

ERCP

The incidence of cholelithiasis during pregnancy is as high as 12%.[5] Complications from cholelithiasis including choledocholithiasis, cholangitis and gallstone pancreatitis may require urgent therapeutic intervention. Although, surgical management is possible, potential maternal and fetal complications associated with surgery are a concern. In many cases, ERCP performed by an experienced endoscopist is a safer alternative.

The incidence of cholelithiasis during pregnancy is as high as 12%.

The largest multicenter study addressing ERCP in pregnancy involved 6 sites and included 29 ERCPs performed on 23 patients.[6] All patients in the study had symptomatic biliary tract disease and the indication for the procedure was suspected choledocholithiasis in 19, severe cholestasis in 2 and recurrent idiopathic pancreatitis in 2. Fifteen of the patients were in the first trimester, 8 were in the second trimester and 6 were in the third trimester. Twenty of the 23 patients underwent therapeutic endoscopy. The only complication was pancreatitis, which occurred in 1 patient. Of the 19 known outcomes, 1 spontaneous abortion occurred 3 months after the procedure, 1 infant died 26 hours after birth and 17 healthy infants were born. Neither of the mortalities was believed to be related to the ERCP.

The largest single center study concerning the safety of ERCP in pregnancy included 15 ERCPs performed on 15 patients over a 5-yr period at Brigham and Women's Hospital in Boston, Massachusetts.[7] In this study, 1 patient was in the first trimester, 5 were in the second trimester and nine were in the third trimester. The most common indications for ERCP were gallstone pancreatitis in 6 patients and choledocholithiasis in 5 patients. Seven of the 15 patients underwent either biliary stent placement or sphincterotomy. The only complication was pancreatitis in 1 patient who underwent sphincterotomy and no fetal deaths were reported. Interestingly, this is the first study to measure fetal radiation during ERCP. In this study, the average fetal dose was 310 mrad, which is substantially lower than 10 rads, the dosage at which concern for teratogenicity occurs.

Case reports and small case series concerning ERCP in pregnancy have been published with similar conclusions.[8,9] ERCP can be safely performed by experienced endoscopists and can be considered in patients with choledocholithiasis, cholangitis or gallstone pancreatitis where therapeutic intervention is necessary.

If possible, ERCP should be performed after the first trimester when organogenesis is complete.

Technical modifications include 1) use of lead shielding 2) minimal use of fluoroscopy and spot radiographs 3) use of a guidewire as opposed to injection of contrast. If possible, ERCP should be performed after the first trimester when organogenesis is complete. Interestingly, in the study by Jamidar et al, the majority of ERCPs were done in the first trimester, which is in contrast to the study, by Tham et al. Lastly, it is important that an experienced endoscopist performs the procedure and an obstetric consultation should be obtained prior to the procedure. If these standards are followed, ERCP with therapeutic intervention can be safely performed in the pregnant patient.

Percutaneous Endoscopic Gastrostomy (PEG)

Excessive nausea, vomiting or anorexia can often be seen in the pregnant woman. These symptoms may place both mother and fetus at risk for malnutrition. PEG placement may become a necessary solution in those patients who cannot sustain adequate nutritional intake. No studies have been published to assess the outcome of pregnant patients undergoing PEG; however, case reports have been published.[10,11] Patients with hyperemesis gravidarum, anorexia nervosa and severe esophagitis have had PEG's safely placed during pregnancy. In all cases both mother and baby had favorable outcomes. These rare case reports are encouraging and offer an alternative to TPN in patients who cannot tolerate oral feedings.

Sedation in Pregnancy

In the ASGE survey, 50% of patients (37/73) underwent upper endoscopy without conscious sedation +/- topical xylocaine. In the same survey, 80% of patients (24/30) underwent lower endoscopy without any sedation. Of those who received sedation, the most common medications were meperidine (Demerol) and diazepam (Valium).[2]

There have been various studies evaluating the safety of benzodiazepines in pregnancy. Overall, diazepam has been most extensively studied. Initial evaluation in the 1970's linked diazepam use with an increased incidence of cleft lip and palate in both humans and mice.[12,13] More recently, this link has been questioned and a true cause and effect is doubted. Despite this recent debate, diazepam remains a category D agent and its use during the first trimester is not advised. Midazolam is more frequently used in endoscopy today. Although, no published studies have examined the effect of midazolam in the first and second trimester, no reports of cleft lip or palate have yet been documented. A few studies have shown that midazolam administration during delivery can cause a transient depression

in fetal respiration, which is a temporary effect that reverses upon elimination of the drug.[14,15]

Meperidine has been extensively studied in pregnancy and is considered a category B medication. In one large study, there was no documented teratogenicity in the offspring of 268 mothers who had first trimester exposure to meperidine.[16] However, during delivery those infants that were exposed to demerol experienced transient respiratory depression and diminished cardiac variability, an effect that was temporary and reversible.

There have been various studies evaluating the safety of benzodiazepines in pregnancy. Overall, diazepam has been most extensively studied.

Propofol has also been used in pregnancy for sedation. No controlled studies have been done with propofol to access its long-term effects in pregnancy however; no birth defects have been directly implicated to this medication.[17]

In conclusion, endoscopy is an important modality for evaluating gastrointestinal symptoms during pregnancy. Upper endoscopy is most commonly performed for symptoms of nausea and vomiting and the most frequent endoscopic finding is esophagitis. Lower endoscopy is most commonly performed for hematochezia and findings consistent with inflammatory bowel disease predominate in the pregnant population. Colonoscopy is not well studied in pregnancy and should only be performed in necessary situations where the information can not be obtained from less invasive modalities. Finally, ERCP should only be performed when a need for therapeutic intervention is highly suspected and confirmed by alternative studies.

Endoscopy appears to be safe in pregnancy. Procedures should be performed after the first trimester if possible. Radiation and excessive sedation should be minimized. Lastly, an experienced endoscopist should perform the endoscopic procedure and the guidance of an obstetrician should be obtained in challenging, complicated cases.

Table 1 FDA Classification of Drugs Used for Endoscopy in Pregnancy

Drug	FDA Class	Comments
Sedation and Analgesic Agents		
Fentanyl (Narcotic agonist)	C	Not teratogenic but embryocidal in rats
Meperidine (Opiate analgesic)	B	Not teratogenic; Crosses the placenta slower than morphine
Diazepam (Benzodiazepine)	D	Possibly associated with neonatal cleft lip and palate and other congenital abnormalities.
Midazolam (Benzodiazepine)	D	Transiently depresses neonatal respiration; Similar to diazepam; however, no teratogenic effects found
Propofol (Anesthetic agent)	B	Not teratogenic; Short acting but can cross placenta
Ketamine (Analgesic/Anesthetic)	B	Not teratogenic; Not studied in the 1st trimester
Lidocaine (Local Anesthetic)	B	Not teratogenic; however pregnant women should be instructed not to swallow
Sedation and Analgesic Reversal Agents		
Naloxone (Opioid reversal agent)	B	Should be restricted to women with clinical signs of opioid toxicity
Flumazenil (Benzodiazepine reversal agent)	C	Few studies; Should be restricted to women with clinical signs of benzodiazepine toxicity
Miscellaneous Endoscopic Agents		
Simethicone (Anti-gas agent)	C	Few studies but probably safe
Glucagon (Antispasmodic)	B	Not teratogenic; probably safe

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Heartburn, Nausea, Vomiting During Pregnancy

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Disorders of the gastrointestinal tract are common during pregnancy. Pregnancy has a major effect on motility throughout the gastrointestinal tract, but has little, if any, effect on gastrointestinal secretion or absorption. Motor dysfunction of the gastrointestinal tract is probably responsible for the common GI symptoms observed during pregnancy: heartburn, nausea and vomiting, hyperemesis and constipation. Many studies suggest that changes in motility are related to increased levels of circulating female sex hormones, particularly progesterone. Anecdotal literature has suggested that the enlarging uterus may be another factor; however, actual evidence to support this is limited.

Due to the concern over the use of systemic medications during pregnancy, it is important for physicians to understand the pathogenesis, natural history, and diagnostic and therapeutic options available for treating pregnant patients with gastrointestinal symptoms. Since most pharmaceutical manufacturers have been unable to perform efficacy and safety studies in pregnant women, physicians are often faced with medical disclaimers when trying to decide whether to use a drug to treat pregnant women. These disclaimers place the responsibility for giving pharmaceutical agents primarily on the prescribing physicians. A very helpful textbook in this area is *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*.[1]

Until better teratology testing becomes available, it is appropriate that clinicians and expectant mothers maintain a high level of concern for the use of prescription and over-the- counter drugs during pregnancy. The major risk to the fetus is encountered during the first trimester of pregnancy when organogenesis is maximal. This should be taken into account when prescribing any pharmaceutical agent. Also, drugs which are known to have a sedative property should be discontinued several weeks before term since a sedated newborn might encounter difficulty breathing independently. Rational approaches to treatment of symptoms of upper gastrointestinal dysfunction during pregnancy will be summarized in this monograph.

Heartburn in Pregnancy

Heartburn is a very common problem during pregnancy being reported by 30% to 80% of pregnant women.[2] It is generally a de novo problem that arises during pregnancy, persists throughout gestation, and resolves with delivery. Uncommonly, it may be an exacerbation of pre-existing gastroesophageal reflux disease. The onset of heartburn

during pregnancy may occur during the first, second, or third trimester but usually occurs around 5 months of gestation and is most troublesome during the last trimester. Classic symptoms of heartburn (substernal burning which is typically worse after meals) and acid regurgitation are similar to those seen in non-pregnant patients. Symptoms are usually mild and patients rarely have complications such as erosive esophagitis, strictures or bleeding.[3]

The diagnosis of heartburn during pregnancy is usually made by taking a careful history. The history is usually classical and no further diagnostic tests are required before treatment is begun. Endoscopy is rarely needed but can be done safely, if needed, with standard oxygen monitoring techniques. Meperidine and midazolam are probably safe to administer, particularly after the first trimester, although these drugs are not approved for these indications by the FDA. In atypical cases, ambulatory pH studies may be performed. There is no role for radiographic studies in the evaluation of the pregnant patient with suspected reflux disease.

The etiology of heartburn in pregnancy has been studied extensively. The studies show that lower esophageal sphincter (LES) pressure progressively decreases during pregnancy. Although absolute pressure may not begin to change until after 20 weeks, earlier in pregnancy the sphincter does not respond as well to physiologic challenges such as abdominal compression, protein meal, and provocative challenges such as pentagastrin, methacholine, and edrophonium.[4] Nearly all women have low LES pressure by 36 weeks, which returns to normal in the post-partum period.[5] Human and animal studies show that the decrease in LES pressure is primarily related to the elevated levels of progesterone, although estrogen may be necessary for a priming effect.[6] Increased intraabdominal pressures as a result of the enlarging uterus may further compromise an already weakened LES.

Pregnant women with mild reflux symptoms usually do well with simple lifestyle changes.[2] These modifications may include avoiding eating late at night or before retiring to bed, raising the head of the bed by six inches and avoiding foods and medications that cause heartburn. Non-systemic drug therapy is a logical first step in a pregnant patient not improving with lifestyle modifications (Table 1). Antacids, both magnesium and aluminum containing products, are safe and effective in treating the heartburn of pregnancy. Sodium bicarbonate containing antacids should be avoided since they may lead to metabolic alkalosis and fluid overload in both the fetus and mother. Antacids may also interfere with iron absorption. Sucralfate, like antacids, appears to be safe since virtually none of the drug is absorbed. In a recent randomized study, sucralfate was superior to placebo in the relief of heartburn and regurgitation in pregnant patients.[7]

Sodium bicarbonate containing antacids should be avoided since they may lead to metabolic alkalosis and fluid overload in both the fetus and mother.

In pregnant patients with more severe heartburn refractory to non-systemic therapy, histamine-type II (H-2) receptor antagonists may be used. These drugs cross the placental barrier and are excreted in breast milk. Animal studies do not reveal evidence of teratogenicity. Safety in humans has not been studied in a prospective fashion, but all four available drugs (cimetidine, ranitidine, famotidine, and nizatidine) are FDA category B drugs for the use during pregnancy. There is extensive anecdotal literature with cimetidine and ranitidine suggesting that pregnant women taking these drugs from the first trimester through their entire pregnancy have delivered normal babies.[2] There are much fewer reports about the safety of famotidine and nizatidine in pregnant women. Ranitidine is the only H_2 antagonist which has specifically been studied during pregnancy. In a double blind, placebo controlled, triple crossover study, ranitidine taken once or twice daily was found to be more effective than placebo in

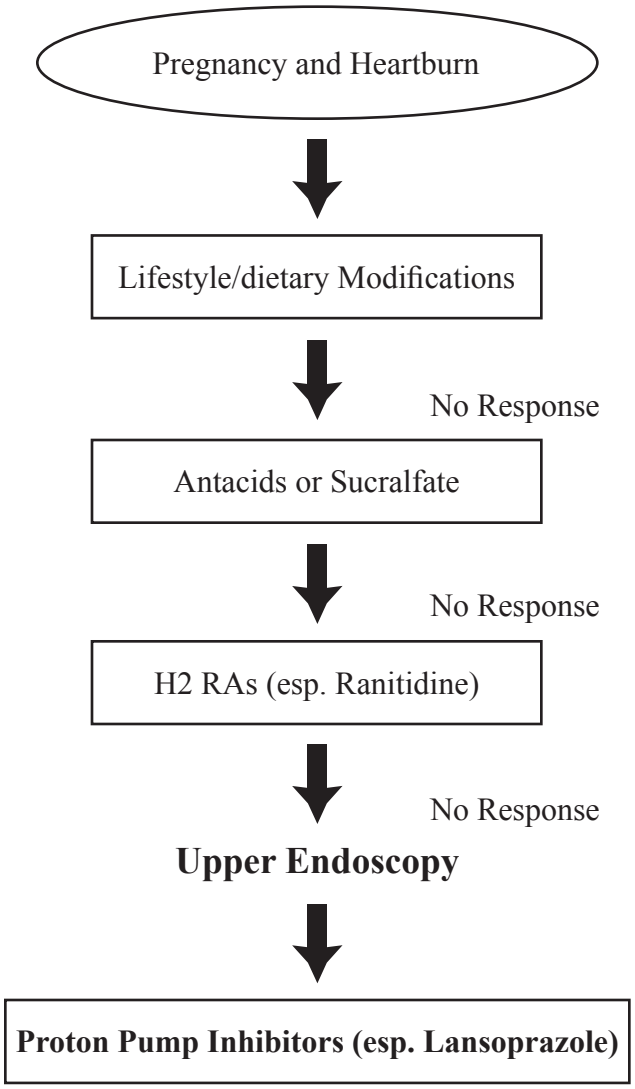
reducing the symptoms of heartburn and acid regurgitation.[8] It is recommended that H_2 antagonists be started at a once a day dose especially after the evening meal when symptoms may be worse. The dose can be increased to twice a day if necessary.

Proton pump inhibitors (PPIs) appear in breast milk and cross the placenta. Omeprazole, the first PPI, has been associated with toxicity in both rabbits and rats when given in high doses causing damage to the embryo, fetal resorption and disruption of the pregnancy.[2] Therefore, the FDA categorizes omeprazole as a class C drug for use during pregnancy. The other PPIs are class B drugs but their use during pregnancy should be reserved for individuals with well defined complicated GERD who are not responding to H_2RAs. The most anecdotal safety data is available for lansoprazole use during pregnancy. Very little is known about human safety during pregnancy with the newer PPIs.

Figure 1 is a suggested algorithm for the treatment of gastroesophageal reflux disease in pregnant patients. Ranitidine is the H_2 antagonist of choice because of efficacy studies and lansoprazole is probably the preferred PPI because of case reports of safety in human pregnancies.[2]

Although gestational GERD symptoms typically resolve with delivery, women may still experience reflux symptoms post-partum that require ongoing medical therapy. Table 2 summarizes the safety of GERD medications during breastfeeding. Antacids and sucralfate are not concentrated in breast milk and are therefore safe during lactation. All H_2RAs are excreted in human breast milk. In 1994, the American Academy of Pediatrics classified cimetidine as compatible with breastfeeding.[9] Ranitidine and famotidine are also safe during breastfeeding, but nizatidine should be avoided based on adverse effects noted in the offsprings of lactating rats receiving this drug.[2] Little is known about PPI excretion in breast milk or infant safety in lactating women. Therefore these medications are not recommended if the mother is breastfeeding.

Figure 1



Aspiration During Pregnancy

Pregnant women requiring anesthesia during labor are at a high risk for aspirating gastric contents. In fact, aspiration during labor is the most frequent cause of obstetrical anesthesia morbidity and mortality, accounting for 50% of deaths.[2] Factors predisposing the obstetrical patient to aspiration are essentially the same as those promoting gastroesophageal reflux with the addition of recumbancy and the administration of anesthetic agents, which may decrease LES pressure and slow gastric emptying.

The prevention of aspiration and aggressive control of acid secretion are very important in women undergoing general anesthesia at the time of delivery. Since the pH of the gastric aspirate is the important factor determining the severity of chemical pneumonitis, the thrust of preventing aspiration pneumonia is aimed at raising the pH of the gastric secretions. Antacids, H_2 antagonists and omeprazole may be effective in this acute setting. Promotility drugs, such as metaclopramide may improve gastric emptying during labor, help prevent aspiration and are not toxic to the fetus.[10]

Nausea and Vomiting During Pregnancy

The single most common gastrointestinal complaint in pregnancy is nausea, occurring in 50% to 90% of women. Additionally, vomiting is an associated problem in 25% to 55% of pregnancies.[11] Vomiting is most common in the first trimester, peaking around 10 to 15 weeks gestation, and subsiding by 20 weeks gestation. Nausea and/or vomiting is often the initial indication that a patient is pregnant. Symptoms usually occur in the early morning ("morning sickness") and improve later in the day. Nausea and vomiting during pregnancy usually is a self-limited problem, disappearing by the fourth month of pregnancy. The prognosis for the mother and infant is excellent. There is no correlation with the complications of pregnancy including diabetes, hypertension, proteinuria, preeclampsia and anemia. In addition, there are no increased risks of low birth weight infants, increased fetal deaths, or increased congenital malformations. There is speculation that nausea and vomiting is a good prognostic sign in pregnancy and that women who experience it are less likely to have miscarriages or undergo premature labor. This symptoms complex is more common in primigravidas, younger women (especially less than 20 years of age), less educated individuals, overweight patients and non-smokers.[12]

The etiology of nausea and vomiting during pregnancy is still unknown. Alterations in gastric motility and gastric tone due to elevated levels of progesterone have been implicated. Animal studies show that progesterone is a potent inhibitor of gastric antral contractions.[13] Premenopausal women have slower gastric emptying rates than men and post-menopausal women suggesting a hormone acting to inhibit gastric emptying.[14] Only limited studies of gastric function have been performed in pregnant women. The few gastric emptying studies, using scintigraphy, have employed liquid meals and show no delay in emptying in the first and second trimesters of pregnancy. However, these studies were not performed with solid meals or when the patients were nauseated. Animal studies show that the there is a delay in gastric emptying during the third trimester of pregnancy. This delayed emptying persists in the immediate post-partum period but returns to normal by four days after delivery, suggesting that this pregnancy-induced gastroparesis is from gastric motor dysfunction and not secondary to the effects of an enlarged uterus. More recently, studies using cutaneous EGG have found an increased prevalence of gastric dysrhythmias such as bradygastria and tachygastria, in patients with nausea.[15] These gastric dysrhythmias correlated with nausea during pregnancy and resolve during the post-partum period.

Animal studies show that pregnancy delays small bowel transit and slows the migrating motor complex.

Another contributing factor to nausea and vomiting may be delayed small bowel transit. Animal studies show that pregnancy delays small bowel transit and slows the migrating motor complex. Using the lactulose breath test, studies in women during the third trimester of pregnancy have confirmed delayed small bowel transit which reverted to normal after completion of the pregnancy.[16]

Psychological factors may also contribute to nausea and vomiting during pregnancy. Several studies have shown that these symptoms are more common in

women with undesired pregnancies or negative relationships with their mothers.[17]

Non-pharmacologic treatment approaches to nausea and vomiting in pregnancy include reassurance, small frequent feedings (6 feedings per day), restricting quantities of undigestible material, decreasing the fat which may delay gastric emptying, and encouraging intake of carbohydrates.

Antiemetics should be used cautiously during pregnancy (Table 3). The potential for embryo toxicity and increased neonatal mortality in animals has been shown for some phenothiazines and their use is probably best avoided. Phenothiazines cross the placenta and are eliminated from fetal and neonatal tissue more slowly than adults, therefore potential toxicity can occur. The use of phenothiazines in pregnancy reveal conflicting data regarding teratogenicity and therefore these drugs have an FDA C classification. Antihistamines such as meclizine (Antivert), dimenhydrinate (Dramamine), and diphenhydramine (Benadryl) have been suggested to be without adverse fetal effects in humans.[11]

Bendectine (doxylamine succinate plus pyridoxine HCl), a previously used agent for nausea and vomiting in pregnancy, has been withdrawn from the market due to suspected teratogenicity. Pyridoxine (vitamin B6) alone may be a therapeutic alternative in patients with severe nausea and vomiting, since a recent study suggests it may be of benefit in relieving symptoms.[18]

Metoclopramide may be an alternative drug for treating nausea and vomiting during pregnancy. Although it crosses the placenta, this drug has not been reported to cause teratogenetic effects in animals. While human experience with metoclopramide in pregnant women is limited, no fetal abnormalities have been reported in several case series.[11]

Alternative medical treatments have been proposed for treating patients with nausea during pregnancy because of their general safety. Such approaches include the use of ginger, transcutaneous nerve stimulation, acupressure and psychotherapy.

Nutritional support is reserved for patients who continue to have severe intractable symptoms and weight loss despite appropriate therapy, placing the mother and the fetus at significant nutritional risk.

Table 1 FDA Classification of Drugs Used for Gastroesophageal Reflux Disease in Pregnancy

Drug	FDA Class	Comments
Antacids		
Aluminum, calcium- or magnesium-containing antacids	None	Most are safe for use during pregnancy and for aspiration prophylaxis during labor because of minimal absorption.
Magnesium trisilicates	None	Avoid long-term, high-dose therapy in pregnancy.
Sodium bicarbonate	None	Not safe for use in pregnancy as causes fluid overload and metabolic alkalosis.
Mucosal Preotectant		
Sucralfate	B	No teratogenicity in animals. Generally regarded as acceptable for human use due to minimal absorption.
H2 Receptor Antagonists		
Cimetidine	B	A prospective, controlled study suggests acceptable for human use.
Ranitidine	B	Same as above. Ranitidine is the only H2RA whose efficacy during pregnancy has been established.
Famotidine	B	Same as cimetidine, but paucity of safety data in humans.
Nizatidine	B	Not recommended during pregnancy. In animals, spontaneous abortion, congenital malformations, low birth weight and fewer live births have been reported. Little data in humans.
Promotility Agents		
Cisapride	C	Embryotoxic and fetotoxic in animals. Recent prospective controlled study in humans suggests acceptable in pregnancy, but drugs recently removed by FDA for fatal cardiac arrhythmias.
Metoclopramide	B	No teratogenic effects in animals or humans reported.
Proton Pump Inhibitors		
Omeprazole	C	Embryotoxic and fetotoxic in animals. Case reports in human suggest similar concerns. Acceptable for use for aspiration prophylaxis in labor.
Lansoprazole	B	No fetal teratogenicity or harm. Limited human pregnancy date. Use is acceptable for aspiration prophylaxis during pregnancy.
Rabeprazole	B	No fetal teratogenicity or harm. Limited human pregnancy date. Use is acceptable for aspiration prophylaxis during pregnancy.
Pantoprazole	B	No fetal teratogenicity or harm. Limited human pregnancy date. Use is acceptable for aspiration prophylaxis during pregnancy.
Esomeprazole	B	No fetal teratogenicity or harm. Limited human pregnancy date. Use is acceptable for aspiration prophylaxis during pregnancy.

Table 2 Safety of GERD Medications During Lactation

Drug	Safety	Comments
Antacids	Yes	Not concentrated in breast milk.
Sucralfate	Yes	Minimal, if any, excretion in breast milk.
H2 Receptor Antagonists		
• Cimetidine	Yes	American Academy of Pediatrics classified as compatible with breast feeding.
• Ranitidine	Yes	Excreted in breast milk in concentrations similar to cimetidine.
• Famotidine	Yes	Lowest concentrations in breast milk of all H2RAs.
• Nizatidine	No	Growth depression in pups of lactating rats.
Proton Pump Inhibitors	No	Little known of excretion in breast milk. Growth depression in pups of lactating rats receiving omeprazole and rabeprazole.

Table 3 FDA Classifications of Drugs Used for Treatment of Nausea and Vomiting of Pregnancy

Generic Drug Name	Trade Drug Name	FDA Class	Comments
Pyridoxine	Vitamin B6	A	Safe and effective in humans. Component of Bendectin.
Doxylamine	Unisom®	B	Component of Bendectin. Available over the counter.
Cyclizine	Marezine®	B	
Meclizine	Antivert®	B	Conflicting reports on safety and efficacy.
Dimenhydrinate	Dramamine®	B	
Diphenhydramine	Benadryl®	B	
Metoclopramine	Reglan®	B	Safe and effective.
Scopolamine		C	Congenital malformation in animals.
Promethazine	Phenergan®	C	
Prochlorperazine	Compazine®	C	Clinically efficacious, but conflicting safety reports.
Chlorpromazine	Thorazine®	C	
Trimethobenzamide	Tigan®	C	
Droperidol	Inapsine®	C	Combined with Benadryl®, effective without adverse outcomes.
Ondansetron	Zofran®	C	Conflicting data on safety.

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Hyperemesis Gravidarum and Nutritional Support

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"Morning sickness" is an event reportedly affecting 50% to 90% of all pregnant women. Severe vomiting, to the point of affecting the patient's nutritional status, also known as *hyperemesis gravidarum,* only occurs in approximately 2% of all cases. Diagnosis is made when the patient begins to lose weight, secondary to both dehydration and malnutrition. At this point, hospitalization may become necessary to correct the ongoing metabolic abnormalities including:

- Hypokalemia
- Acid/base disturbances
- Metabolic ketosis

Initial treatment should consist of making the patient NPO, IV hydration, and correction of any ongoing electrolytes or acid/base abnormalities. Sedation and/or antiemetics may be considered if making the patient NPO does not stop the intractable vomiting. With conservative treatment, consisting mostly of hydration while the patient is NPO, in the majority of cases this condition begins to resolve, and refeeding may be started within 24 to 48 hours after the vomiting ceases. When it does not, parenteral nutrition may be considered.

Initial reports on the use of parenteral nutrition during pregnancy date to the early 1970's, with patients who had been on home parenteral nutrition for other reasons, such as Crohn's disease and who subsequently became pregnant. The success of these early cases demonstrated the efficacy of parenteral nutrition in maintaining a normal pregnancy and with the birth babies without any significant developmental abnormalities. Since that time, many reports have appeared in the literature demonstrating the safety and efficacy of parenteral nutrition in the treatment of refractory hyperemesis.

Liver Abnormalities in Hyperemesis

Liver disease in pregnancy includes liver disorders present at the time of conception, those that occur coincidentally but not exclusively in pregnancy, and those that occur only in pregnancy, Hyperemesis falls into this latter category. Abnormal serum aminotranferase levels occur in about 50% of patients who develop clinically significant hyperemesis. Although this elevation is usually in the 100% to 300% range, larger elevations (ranging from 7 – 22 times the upper limits of normal) may also be seen. In a retrospective analysis of 80 patients with hyperemesis, Morali, et al demon-

strated abnormal AST and ALT levels (approximately 4 times the normal level) in 16% of cases. The mean gestational age of the group with liver function abnormalities was 14 weeks +/- 10 days versus 6.3 weeks +/- 14.7 days in the group with normal liver function. An additional study by Wallstedt, et al noted that 50% of patients hospitalized with hyperemesis exhibited abnormal liver function. Liver biopsies done in patients with abnormal LFTs have included the following findings, central zonal vacuolization with cellular dropout, ballooning of hepatocytes, and hepatic necrosis. Of interest no evidence of nonspecific hepatitis was noted. The abnormalities noted above all resolved concurrently with resolution of the hyperemesis or termination of the pregnancy.

Treatment of Hyperemesis

Once the patient has been stabilized by rehydration, initial treatment should be aimed at attempts to resume enteral feeding. These should start with water by mouth, slowly advancing through clear liquids to a bland diet of high-starch, low-fat foods such as crackers and plain baked potatoes. If these are well tolerated the patient may be slowly advanced to a regular diet. Relapse is common on the first feeding attempt, and should be treated by again placing the patient NPO and, when the nausea abates, attempting refeeding as noted above.

Herbs useful in the treatment of nausea in pregnancy include ginger, raspberry leaf, peppermint or spearmint.

Alternative medical treatment options are available and include herbal remedies. Herbs useful in the treatment of nausea in pregnancy include ginger, raspberry leaf, peppermint or spearmint. All of these can be used as a tea; however, mint teas as well raspberry leaves have a history of being an aborfacient and should be used with caution and only in very small doses. Their use if contraindicated in patients with a history of miscarriage. Ginger has been reported in the Chinese literature to be potentially mutagenic/abortafacient but only in doses far exceeding normal dietary intake (20 to 26+ gms/day). There is no contraindication to the use of ginger tea/ale in pregnancy; however, dried ginger root is contraindicated since the active components are greatly concentrated in the dried root. Animal data suggest that ginger's effect is due to a direct effect on the stomach and not any central effect. Many studies have found ginger preparations to be superior to placebo the treatment of hyperemesis and in doses limited to 1 gm/day of dried root there was no increase in prenatal morbidity or mortality.

If refeeding by mouth is unsuccessful, reports in the literature now indicate that a trial of slow, isotonic, enteric feedings via a naso-enteric tube may be successful in establishing adequate caloric intake as well as maintaining hydrational status. This technique has been successful both in the hospitalized and ambulatory, outpatient. These feedings should be started slowly and increased, as tolerated, with the goal of supplying all necessary nutrients through a combination of enteral and, if necessary, parenteral feedings. Once the nausea has decreased to a level that liquids are tolerated, oral feedings, as outlined above, should be started. Enteral feedings should be stopped one half to one hour prior to each attempt at oral refeeding to minimize any gastric distention and reduce the risk of vomiting and aspiration.

The use of percutaneous gastrostomy or jejunostomy for feeding has also been reported in isolated case studies but there have been no prospective, randomized trials to document its usefulness or safety.

When all attempts at enteral feedings are unsuccessful, parenteral nutrition should be started to avoid possible fetal complication secondary to severe malnutrition. The successful use of both central and peripheral total parenteral nutrition have been reported although peripheral nutrition has been reported used in in-patients only.

Protein/Calorie Requirements

Caloric and protein requirements are equivalent for the pregnant patient whether the patient is fed enteraly, parenteraly or by a combination of both methods. The normal caloric requirements of pregnancy are calculated as either 1.3 times the estimated basal energy expenditure (BEE) or as the non-pregnant requirement plus and additional 300 kcals/day. Protein requirements, in a patient with normal hepatic and renal function, are estimated to be approximately 1.3 gms/kg/day. These values are based on the calorie/protein needs required to produce the normal weight gains of pregnancy and must be adjusted for a patient who started out either markedly obese or malnourished. No clear consensus exists as to the correct parenteral amino acid solution to use during pregnancy, however, most institution use an adult, balanced amino acid formulation as opposed to a pediatric one.

Carbohydrate Requirements

Carbohydrate requirements are the same for pregnant and non-pregnant women. However, care should be taken to avoid persistent hyperglycemia during pregnancy. Blood glucose levels in the 150 to 190 mg/dL range, which would be well tolerated in the non-pregnant woman, run the theoretical risk of producing the same problems, in mother and fetus, as the persistent hyperglycemia of gestational diabetes. It is normally advisable to maintain blood glucose levels in the 90 to 120 mg/dL range. In patients who are maintained on parenteral nutrition past the 20th week of pregnancy, particularly in those with a previous history of gestational diabetes, blood sugars must be closely monitored for the development of gestational diabetes associated with the diabetic effects of placental lactogen.

Fat Requirements

The fetus for normal neurological development requires essential fatty acids. It has been clearly demonstrated, in premature infants, that essential fatty acid deficiency produces diffuse neurological defects, which cannot be later corrected by the addition of sufficient fatty acids to the diet. In many institutions it is the policy to give daily lipids to pregnant patients, not only to supply needed calories but the required essential fatty acids. Concerns have been raised in the past as to the possible effect of fat infusion on promoting premature labor by the increase in uterine irritability, through prostaglandin mediation, producing deleterious fetal effects via placental fat emboli impairing placental function, or by correlation with the know effects of fat infusions on the premature infant.

It has been clearly demonstrated, in premature infants, that essential fatty acid deficiency produces diffuse neurological defects, which cannot be later corrected by the addition of sufficient fatty acids to the diet.

Most reports of increased uterine irritability have been in patients who received infusions of 500 ccs or more 10% or 20% lipid emulsion over 8 to 12 hours. In our experience, fat infusions, given over 24 hours as part of a total nutrient admixture, have not produced any increase in premature labor or uterine contractions. The only prospective study of possible placental effects of lipids showed no evidence of fatty infiltration or fat emboli in patients who received intravenous fat infusions prior to delivery.

Vitamins and Minerals

Oral vitamin and mineral requirements, well established for a normal pregnancy, must be adjusted when parenteral nutrition is used to compensate for bypassing the gastrointestinal tract. In particular, many vitamin and mineral requirements, such as vitamin D and calcium but be decreased to prevent fetal overload, while others must be supplemented since some injectable vitamin preparations supply inadequate amounts. In particular it is important that all pregnant women

receive at least 400 mcgs of folic acid per day to help prevent neural tube defects.

Venous Access

Most of the reported complications of TPN use in hyperemesis have been related to the placement and use of a central venous catheter. These have included complications common to all patients including, bacteremia, sepsis, pericardial tamponade and subclavian vein thrombosis. While there is a know increase in hypercoagulability in pregnancy, the few reports of TPN use in pregnancy do not reveal an increased rate of central line occlusion or venous thrombosis.

Monitoring of Pregnant Patients on TPN

All pregnant women requiring parenteral nutrition should be closely monitored to prevent any possible complications. Biweekly laboratory evaluation including a basic electrolyte panel should be performed and an expanded panel including liver function and coagulation studies at least every other week once the patient is stable. Particular attention must be paid to any sudden increases in weight or blood sugar and the TPN formulation adjusted accordingly. As in any pregnant woman, glucose tolerance should be reassessed at 20 weeks to watch for the possible development of gestational diabetes. If this occurs, it is treated by lowering of carbohydrate intake, if possible and the administration of parenteral insulin as required. Nitrogen balance studies and possible fetal sonography may be useful in monitoring the nutritional status of the mother and fetus. Close communication between the nutrition support team and obstetrician should avoid any potential problems.

Table 1 Parenteral Nutrient Requirements in Pregnancy

Nutrient	Parenteral Nutrition
Calories	Normal, estimated BEE plus 300 kcals/day
Protein	~ 1.3 gms/kg*day
Carbohydrates	3 – 7 gms/kg*day
Fat	Less than 1 gm/kg*day infused over 24 hrs (N.B. at least 4% of calories should come from EFA's to prevent deficiency)
Minerals and Trace Elements	
Calcium	250 mg
Phosphorus	30-45 mM
Magnesium	10 – 15 mg
Zinc	2.5 - 3 mg
Copper	0.5 – 1.5 mg
Manganese	.15 - .8 mg
Iodine	50 mcg
Iron	3 – 6 mg
Chromium	10 – 15 mcg
Selenium	20 – 40 mcg
Vitamins	
A	800 mcg retinol equivalent
D	200 IU
E	10 mg
K	65 mcg mcg*
C	70 mg
Thiamin	1.4 mg
Riboflavin	1.4 mg
Niacin	18 mg
B6	1.9 mg
Pantothenic acid	6 mg
B12	2.6 mcg
Folic acid	600 mcg*
Biotin	30 mcg

Adapted from Parenteral Nutrition, Rombeau and Caldwell (ed), WB Saunders, 1993 Philadelphia

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Liver Diseases in Pregnancy

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During pregnancy the human body undergoes several changes in the process of its adaptation to the growing fetus. Although these changes are physiological, there is potential for morbidity and mortality to both mother and fetus. For instance, the liver could be the target of diseases specific to the pregnancy such as intrahepatic cholestasis of pregnancy and acute fatty liver of pregnancy, and there are no available means by which to predict with certainty how and when such illnesses may occur. However, when appropriately diagnosed and managed, the outcome may be favorable and the liver disease could resolve without any chronic consequences. In addition, morbidity is more likely in the presence of a preexisting liver disease as in autoimmune hepatitis or when a new onset liver disease occurs during pregnancy as in herpes simplex hepatitis.

A complete understanding of the physiological changes that affect pregnancy and of the different liver diseases that occur during pregnancy is essential for early recognition and management of pregnancy-associated liver disorders.

In this chapter we discuss physiological changes of pregnancy, liver disorders that are exclusive or unique to pregnancy, liver diseases that may occur during pregnancy or intercurrent liver diseases in pregnancy, and changes that occur when a woman with a preexisting liver disease becomes pregnant.

Physiological Changes of Pregnancy (Table 1)

Several physiologic changes occur during pregnancy and could pose difficulty in evaluating hepatobiliary function because they may be misinterpreted as pathological.

For example, the blood volume expands during pregnancy due to retention of salt and water. This induces a state of hemodilution, an increase in cardiac output, and a reduction in systemic vascular resistance and systemic blood pressure. These changes peak during the second trimester then plateau until delivery. Consequently serum levels of uric acid, albumin, total protein and hematocrit are decreased. On the other hand, serum alkaline phosphatase levels may be elevated three to four fold due to placental production while serum values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), bilirubin and prothrombin time remain in the normal range.

Female sex hormones affect the hepatobiliary system in several ways some of which could include intrahepatic cholestasis (by impairing activity of bile acid transporters at the canalicular and basolateral cellular membrane level), tumor formation (adenoma) and growth of hemangioma, peliosis hepatis, gallbladder disease and hepatic vein thrombosis.

Estrogens promote biliary cholesterol saturation and inhibit the hepatic synthesis of chenodeoxycholic acid, while progesterone decreases the contractility of the gallbladder and contributes to lithogenicity resulting in sludge and gallstone formation.

Pregnant women who have an inherited thrombophilia such as factor Leiden are at great risk for hepatic and portal vein thrombosis.

The concentration of clotting factors is affected in pregnancy. There is a mild decrease in the concentration of antithrombin III, protein C and protein S, an increase in factors 1 to 10 and factor 12, and an increase in the concentration of fibrinogen favoring a hypercoagulable state. Pregnant women who have an inherited thrombophilia such as factor Leiden are at great risk for hepatic and portal vein thrombosis. Platelet levels are usually within normal limits or mildly decreased during pregnancy.

Healthy pregnancy is associated with suppression of a variety of humoral and immune mediated immunological functions in order to accommodate the semiallogenic fetus. T helper Th1 cells and T cytotoxic Tc 1 cells are suppressed, and there is up-regulation of T helper 2 cells. Moreover, polymorphonuclear leucocyte chemotaxis and adherence functions are depressed.[1] This may account in part for the improvement observed in some women with autoimmune hepatitis and the increased susceptibility to certain infections in pregnancy.

The serum concentration of LDL- cholesterol, HDL-cholesterol, lipoproteins, apolipoprotein and leptin increase during pregnancy. This allows for storage of fat and supply of energy to the growing fetus. With progression of the pregnancy, fetal nutritional demands increase and maternal fat storage decreases. Consequently, serum concentrations of lipid components start to decrease toward the end of pregnancy and quickly return to normal after delivery particularly when the mother is breastfeeding.

Due to volume expansion and glomerular hyperfiltration, serum levels of urea nitrogen and creatinine drop. Creatinine concentration may reach a nadir of 0.4 mg/dL thus values of 0.9 mg/dL highly suggest kidney disease and should prompt further evaluation.

The size of the liver is generally unchanged during normal pregnancy and liver histology remains essentially normal throughout gestation.

Imaging in Pregnancy

When diagnostic imaging is needed to work up liver tests abnormalities, ultrasound US of the liver becomes the modality of choice due to its safety to the fetus.

Magnetic Resonance Imaging (MRI) may also be used in pregnant women if US or other non-ionizing forms of diagnostic imaging are not sufficient or if the examination provides important information that would otherwise require exposure to ionizing radiation (eg, fluoroscopy, computed tomography). These were the basic recommendations of the Safety Committee of the Society for Magnetic Resonance Imaging that were subsequently adopted by the American College of Radiology and The American College of Obstetricians and Gynecologists. These recommendations are considered to be the standard of care with respect to the use of MR procedures in pregnant patients. [2]

CT scan involves radiation to the fetus while MRI safety in pregnancy makes it a better alternative study.

Endoscopic retrograde cholangio-pancreatography (ERCP) also involves radiation to the fetus but can be safely used when appropriately indicated and when safety measures can be followed.[3] (Refer to section on Endoscopy in Pregnancy)

Safety of Drugs in Pregnancy[4] (Table 2)

The choice of drugs during pregnancy should be based on the United States Food and Drug Administration classification (FDA) for drugs and fetal risk. The US FDA classifies all drugs into five categories based on the level of teratogenicity in animals and human studies. Not all drugs have been tested in pregnant women, thus absolute safety is not guaranteed for any medication. General principles of medication use during pregnancy including endoscopic medications involve use of minimal effective dose, avoidance of unnecessary medications, and preferable use of Food and Drug Administration category B medications. The mother should be informed of the teratogenic risks and benefits of medications to be used, and of the consequences of withholding treatment. Such discussions should occur in liaison with her treating obstetrician and should be carefully documented.[5]

Liver Disorders Unique to Pregnancy (Table 3)

Hepatic Involvement in Hyperemesis Gravidarum:

Hyperemesis gravidarum refers to intractable and severe nausea and vomiting during pregnancy associated with dehydration, ketosis and weight loss at which time Intravenous hydration is required. The weight loss usually exceeds 5% of pre-pregnancy body weight. Hyperemesis gravidarum occurs in less than 2% of primiparous pregnancies during the first trimester and commonly resolves by the 20th week of gestation without untoward effects on either mother or baby.

Although not a primary liver disorder, liver dysfunction and jaundice are common in patients with hyperemesis gravidarum. Elevated values of ALT and AST occur in up to 50% of patients with values typically between 2 and 3 times normal limits and seldom exceeding 200 U/L.[6] Mild hyperbilirubinemia may also be present.

Hepatic complications of hyperemesis gravidarum are mild and often resolve without hepatic consequences.

Hepatic complications of hyperemesis gravidarum are mild and often resolve without hepatic consequences. Prognosis is excellent for both mother and baby. Liver biopsy is not necessary and will likely show normal liver or nonspecific hepatitis in the more severe cases of malnutrition. Treatment is focused on controlling vomiting and preventing dehydration and starvation at which time hepatic abnormalities rapidly improve. Treatment requires IV hydration and may necessitate enteral and parenteral feedings to avoid severe malnutrition. Recurrences are likely in subsequent pregnancies.

Acute Fatty Liver of Pregnancy (AFLP):

AFLP is a potentially fatal condition of the third trimester with an estimated incidence of one case per 13,000 pregnancies. AFLD may affect pregnant women of any age but is most commonly reported in primiparous women over the age of thirty and in women with multiple fetal gestations and/or carrying a male fetus.[7]

Initial symptoms are typically nonspecific and include nausea, vomiting, epigastric or right upper quadrant abdominal pain mimicking biliary tract disease or acute pancreatitis. Jaundice is a late sign and typically occurs 1-2 weeks after the onset of symptoms. Pruritus is uncommon and should suggest an alternative diagnosis such as intrahepatic cholestasis of pregnancy.

Moderate elevations of liver enzymes (ALT, AST) and bilirubin, and elevation of serum creatinine and uric acid are common. The modest abnormality of aminotransferases can be misleading and may not accurately reflect the degree of liver injury. Frank liver failure associated with hepatic encephalopathy, jaundice, renal failure, hypoglycemia and coagulopathy, may present as early as 2 weeks after the onset of symptoms.

A state of disseminated intravascular coagulation is commonly seen in patients with AFLP. Prothrombin time and partial thromboplastin time are prolonged. Fibrinogen level is decreased and anti-thrombin III activity is profoundly decreased in patients with AFLP.[7] These abnormalities will resolve promptly after delivery and treatment with anticoagulation factors is not necessary unless the patient is bleeding or surgery is anticipated. Features of preeclampsia (hypertension $\geq$ 140/90 after 20 weeks of gestation and proteinuria $\geq$ 300 mg /24 hours)[8] are common in patients with AFLD occurring in over 50% of cases.

Delivery of the fetus should be considered as soon as the diagnosis of AFLP is made and before frank liver failure ensues at which time liver transplantation becomes necessary.

It is proposed that the underlying mechanism of AFLP consists of a fatty acid oxidation disorder.

The etiology and pathogenesis of AFLP are not clearly understood. It is proposed that the underlying mechanism of AFLP consists of a fatty acid oxidation disorder. Fatty Acid Oxidation Disorders are autosomal recessive disorders involved in the transport and oxidation of fatty acids in the mitochondrion. Byproducts of fatty acid oxidation provide the energy necessary for the growth of the fetus. Defects in fatty acid oxidation lead to the accumulation of triglycerides in the hepatocyte and the formation of steatosis.

AFLP occurs in women who have fatty acid oxidation disorder of which the most common is the inherited deficiency of the enzyme LCHAD or Long Chain 3-hydroxylacyl-coA dehydrogenase. This enzyme is involved in the final step of beta-oxidation of fatty acids in the mitochondrion of the hepatocyte. Deficiency of this enzyme is associated with the accumulation of fatty acids in the cell with a resultant lack of energy fuel necessary for the growth of the fetus. In the last trimester of pregnancy, the metabolic demands of the fetus increase, and when affected mothers with one defective allele for LCHAD are pregnant with an affected baby (with 2 alleles, one allele inherited from each parent), acute fatty liver of pregnancy will ensue.[9] While not proven, additional triggering factors such as drugs (aspirin and non-steroidal medications) may further impair beta-oxidation.

Liver biopsy is not necessary when the clinical diagnosis is clear. Centrilobular microvesicular fatty infiltration of hepatocytes is the typical histopathological feature of AFLP.

Delivery of the fetus will unload the excess flux of fatty acids to the liver leading to rapid recovery. Recurrence of AFLP is estimated to occur in about 25% of subsequent pregnancies due to the autosomal recessive nature of LCHAD. However the exact rate of recurrence is hard to estimate and the decision to proceed with another pregnancy should be carefully discussed with the patient and her managing physicians because of the devastating nature of AFLD.

Infants homozygous for LCHAD and born to heterozygous mothers suffer from failure to thrive, hepatic failure, cardiomayopathy, microvesicular steatosis, hypoglycemia and death.

It is recommended that in all cases of AFLP, both baby and mother be tested for the common LCHAD mutation along with screening the babies for abnormal organic acids, acyl CoAs and acyl carnitines and other

disorders of FAO. (See specific recommendation below).

Imaging studies including ultrasound and magnetic resonance imaging (MRI) often show the presence of fatty liver, although the absence of fatty infiltration of the liver by radiological imaging does not exclude the diagnosis of AFLP.

Prompt assessment and management of patients with possible AFLP is essential. The following would be some specific suggestions:

A) Although there is no specific therapy for AFLP, prompt termination of pregnancy as soon as the diagnosis is made should be considered due to the high fatality of this disorder for both the mother (5%-27%) and her unborn infant (8%-32%). Overall survival is expected to improve with prompt termination of pregnancy. After delivery, liver enzymes rapidly improve and abnormal liver histology resolves over several weeks. Chronic liver disease does not result from AFLD.

B) It is recommended that in all cases of AFLP, both baby and mother be tested for the common LCHAD mutation. Babies should also be screened for abnormal organic acids, acyl CoAs and acyl carnitines to exclude other metabolic disorders that may trigger AFLP.

C) Babies with the LCHAD should adhere to a diet that provides age appropriate proteins, multivitamin, medium chain triglycerides that constitutes 20% of total energy requirements, and limits the long chain fatty acids to less than 10% of total energy requirement.[10]

D) Liver transplantation has been successfully undertaken in women with liver failure due to AFLP suggesting that prompt referral to a transplant center should be initiated as soon as the diagnosis is made.

E) AFLP appears to be sporadic in patients without a documented genetic mutation of fatty acid oxidation, although recurrence during a follow-up pregnancy has been reported.

Intrahepatic Cholestasis of Pregnancy (IHCP):

IHCP is a cholestatic disorder that is relatively benign for the mother. It occurs during the third trimester of pregnancy and rarely presents before 26 weeks of gestation. It disappears soon after delivery and often recurs with subsequent pregnancies. Although it is not typically life-threatening, IHCP may be associated with visible jaundice and significant pruritus which differentiates it from AFLP.

Although it is not typically life-threatening, IHCP may be associated with visible jaundice and significant pruritus which differentiates it from AFLP.

IHCP is believed to be one of the most common causes of jaundice during pregnancy. The incidence varies depending on the geographic areas. It is more frequent in Scandinavian countries and in Chile reaching up to 6.5 percent of all pregnancies. In North America, Asia and Australia the incidence is reported to be as little as 1 to 2 per 10,000 pregnancies. IHCP occurs more commonly in multiparous women with multiple fetal gestations and in those with a personal or a family history of IHCP.

The etiology and pathogenesis of IHCP remain unknown and could be multifactorial. There seems to be a genetic mutation in the MDR3 canalicular transporter of phospholipids involved in bile secretion which leads to the accumulation of bile acids. The rise in the concentration of estrogens and progesterons during pregnancy may further impair the function of the transporters leading to IHCP.[11]

Pruritus is the main feature of IHCP and is present in all patients. Pruritus can be disabling and most commonly involves the hands and feet although it can be generalized. Jaundice occurs 2-4 weeks after the onset of pruritus in 10%-25% of affected women. Other symptoms include nausea, vomiting and abdominal pain.

Laboratory assessment shows a marked elevation of alkaline phosphatase and serum bile acids. Serum transaminases are typically mildly elevated. Total and direct bilirubin levels are increased in up to one-third of patients but total bilirubin levels are rarely greater than 5 mg/dl. Interestingly serum level of Gamma Glutamyl Transferase GGT is normal or slightly elevated.

Liver biopsy is usually not needed to make the diagnosis of IHCP. Typical histologic findings include centrilobular cholestasis, canaliculi containing bile plugs, and bile pigment in hepatocytes. Inflammation and necrosis are not usually observed in the portal tracts.

Therapy of IHCP is aimed at ameliorating the pruritus in the mother and improving fetal outcome. Cholestyramine has been used in the past for the management of pruritus but was found to worsen fetal outcome by increasing the risk of fetal hemorrhage due to vitamin K deficiency and should be avoided.

Fetal hemorrhage has been reported in association with IHCP due to vitamin K deficiency.

Fetal hemorrhage has been reported in association with IHCP due to vitamin K deficiency. Thus all patients with IHCP with prolonged cholestasis should be monitored with prothrombin time and vitamin K deficiency corrected.

Ursodeoxycholic acid (UDCA) (FDA Category B) has been tested in randomized clinical trials and is considered the treatment of choice in pregnant women with IHCP due to its documented efficacy and safety to the fetus after the first trimester. UDCA is a hydrophilic bile acid that modifies the bile acid pool composition in replacing toxic bile acids. It decreases the passage of maternal bile acids to the fetal placental unit and improves the function of bile acid transporters. When given to women with severe symptoms of IHCP, at 1 gram divided into three daily doses, significant relief from pruritus and marked reduction of serum bile acids occured after one week of therapy. Liver test abnormalities were also noted to be improved without maternal or fetal toxicity.[12]

Maternal outcome is favorable in IHCP although poor weight gain due to anorexia and vomiting can occur. The pruritus disappears within 48 hours of delivery in most cases. Biochemical abnormalities and liver histology resolve after several weeks. Long-term follow-up studies have shown that women with IHCP are at increased risk for gallstone related hepatobiliary disorders.[13]

Fetal outcome is less benign however, with increased risk of premature delivery, neonatal death (stillbirth), and meconium staining of amniotic fluid. Fetal mortality in the absence of therapy averages 11-20%. The mechanism of fetal complications associated with IHCP is not known although it has been proposed that elevated serum bile acids may stimulate uterine muscle contractions and may lead to fetal anoxia. Because of the potential for serious fetal complications in pregnant women with IHCP, it is recommended that aggressive monitoring for fetal distress during the third trimester should be done. The role of UDCA on fetal outcome is not clearly established, and while elevated serum bile acid levels $\geq$ 40 micromol/L have been reported in association with more severe disease and fetal distress, babies should be delivered promptly after lung maturity regardless of bile acid levels to avoid fetal compromise.

Hemolysis, Elevated Liver Enzymes, and Low Platelets Syndrome (HELLP Syndrome):

The HELLP syndrome complicates 0.1% of all pregnancies and up to 10% of the pregnancies that are associated with pre-eclampsia.

Diagnostic criteria for the HELLP syndrome include hemolysis (abnormal red blood cell morphology based on examination of the peripheral smear, and/or elevated lactic dehydrogenase, elevated indirect bilirubin, drop in hemoglobin and low serum haptoglobin levels), in association with moderate elevation of serum transaminases (ALT and AST), and thrombocytopenia (platelets count less than 100,000).[14]

The HELLP syndrome presents clinically during the second half of pregnancy, usually in the third trimester. However, up to 30% of patients are diagnosed with HELLP syndrome after delivery.[15] Early clinical presentation consists of nonspecific gastrointestinal symptoms such as nausea and vomiting. Epigastric and right upper quadrant abdominal pain are common affecting 65% of patients with HELLP syndrome, with some women exhibiting significant hepatic tenderness on physical examination. In rare cases (8% to 10%) ascites may be present.

Characteristic laboratory abnormalities include moderately elevated values of serum aminotransferases (AST and ALT levels of 200-700 IU/L) with AST reaching levels as high as 6000 IU/L. In most instances, patients are not jaundiced and hepatic synthetic functions are preserved. Mild elevation of serum bilirubin may reflect hemolysis. Mild renal dysfunction (elevated blood urea nitrogen and creatinine) is universal in these patients. In rare instances HELLP syndrome may be severe and associated with disseminated intravascular coagulation (DIC).

Urgent delivery is the only definitive treatment for HELLP syndrome and should be undertaken as soon as recognized given the high maternal and fetal morbidity. The severity of HELLP syndrome may worsen during the 24 hours after delivery but rapid resolution is expected. Delivery should take place within 24 hours of the diagnosis of HELLP syndrome or after a few days of high-dose steroid therapy if diagnosis is made before 34 weeks of gestation to produce lung maturity of the fetus. High-dose steroid therapy may also have some maternal benefit.[16]

Maternal mobidity from HELLP is frequent especially in severe cases where platelet counts are below 50,000 mm^3 or with DIC. Hypertension, ecclampsia (features of preecclampsia with seizures), pulmonary edema and acute renal failure may occur. Maternal mortality ranges from 0% to 3.5%. Long-term outcome after resolution of HELLP syndrome is excellent and recurrences are reported in the order of 5% to 27%.[17]

HELLP syndrome is even more dangerous to the fetus than it is to the mother.

HELLP syndrome is even more dangerous to the fetus than it is to the mother. It is associated with a high rate of intrauterine growth retardation and prematurity (35%). Neonatal death rates of 6% to 37% have been reported and are thought to be related to abruptio placentae and fetal hypoxia.

Acute hepatic subcapsular hemorrhage with hepatic rupture is a rare but devastating syndrome that is presumed to be a complication of pre-eclampsia and HELLP syndrome often resulting in death of both mother and fetus (50%-70%). The frequency of this syndrome has been estimated to be between 1% and 2% of patients with pre-eclampsia.[18] In severe cases, patients present acutely with shock and hemoperitoneum. Some patients report episodes of right upper quadrant pain during the few days prior to having severe symptoms. Survival is based on findings at the time of presentation. Patients with a contained hematoma may have resolution with medical support while survival of an untreated hepatic rupture has not been

reported. Management consists for the most part in surgical repair although angiographic hepatic arterial embolization and liver transplantation were successful in case reports.

Intercurrent Liver Diseases in Pregnancy

Viral Hepatitis:

Acute viral hepatits is the most common cause of jaundice in pregnancy averaging 1-2/1000. The outcome is usually benign except in viral hepatitis E and Herpes Simplex hepatitis. While infections with viral hepatitides in pregnancy may not always affect the outcome of the pregnancy, transmission to the newborn is always a concern as will be discussed below. Diagnosis of viral hepatitis in pregnancy is not different from the diagnosis in the non pregnant state and will not be discussed in full detail in this chapter.

Hepatitis A virus infection (HAV)

Acute hepatitis A in pregnancy is self limited and maternal fetal transmission is very rare and only reported in a few cases.[19] Transmission may occur if delivery takes place during the incubation period because of viral shedding and contamination during vaginal delivery. The risk of premature labor may be increased in women who are seriously ill during the third trimester. Treatment is supportive. IgG antibodies to HAV infection are passively transmitted to the newborn, which may lead to protection of the infant in the first several months of life. The Advisory Committee on Immunization Practices recommends vaccination of all children starting at the age of 12 months.[20] The hepatitis A vaccine is produced from inactivated HA virus. There is no evidence of risk to the fetus, the mother or the infant from vaccinating pregnant or breastfeeding mothers with inactivated virus. Pregnant women traveling to highly endemic areas for Hepatitis A may receive Hepatitis A vaccine and hepatitis A immunoglobulin for urgent prophylaxis.

Hepatitis B virus infection (HBV)

If acute hepatitis B occurs during pregnancy, the outcome of the pregnancy is no different from the non pregnant state. A major concern is the transmission of hepatitis B to the fetus. It is highest and on the order of 90% when the mother is positive for hepatitis B envelope antigen (HBeAg), has high viral deoxyribonucleic acid (DNA) levels or when maternal infection occurs in the third trimester. Rates of transmission average 10% when e Ag is negative or maternal infection occurs in the first trimester**.** Perinatal and early childhood contaminations as a result of the stability of HBV in the environment could result in an estimated 30%-40% of chronic infections. HBV is viable for more than 7 days at room temperature on environmental surfaces and at concentrations as low as 10^{2-3} virions/ml even in the absence of visible blood. Children chronically infected with HBV are at risk of developing hepatocellular carcinoma, chronic liver disease and death.

The CDC recommends screening all pregnant women for hepatitis B surface antigen HBsAg and administration of hepatitis B vaccine to all newborns.

The CDC recommends screening all pregnant women for hepatitis B surface antigen HBsAg and administration of hepatitis B vaccine to all newborns. If mother is HBsAg positive, their newborns should receive hepatitis B immunoglobulin HBIG and begin hepatitis B vaccination series within the first 12 hours of birth. For all other newborns, the first dose of vaccine should be given within one month of birth and the vaccine series completed within the first 6 months of life.[21]

HBV vaccine derives from inactivated virus and limited data indicate no apparent risk for adverse events in the developing fetus when administered to pregnant women or breastfeeding mothers. Pregnant women should be vaccinated if at risk for exposure. Although hepatitis B surface antigen (HbsAg) may be secreted

in milk, studies did not show that breastfeeding increases the risk of acquiring HBV in the infants.

The CDC states that the completed vaccination series of HBV affords >90% protective rates in healthy adults younger than 40 years old.[21] Vertical transmission is highest when maternal viral load exceeds >8 $\log_{10}$ IU/ml.[22] Reports of Lamivudine 150 mg given daily during the last month of pregnancy to 8 pregnant women with high viral load of > 1.2 $x10^9$ gEq/M (or > 4x 10^8 copies/ml), and reports of HBIG given intravenously at 200 IU every 4 weeks starting at 28 weeks of gestation to 52 pregnant women with viral load of $4x10^8$ copies/ml have shown more than 50% decrease in vertical transmission when compared to historical controls.[23,24]

Also, a report on 12 pregnant women who were taking Lamivudine prior to pregnancy and voluntarily continued Lamivudine during pregnancy resulted in 100% prevention of vertical transmission compared to 70% in a control group taken from the literature, and there were no untoward effects of Lamivudine on the babies. In this study all newborns in both groups were given appropriate HBV prophylaxis.[25]
Given the limitation of available data, we cannot make recommendations as of yet regarding the administration of Lamivudine to pregnant mothers.

Hepatitis C virus infection (HCV)

Pregnancy is not contraindicated in women chronically infected with viral hepatitis C and chronic HCV infection is not known to affect the outcome of pregnancy. The prevalence of hepatitis C in women of childbearing age is about 1%.

Risk factors associated with perinatal transmission include: [26-29]

A) HCV RNA viremia at the time of delivery (risk of 4.6% versus 0% if no viremia)

B) Viral load greater than 7.6 $x10^6$ genomes copies/mL in the absence of any other risk factor

C) Coinfection with the Human Immunodeficiency virus (HIV), (risk for HCV RNA and HIV positive mothers is 25% versus 3.8% in HCV RNA positive and HIV negative mothers)

D) Duration of rupture of membranes until delivery longer than 6 hours.

E) Internal fetal monitoring

Similar to the recommendations for the general population, antenatal screening for HCV RNA should be proposed to women with risk factors.

The mode of delivery does not seem to affect the rate of transmission from mother to child in the absence of HIV infection. However there are no randomized controlled trials upon which to base any recommendations regarding performing C section versus vaginal delivery. Even though HCV RNA have been detected in breast milk, no definite case of mother to infant transmission of HCV via breast milk has been reported, and breastfeeding is not considered to be a risk factor for mother to infant transmission. It is advisable to avoid breastfeeding if nipples are cracked or bleeding.

Treatment of chronic HCV infection is contraindicated in pregnancy. Treatment should be given and completed at least 6 months before conception or after delivery.

As in the non pregnant state, spontaneous resolution of infection in pregnancy may occur [30] and newborns of infected mothers should not be tested for HCV RNA because of the poor accuracy of PCR tests in the infant.[31] It is proposed that such tests along with hepatic function panel should be performed beyond the age of 3 months and repeated after one year and at 18 months of age.

Treatment of chronic HCV infection is contraindicated in pregnancy. Treatment should be given and completed at least 6 months before conception or after delivery. Interferon is classified as category C by the Food and Drug Administration and Ribavirin is category X.

While there are a few case reports suggesting that interferon is safe in the setting of acute hepatitis C in pregnant women, we strongly encourage postponing therapy until after delivery.

Hepatitis delta virus infection (HDV)

This is the smallest hepatotropic RNA virus that is dependent on HBV for its replication. Coinfection of HBV and HDV together can lead to fulminant hepatic failure. The risk for HDV transmission via breastfeeding is unknown. Preventing HBV through the use of HBIG and hepatitis B vaccination is effective in preventing HDV. Treatment consists of treating viral hepatitis B.

Hepatitis E virus infection (HEV)

This is a non-envelope RNA virus responsible for large epidemics in Asia, the Middleast, Mexico, and Africa. It is rare in the US. It spreads via the fecal–oral route, and has an incubation period of 8-10 weeks. The infection is usually self- limited and does not result in chronic disease.

When HEV infection occurs in the late stages of pregnancy, mortality is at its highest.

The incidence of acute viral hepatitis E is identical in pregnant and non-pregnant persons. However, pregnant women are at high risk for acute and fulminant hepatitis. Mortality rate in pregnancy can reach 25% whereas it is 0.65% in non-pregnant women. When HEV infection occurs in the late stages of pregnancy, mortality is at its highest. Vertical transmission to the newborn occurs in 50% if mothers are positive for HEV PCR at the time of delivery. Premature deliveries, miscarriages and stillbirths have been reported. Breastfeeding is considered safe if mother is stable. Treatment is supportive and there are no vaccines for HEV infection. Pregnant women should avoid traveling to endemic areas of hepatitis E, especially during their last trimester.

Human Immune Deficiency Virus (HIV infection):

While HIV-1 is not a hepatopathogen, it may affect the liver for the following reasons:

1. HIV patients are often co-infected with HCV or HBV viruses. Co-infection can lead to serious consequences including liver cirrhosis and liver cancer. In addition treatment of co-infection may be associated with hepatotoxicity.

2. The center for disease Control [32] recommends using antiretroviral therapy during pregnancy as is recommended for the non pregnant individual to treat maternal infection and to decrease the vertical transmission to the fetus. Maternal fetal transmission of HIV infection has decreased from an average of 30% to less than 2% with adherence to such recommendations. Multiple drugs are often used to enhance efficacy and decrease rate of drug resistance. A common combination of drugs includes 2 Nucleoside Analogs, with either a Non Nucleoside Reverse Transcriptase Inhibitor or a Protease Inhibitor. Mitochondrial toxicity, lactic acidosis, hepatic steatosis and death, preecclampsia and preterm labor in addition to fetal teratogenicity have been described in association with these medications. Drugs notably known for their hepatotoxicity are Nucleoside Analogs and Protease inhibitors.[33]

3. Opportunistic infections are common causes of parenchymal liver disease in AIDS patients.

4. Non Hodgkin lymphoma and Kaposi sarcoma are common hepatic neoplasms.

5. Liver biopsy studies at autopsy in HIV infected patients have shown that the liver is rarely normal. Microvesicular steatosis and granulomas being the most common findings.

Herpes Simples Viral Infections (HSV):

More than 90% of patients infected with genital HSV are asymptomatic and unaware of the infection. Approximately 22% of pregnant women are infected with HSV-2 and have antibodies. Overall 2% of women will acquire HSV-2 during pregnancy.[34] Half of the reported cases of fulminant liver failure in HSV infections occur during pregnancy. Both HSV-1 and HSV-2 are reported in cases of genital HSV infections. Consultation with an infectious disease specialist is strongly advisable.

More than 90% of patients infected with genital HSV are asymptomatic and unaware of the infection.

Patients with HSV hepatitis are usually anicteric at presentation, herpetic vesicles may or may not be seen and symptoms often consist of a benign upper respiratory viral syndrome. Despite its benign presentation, fulminant and disseminated disease may develop and should be considered in any pregnant women presenting in the second part of her pregnancy with fever and flu like symptoms that progress to pneumonitis and or encephalitis even in the absence of skin rash. Aminotransferases are usually very high, and the prothrombin time is abnormal in 91% of patients with HSV hepatitis. Differential diagnosis includes AFLP, HELLP syndrome, or liver infarction. Cultures from cervix, pharynx and oropharynx along with type-specific HSV serology and PCR assays often lead to the diagnosis. Liver biopsy could be helpful if diagnosis remains uncertain. Extensive focal hemorrhagic necrosis and intranuclear hepatocyte inclusions may be seen.

Disseminated disease can be fatal unless treatment is given. Acyclovir (FDA Category B) should be administered as soon as the diagnosis is suspected. It should be given intravenously at a dose of 5-10 mg/kg body weight every 8 hours for 2-7 days or until clinical improvement is observed, followed by oral antiviral therapy to complete at least 10 days of total therapy. Premature delivery is not recommended.[35]

In pregnant patients with symptomatic first episode genital herpes or with recurrent severe HSV infections, oral Acyclovir may be given at 400 mg three times daily for 5-7 days to prevent neonatal infection. Daily maintenance therapy is also recommended in severe recurrent infections. Some specialists recommend routine C- section, others recommend both oral medication and C- section to reduce the risk for neonatal herpes. Neither regimen's efficacy has been clearly established.[36] It is observed however that C-section performed before rupture of membranes may be more effective in preventing transmission to the neonate.

Neonatal infection is the most serious complication of genital HSV-infection, the mortality being 70% if untreated. The greatest risk for fetal and neonatal morbidity occurs with the first episode of HSV infection when high viral titers are shed in the cervix and when infection is acquired during the latter stages of pregnancy. Transmission is estimated to range between 33%-50%. Transmission is low (<1%) when genital herpes occurs during the first half of pregnancy and when disease reactivates in the absence of genital herpes. Treatment of the neonate should begin as soon as the diagnosis is suspected.

Although the safety of systemic Acyclovir therapy in pregnant women has not been definitively established, available data do not indicate an increased risk for major birth defects in women treated with this drug during the first trimester compared with the

general population. Valcyclovir (FDA Category B) is transformed into Acyclovir by first intestinal/hepatic bypass. It has been given to pregnant women with recurrent HSV infections starting at 36 weeks of gestation with improved symptoms in the mother and without untoward effects on the newborn.[37]

Cytomegalovirus Infection (CMV):

Between 50% and 80% of adults in the United States are infected with CMV by age 40. CMV is found in body fluids, including urine, saliva, breast milk, blood, tears, semen, and vaginal fluids. About 1%-4% of pregnant mothers acquire primary CMV infection during a pregnancy and 33% of them pass the virus to their unborn babies.

Similar to the non pregnant individual, most pregnant women with CMV infections are asymptomatic. If symptomatic they may display a mononucleosis-like illness consisting of fever, flu like symptoms, asthenia, abnormal transaminases and lymphocytosis. Diagnosis of CMV infection is based on results of either serologic studies, liver biopsy, or both. Treatment is supportive and prognosis is usually benign for the mother.

In the newborn, CMV infection is one of the most common causes of congenital infections in developed countries with reported incidence close to 2%.

In the newborn, CMV infection is one of the most common causes of congenital infections in developed countries with reported incidence close to 2%. When infection takes place in the first 22 weeks of pregnancy, vertical transmission is highest and can be associated with mental retardation and congenital malformations (low birth weight, jaundice, hepatosplenomegaly, skin rash, microcephaly sensorineural hearing loss and chorioretinitis). Ultrasound and amniocentesis for DNA by PCR, MRI and fetal blood sampling can provide the diagnosis of intrauterine CMV infections. Early termination of pregnancy has been considered in cases of severe fetal malformations.

The effects of congenital CMV infection on the infant may vary from a congenital syndrome to an asymptomatic course.[38] Approximately 90% of congenitally infected infants are asymptomatic at birth but may still present handicaps at a later age.
There is currently no reliable prognostic marker for antenatal screening. Moreover, no prenatal treatment has proven to be effective and safe.

Alcohol Use:

In 2003, the National Survey on Drug Use and Health reported that 9.8% of pregnant women used alcohol and 4.1% admitted binge drinking.[39] A safe level of prenatal alcohol consumption or duration of consumption has not been determined. Epidemiologic data suggest that women are more sensitive to alcohol than men and can present with severe liver disease that progress more rapidly for the same amount and duration of alcohol ingestion. Female sex hormones potentiate the adverse effects of alcohol on the liver, and pregnant women who continue to drink may present with acute alcoholic hepatitis and alcohol related liver injury.

Prenatal exposure to alcohol may lead to miscarriages, stillbirths, prematurity, growth retardation and malformations attributed to the fetal alcohol syndrome which includes growth retardation, behavioral disturbances, brain defects, cardiac defects, spinal defects and craniofacial anomalies.[40] Cerebellar and basal ganglia damage from alcohol have also been described in association with dysfunction of gross and fine motor skills, and alcoholic liver disease in the neonate has been reported.

The US surgeon general and the secretary of health and human services recommend abstinence of alcohol for women planning pregnancy, at conception and during pregnancy.

Pregnancy in Patients with Preexisting Liver Disease

Portal Hypertension:

Pregnancy is an attainable goal in women with cirrhosis however it is rare due to a high incidence of anovulation and infertility related to the cirrhosis itself and to the usually advanced age of the patient. If pregnancy occurs, mortality and morbidity are high. Amenorrhea, oligomenorrhea, bleeding, metrorrhagia, increased fetal wastage (30%-40%), prematurity (25%), stillbirth and intrauterine growth retardation can occur. Fertility may be preserved in non-cirrhotic individuals with portal hypertension and conserved liver function.[41]

Identification of the causes of cirrhosis, especially if infectious or hereditary, which can have the potential to be transmitted to the newborn, is important. If cirrhosis is compensated, pregnancy can be allowed to proceed to term or until fetal maturity has developed. Delivery with C-section should be based on obstetrical reasons only. Early epidural anesthesia is preferred to avoid increased intraabdominal pressure and variceal bleeding related to Valsalva maneuver.

If variceal bleeding occurs in pregnancy, Octreotide (FDA Category B) and variceal banding should be used because they are effective and safe.

Studies from countries where pregnancies in patients with non-cirrhotic portal hypertension are frequently seen report that esophageal bleeding is the most common complication. Perinatal mortality of 33% and a miscarriage rate of 29% have been described. Prevention of esophageal bleeding with non-selective beta blockers and variceal band ligation has been shown to be effective and low risk. If variceal bleeding occurs in pregnancy, Octreotide (FDA Category B) and variceal banding should be used because they are effective and safe.[42]

Autoimmune Hepatitis (AIH):

Autoimmune hepatitis is a progressive liver disease that predominantly affects women of all ages. Women with AIH can become pregnant and carry successful pregnancies to term with the expectation of delivering a normal baby. However the disease activity is unpredictable in pregnancy. Attenuation of disease activity and spontaneous remissions have been reported due to the immune tolerance induced by the pregnancy. Flares of the disease have also been described in 11% of cases during pregnancy and up to 50% in the postpartum period. Maternal deaths due to liver decompensation, variceal bleeding and porto-pulmonary hypertension have been reported especially when treatment is withdrawn. Preterm delivery and fetal loss occur in 24% of cases.

Corticosteroids (FDA Category C) remain the treatment of choice in autoimmune hepatitis. They induce rapid remissions during an initial episode and during a flare when dose is increased. They appear to be safe during pregnancy albeit with a marginal risk for oral cleft defect in the newborn when given in the first trimester.[43]

Azathioprine has been used to maintain remission during pregnancy. While it is graded FDA Category D based on experimental models in mice, human experiments did not reflect teratogenicity and it is probably safe to use in pregnancy.[5] Data derived from studies of pregnant women with inflammatory bowel disease suggest that it is likely to be safe when given at doses less than 100 mg a day.[44]

Successful therapy should not be withdrawn during pregnancy as it may precipitate a flare or liver failure.

Wilson Disease:

Wilson disease is an inherited recessive disorder of copper transport in the golgi apparatus of the hepatocyte. It leads to the accumulation of copper in the liver, brain and other organs. It is a disease of the young thus affecting women of childbearing age. In the absence of treatment, cirrhosis of the liver, fulminant hepatic failure and advanced psychiatric and neurologic damage may occur. While fertility is decreased in patients with Wilson disease, women have become pregnant when appropriately diagnosed and treated. Treatment should be initiated as soon as diagnosis is made during pregnancy and regardless of the stage of pregnancy. Treatment should be maintained throughout pregnancy because its interruption could result in fulminant liver failure. Dose reduction in the order of 25-50% of pre-pregnancy maintenance therapy for both chelators D- penicillamine and trientene is required so that copper is not depleted from the body and wound healing is not impaired if C-section is to be performed.[45] In addition, Copper depletion may be associated with congenital malformations.

While fertility is decreased in patients with Wilson disease, women have become pregnant when appropriately diagnosed and treated.

D-penicillamine is FDA Category D. It has been associated with teratogenic abnormalities in 5% of infants (cutis laxa, micrognathia, low-set ears, inguinal hernias, and joint mobility).[46] The suggested dose in pregnancy is <500 mg/day and it should be decreased to 250 mg /d during the last 6 weeks of pregnancy and through delivery.[47] D-penicillamine has anti-pyridoxine effects and should be supplemented with daily pyridoxine dose of 25-50 mg. It enters breast milk and breastfeeding is contraindicated even in relatively low doses.[48]

Trientene is FDA category C and its dose should be decreased to less than 500mg /day in pregnancy.

Zinc sulfate (FDA Category C) is probably safe during pregnancy and breastfeeding. It is usually given at a dose of 50 mg orally three times daily and does not require dose adjustment.[49]

Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis:

A few cases of pregnancy have been described in women with primary biliary cirrhosis (PBC). This is partly due to the later age at presentation of the disease. Although reports suggest an increased risk for premature delivery, still births and liver failure, there are no good data on the outcome of pregnancy in women with PBC. When pregnancy occurs, PBC may induce a new onset pruritus. Diagnosis and management are similar to the non pregnant state. Upper endoscopy is recommended [50] in order to screen for esophageal varices. Nonselective beta blockers and banding ligation should be given if necessary. Ursodeoxycholic acid or UDCA (FDA category B) is the treatment of choice due to its safety as discussed earlier.

Primary sclerosing cholangitis is rarely described in pregnancy. Abdominal pain and pruritus seem to be the major symptoms in pregnancy. Diagnosis and therapy are similar to the non pregnant state.

Budd-Chiari Syndrome:

Budd-Chiari syndrome (BCS) is a rare disorder caused by obstruction of hepatic venous outflow due to thrombosis of hepatic veins or the terminal portions of the inferior vena cava. This leads to sinusoidal congestion, ischemic injury to liver cells and portal hypertension. Budd-Chiari syndrome can be idiopathic in 10%-30% of patients. However, it is increasingly recognized in patients with more than one etiology for hypercoagulability as in primary myeloproliferative disorders, factor V Leiden, antiphospholipid syndrome and paroxysmal nocturnal haemoglobinuria.[51] Due to its prothrombotic state, pregnancy may precipitate

BCS in subjects with these predisposing factors. Factor V Leiden is a major cofactor in the development of Budd-Chiari syndrome during pregnancy.

The clinical picture may consist of an indolent course (chronic or subacute where unexplained liver dysfunction and ascites are the predominant clinical features) or an acute/fulminant hepatic failure due to massive ischemic necrosis of the liver. Abdominal pain, hepatomegaly and ascites are the main clinical manifestations. Proper imaging studies with Doppler ultrasound and MRI are often required and are the imaging modalities of choice during pregnancy. Treatment with anticoagulation (heparins being the safest in pregnancy), diuretics, angioplasty, stenting and porto-caval shunts may be required depending on the acuity of the presentation. In more acute cases, reports of C-section and liver transplantation have resulted in good outcome for both mother and child, although maternal deaths have also been reported.

Gallstone Disease in Pregnancy:

As discussed earlier, pregnancy is a risk factor for lithogenicity. The risk for sludge and gallstone formation doubles by the end of gestation in comparison with the first trimester (10% versus 5% respectively), and it is further increased with parity. Gallstones are found in 6.5% to 8.4% of nulliparous women, and in 18.4% to 19.3% of women with two or more pregnancies.[52] Most sludge and a third of gallstones disappear spontaneously after pregnancy without resulting in symptoms. Acute cholecystitis and gallstone pancreatitis rarely occur during pregnancy (<1/8000) but they require immediate attention. Medical intervention is often effective however surgical management may be necessary. Laparoscopic cholecystectomy with bile duct exploration and ERCP with sphincterotomy have been successful when performed in experienced hands and when performed during the second trimester at which time the organogenesis of the fetus is completed and the size of the uterus does not interfere with the operation. For more details, see section on Surgery during Pregnancy.

Liver Transplant and Pregnancy

Infertility is common in women with end stage liver disease but is usually restored within 8 months after liver transplantation. Most information regarding pregnancy among women with solid organ transplantation comes primarily from 3 registries: The European Dialysis and Transplant Association Registry, the United Kingdom Transplant Pregnancy Registry and the National Transplantation Pregnancy Registry in the US (NTPR).[53]

Fetal teratogenicity from immunosuppression was not different from that of the general population and pregnant women should continue their immunosuppressive therapy throughout pregnancy.

All three registries show similar trends in outcomes of pregnancy. Over 14,000 births among women with solid organ transplantation have been reported in the world. The NTPR reports that the average time from transplantation to conception is around 3-4 years, live births occurred in >75%, prematurity in 39%, C sections in 35%, and preeclampsia in 23%. Pregnancy did not seem to compromise the function of liver allograft when the allograft was stable before pregnancy, and rejection episodes were observed in 8% during pregnancy. Fetal teratogenicity from immunosuppression was not different from that of the general population and pregnant women should continue their immunosuppressive therapy throughout pregnancy. Most common immunosuppressive agents used were Cyclosporine A (FDA Category C), Azathioprine (FDA Category D) and Prednisone (FDA Category C).[54] Teratogenicity of Sirolimus and Mycophenolate Mofetil has not been well determined yet.

Complications of pregnancy after the first year post transplantation were lower than if pregnancy occurred during the first year post transplantation. This is attributed to a more stable allograft function and to minimal immunosuppressant use after the first year. It is advised that all solid organ recipients wait about 2 years after transplantation before conception to ensure a better outcome.

Fertility issues in transplant recipients should be discussed with all transplanted women of childbearing age, as well as counseling regarding conception, timing of conception, outcome of pregnancy, and methods of contraception. Furthermore, the transplant recipient should be encouraged to discuss and have a total understanding of the short and long term health risks that could potentially affect her and the well being of her child.

Conclusion

Liver disease in pregnancy may manifest as a benign entity that resolves with delivery of the fetus without any consequences, or a more serious disease that could adversely affect the overall well being of both mother and baby potentially resulting in liver failure and death. Although there are no available clinical markers by which to predict with certainty how and when such situations may be encountered, prior history of liver disease, knowledge of the patient's risk factors for liver disease and the gestational age of the pregnancy are the best guides to a differential diagnosis.

While pregnancy is not reported to increase the susceptibility to drug induced liver disease, drug hepato-toxicity should always be considered in pregnant women taking prescription or non prescription medications.

Preventive measures that include early prenatal care, avoidance of risky behaviors that could increase a woman's chance of acquiring infections, and cessation of smoking and alcohol are monumental in decreasing morbidity and mortality in pregnancy. Furthermore, women with preexisting liver disease should discuss with their treating physician(s) the potential risks associated with a future pregnancy. Methods of contraception should be undertaken if pregnancy is not desired while adjustment of medications and timing of conception should be discussed if pregnancy is anticipated. In addition, early referral to a tertiary care center and a coordinated team approach that involves the obstetrician, the primary care physician, the hepatologist and the transplant surgeon are crucial in safeguarding a good fetal and maternal outcome.

Although liver disease in pregnancy is associated with an increased risk for morbidity and mortality, clinical outcomes have improved for both mother and baby, and pregnancy is not contraindicated in patients with liver disease or in patients who have had a liver transplant.

Table 1 Physiological Changes During Pregnancy

Increase	1. Blood volume, heart rate and cardiac output rise by 35%-50% and peak at 32 weeks. Further increase by 20% occur in twin pregnancies 2. Alkaline phosphatase levels rise 3 to 4 fold 3. Clotting factors: 1, 2, 5, 7, 8, 10 and 12 4. Ceruloplasmin 5. Transferrin 6. ESR, CRP, C3 and C4
Decrease	1. Gallbladder contractility 2. Hemoglobin 3. Uric Acid 4. Albumin and total protein 5. Antithrombin III and protein S 6. Systemic vascular resistance 7. Modest decline in blood pressure 8. Modest or no decline in platelet levels
No Change	1. Liver transaminase levels (AST, ALT) 2. GGT 3. Bilirubin level 4. Protime 5. Blood flow to the liver

Table 2 FDA Classification of Drugs Used for Liver Disease in Pregnancy

Drug	FDA Class	Comments	Breastfeeding
Ursodeoxycholic Acid	B	No evidence of risk in humans. No teratogenicity in rodents	No reports on its use in breastfeeding mothers
Lamivudine	C	Animal and human data suggest low risk to developing fetus	No reports on use in breastfeeding mothers
Acyclovir	B	No adverse effects on fetus or newborn	Compatible with breastfeeding
Valcyclovir	B	No apparent risk	No reports, but American Academy of Pediatrics considers it compatible with breastfeeding
Interferon Alfa	C	No significant risk. Caution due to its antiproliferative activity	No reports in breastfeeding
Ribavirin	X	Contraindicated. Due to fetal toxicity	No data in breastfeeding
Octreotide	B	Not toxic to animals. Not enough data in humans but no reported toxicity	No reports but risk appears non-existent
Corticosteroids	C, (D in first trimester)	Small risk for cleft palate	Limited data but American Academy of Pediatrics considers it compatible with breastfeeding
Azathioprine	D	Teratogenic in rabbits. Intrauterine growth retardation in humans	No data
D-penicillamine	D	Reduce dose to <500 mg/d and <250 mg in the last 6 weeks of gestation	Enters breast milk thus avoid in breastfeeding
Trientene	C	Teratogenic in rodents	No data
Zinc sulfate	C	Not enough data	No data
Propranolol	C	IntraUterine Growth Retardation. Bradycardia, hypoglycemia to newborn if given near delivery	Limited data but American Academy of Pediatrics considers it compatible with breastfeeding

Table 3 Liver Diseases Unique to Pregnancy

Disorder	Gestational age at presentation	Symptoms	Specific labs	Outcome	Treatment
HG	1st trimester	Nausea and vomiting.	AST,ALT < 200	Benign for mother and child Likely recurs	IV fluids Thiamine Pyridoxine Promethazine: FDA C
AFLP	3rd trimester	Nausea vomit abdominal pain Progress quickly to FHF, 50% have eclampsia	AST,ALT >300 Bilirubin high DIC Uric acid high	Maternal mortality 30%, Fetal mortality up to 35%. Recurs	Prompt delivery Liver transplant if FHF
IHCP	3rdtrimester	Pruritus	GGT≥ normal Bile Acids high PT normal Bilirubin ≤5 AST,ALT<300	Increase maternal gallstones related disorders Risk for fetal distress+ Often recurs	Actigall Delivery when fetal distress is imminent
HELLP	Beyond 22 weeks and after delivery.	Abdominal pain Mild renal failure 20% progress from eclampsia	Platelets <100,000 Hemolysis, DIC	Maternal mortality up to 3.5% and fetal death 6-37 % Hepatic rupture is associated with 60% maternal mortality Likely recurs	Prompt delivery

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Surgical Problems in the Pregnant Patient

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All gastrointestinal disorders can present during pregnancy, and in fact 0.5-1% of all pregnant women require surgery.[1] While in general the principles of diagnosing and treating a pregnant woman with an acute surgical abdominal problem remain the same as those governing the treatment of the non pregnant patient, some important differences are present and can pose problems. As a general rule the condition of the mother should always take priority because proper treatment of surgical diseases in the mother will usually benefit the fetus as well as the mother.

Various anatomic and physiologic changes occur during normal pregnancy, which can alter the presentation of conditions that require surgery: anatomic displacement of the intraperitoneal organs by the gravid uterus, decreased venous return due to pressure exerted on the inferior vena cava by the enlarging uterus, increased cardiac output and heart rate, physiologic anemia, leukocytosis and tachycardia, decreased gastric motility, increased gastric acidity, increased minute ventilation, and decreased functional residual capacity. Diagnosis can be difficult as the enlarged uterus stretches the abdominal wall and compresses the viscera, which results in a diminished response to peritoneal irritation and altered or referred pain perception, making localization more difficult. In addition, various signs and symptoms that normally occur during pregnancy such as morning sickness can be confused with symptoms of acute gastrointestinal disorders, such as nausea, vomiting, abdominal pain and dyspepsia.

Proper evaluation and treatment of the pregnant patient requires good clinical acumen, knowledge of the physiologic changes of pregnancy, as well as the most common GI diseases affecting pregnant woman. A clear treatment plan that avoids procrastination can be made after careful review of the history, a physical exam performed with the gravid uterus in mind, and judicious use of radiologic studies. If imaging is necessary, fetal radiation can be avoided by using lead shielding to protect the fetus. Elective procedures can be delayed until after delivery. The risks of general anesthesia is least during the second trimester, when organogenesis is complete and risk of inducing preterm labor is minimal so semi-elective procedures should be delayed until then. Recent reports suggests that the risk of fetal wasting and teratogenicity from gastrointestinal operations during pregnancy are minimal.[2,3,4]

General Guidelines for Surgery During Pregnancy

Although non obstetrical general surgery is not rare, it is always very stressful and anxiety producing for the pregnant woman even if the outcome is successful. Thoughtful and comprehensive preoperative counseling about dangers to the fetus is an important component of care. Consultation and frequent communication with obstetrical colleagues is crucial. It is important to remember that physiologic changes during pregnancy alter the maternal response to stress. Preoperatively, maintenance of adequate hydration, availability of blood for transfusion and maternal blood oxygenation and pH to avoid acidosis should be ensured. DVT prophylaxis with intermittent pneumatic compression devices should be employed and fetal monitoring should be done throughout the perioperative period. Tocolytics should be administered only for documented or perceived contractions, not prophylactically.

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Intraoperatively, the patient should be placed in the slight left lateral position to prevent uterine compression of the vena cava and left iliac vein. Monitoring of maternal blood gases should be considered, especially for laparoscopic procedures as CO2 insufflation can induce maternal hypercapnia, which can lead to fetal hypercapnia, tachyardia and hypertension.[6] Measures should be taken to avoid aspiration as the pregnant patient is at increased risk of aspiration due to decreasing gastrointestinal motility and intraabdominal organ compression. Progesterone also has a relaxant effect on smooth muscle, diminishing esophageal sphincter competency. For laparoscopic surgery, open access using the Hasson technique will minimize potential injury to the fetus and port entry sites should be placed above the level of the uterus. Low pressure pneumoperitoneum should be utilized.[6] For open procedures, the uterine size, the specific surgical disorder, and the anticipated type of surgery to be performed will determine the abdominal incision. The uterus should be manipulated as little as possible. Fetal monitoring should be continued in the postoperative period.

Appendicitis

Appendicitis is by far the most common surgical emergency in the pregnant patient. It occurs once in every 1500-2000 pregnancies, with approximate equal frequency in each trimester.[7] Management of appendicitis during pregnancy is a surgical emergency and perforated appendicitis is the number one surgical cause of fetal loss during pregnancy. Women who are pregnant have the same risk of developing appendicitis as non pregnant women. In the first two trimesters the diagnosis of appendicitis is essentially the same as in non-pregnant women. The signs and symptoms of acute appendicitis are similar to those in non-pregnant patients and includes anorexia, nausea, vomiting and periumbilical pain that migrates to the location of the appendix. Nausea and vomiting may be difficult to distinguish from symptoms due to pregnancy but localizing right lower quadrant tenderness remains a reliable sign.

Early during pregnancy, peritoneal irritation develops in the right lower quadrant but after the fifth month of gestation, 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. The tenderness also becomes less localized as distention of the abdomen lifts the peritoneum away from the inflamed appendix and cecum.[8] Nearly all patients with appendicitis will develop right sided abdominal pain, and tenderness is still the most important clinical finding. Abdominal guarding, rebound tenderness and referred tenderness occurs in approximately 70% of patients, but guarding is not as reliable a sign given laxity of the abdominal musculature. Rectal or pelvic tenderness is not as common given cephalad move-

ment of the appendix out of the pelvis due to the gravid uterus. In the latter months of pregnancy, the enlarging uterus may interfere with the normal ability of the omentum and bowel to wall off the inflammatory process. Fever is less common (25% of patients) and leukocytosis is difficult to interpret as this is normal in pregnancy, however, the presence of bandemia should be a clinical clue. Physical exam on presentation remains the most reliable diagnostic tool but radiologic studies are sometimes needed to rule out other causes of abdominal pain, such as ovarian torsion, ovarian cysts, degenerating fibroids, pancreatitis, pyelonephritis, urolithiasis or biliary tract disease. Ultrasound is a safe, reliable imaging method, especially early in pregnancy and an accomplished ultrasonographer may be able to locate a swollen or inflamed appendix and look for a periappendiceal abscess. A high index of suspicion is needed so an early diagnosis can be made since perforation can lead to a 20-25% rate of fetal loss and a 4% maternal mortality, whereas uncomplicated acute appendicitis only results in a fetal mortality of less than 5%.[2,9]

Laparoscopic appendectomy can be performed safely during the first two trimesters, but is difficult to perform when the uterus is above the umbilicus.

A higher rate of negative appendectomy is acceptable in the pregnant patient given the clearly worse outcomes with perforation. Diagnostic laparoscopy is useful in equivocal cases, and has reduced the rate of false positive appendectomy to 15%.[9] Of note, pyelonephritis is the most common misdiagnosis in patients with acute appendicitis in pregnancy. Once appendicitis is suspected or diagnosed immediate surgical intervention is recommended to avoid perforation. There is no role for non-operative management. Simple acute appendicitis has very little maternal mortality rate and the risk of fetal loss is low but maternal and fetal complications escalate with peritonitis. Patients with acute appendicitis should receive preoperative antimicrobial therapy with a cephalosporin and anaerobic coverage should be also provided. Laparoscopic appendectomy can be performed safely during the first two trimesters, but is difficult to perform when the uterus is above the umbilicus.[10] In an open operation, a standard muscle splitting incision placed over the location of maximal tenderness can be used. It is prudent to use a longer incision, and the incision is gradually moved more laterally and cephalad to McBurney's point as the pregnancy progresses. It is important not to place retractors medially against the uterine surface since this can lead to uterine irritability and onset of labor. In the case of suspected rupture with peritonitis a midline incision is often used and skin closure is not performed to avoid wound infections. An appendiceal abscess can be treated by percutaneous drainage and antibiotics. An interval appendectomy can be performed at a later date, as long as the patient improves with the initial drainage and antibiotic therapy.

Biliary Tract Diseases

Biliary tract disease is the second most common gastrointestinal disorder requiring surgery during pregnancy.[9,11] Pregnancy predisposes to gallstone formation and gallstones occur in approximately 7% of nulliparous women but 19% of women with two or more pregnancies.[12] Gallstones and sludge are most likely caused by biliary stasis, prolonged intestinal transit, and increased cholesterol saturation of bile. The frequency of biliary colic during pregnancy is controversial, and the recommended therapeutic approach is conservative. One to eight of 10,000 pregnant women will suffer from acute cholecystitis and when essential, invasive procedures are well tolerated especially when performed during the second trimester.[13] Maternal and fetal complications are uncommon and the likelihood of fetal demise or preterm delivery is minimized when elective operations are done in the second trimester. Infection, pancreatitis, gallbladder rupture, or inappropriate delays can lead to increased rates of fetal mortality.[14]

The symptoms of biliary tract disease are very similar to those seen in nonpregnant patients. Common symptoms include anorexia, nausea and vomiting along with abdominal pain in the midepigastric, right upper quadrant or shoulder. Right upper quadrant tenderness and a Murphy's sign is an important clinical sign. Laboratory values may reveal an elevated alkaline phosphatase or bilirubin level. Jaundice, abnormal transaminases, or hyperamylasemia can be a sign of complicated biliary tract disease.[15] Differential diagnoses include appendicitis, pancreatitis, peptic ulcer disease, pyelonephritis and HELLP (Hemolysis, Elevated liver enzymes, Low Platelets) syndrome with hepatic rupture.[16] A right upper quadrant ultrasound should be performed and is accurate 97% of the time in diagnosing cholelithiasis. The ultrasonographic signs of acute cholecystitis remain the same during pregnancy and include gallbladder wall edema, pericholecystitic fluid, an ultrasonographic Murphy's sign or biliary ductal dilatation.[17]

Initial management of biliary tract disease in the pregnant state includes discontinuing oral intake, providing antibiotics and analgesia as well as adequate hydration. Those who fail to respond to medical therapy or have repeated bouts of biliary colic requiring hospitalization should undergo an operation, which is best deferred to the second trimester if feasible.

Laparoscopic cholecystectomy can be performed safely in most pregnant patients, especially during the first two trimesters [2,14,18] and advantages include less pain, and a quicker recovery. An open entry technique is probably safest, though use of the Veress needle with alteration of the entry site has been reported to be safe.[2] All port entry sites should be adjusted to avoid injury to the gravid uterus. During laparoscopic cholecystectomy, the maternal end tidal C02 or arterial C02 levels should be measured and temporary desufflation of the pneumoperitoneum if levels are rising, since hypercarbia can lead to fetal acidosis. Conversion to open cholecystectomy should be considered if C02 levels are rising, there is poor visualization or if prolonged procedure is expected. Routine cholangiography is not advocated but the biliary system can be assessed by intraoperative ultrasound. If choledocholithiasis is found or highly suspected, this can be approached laparoscopically, with an open common duct exploration, or with postoperative endoscopic retrograde cholangiopancreatography (ERCP).[19] Magnetic resonance cholangiography and laparoscopic CBD exploration has also been reported as an option in the management of CBD stones.[20] The safety of ERCP with endoscopic sphincterotomy for stone extraction or stent insertion is addressed elsewhere in this monograph.[21] If endoscopic stone extraction is performed, the fetus should be shielded during fluoroscopy. Decision making about performing ERCP with therapeutic intervention versus laparoscopic cholecystectomy needs to be individualized since both can be safely performed in the pregnant patient.

Pancreatitis

Most pancreatitis during pregnancy is the result of gallstone disease.[5] Signs and symptoms are essentially the same as those in the nongravid state and can include severe abdominal pain radiating to the flank associated with nausea, vomiting, and hyperamylasemia. Diagnosis can be difficult as there is a physiologic increase in serum amylase during pregnancy. A serum amylase that is greater than two times above the upper limit of normal suggests pancreatitis. Serum lipase may also be helpful in the differential diagnosis.

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Pancreatitis does appear to occur more frequently in the third trimester and the immediate postpartum period.[5] Management for the most part is nonoperative as in any other patient with pancreatitis and the general principles of treatment remain the same including bowel rest with or without nasogastric suction, intravenous fluid and electrolyte replacement, and

parenteral analgesics. Important additional measures in the pregnant patient are fetal monitoring, attention to the choice of medication, avoidance of radiation to the fetus and positioning the mother to prevent potential DVT. Parenteral nutritional supplementation should be considered to protect the fetus. CT scanning is generally not needed unless severe necrosis of the pancreas is suspected. Surgical intervention is reserved for those with septic necrosis of the pancreas, ruptured pseudocyst, severe hemorrhagic pancreatitis or persistent biliary obstruction which is not amenable to ERCP clearance.

Trauma

Pregnancy can be complicated by trauma such as motor vehicle accidents, falls or assaults. The approach to the pregnant patient who suffers blunt or penetrating abdominal trauma should follow the principles of Advanced Trauma Life Support (ATLS) used for all patients. The mother must be properly stabilized in order to protect the fetus. Close attention to airway, breathing and circulation, the "ABC's" of trauma management remains the most important principle. In addition, fetal monitoring should be instituted promptly and not delayed until the patient reaches the obstetric area of the hospital.[22] Fetal monitoring should continue for at least 24-48 hours if there are frequent uterine contractions, vaginal bleeding, abdominal tenderness, postural hypotension, or fetal heart rate abnormalities. Fetal death is more likely with greater severity of maternal injury and with mechanisms of injury such as ejection from a vehicle, motorcycle and pedestrian collisions or assaults. Maternal death, maternal tachycardia or abnormal fetal heart rate are all significant risk factors for increased fetal death.[23,24]

Both ultrasound, using the FAST technique (Focused Abdominal Sonography for Trauma), and abdominal CT scanning are important tools in the evaluation of the pregnant trauma patient. The sensitivity and specificity of abdominal ultrasonography in pregnant trauma patients is similar to that seen in nonpregnant patients.[25] Ultrasound is especially useful for detecting fetal distress while CT can demonstrate uterine rupture and retroperitoneal hemorrhage as well as concurrent evaluation of other organs in the pregnant trauma patient.[24] A Kleihauer-Betke test may show evidence of fetomaternal hemorrhage and is recommended for Rh-negative patients.[5] Blood transfusion if necessary should be cross matched, if time is of the essence non crossmatched O-negative blood should be given to avoid antibodies to Rh and sensitization in future pregnancies.

Intestinal Obstruction

Intestinal obstruction is the third most common non-obstetric reason for laparotomy during pregnancy (following appendicitis and biliary tract disease). It occurs most commonly in the third trimester.[5] Acute abdominal pain and vomiting and obstipation from intestinal obstruction in pregnancy can be caused by adhesions, volvulus, intussusception, hernias or neoplasm. Intussusception from Non-Hodgkin's lymphoma is infrequently diagnosed during pregnancy.

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The diagnosis of intestinal obstruction is confirmed with a serial acute abdominal series. Volvulus should be suspected when there is a single, grossly dilated loop of bowel. Persistent abdominal pain aggravated by changes in position and by increases of intra-abdominal pressure should always be investigated, even when a bulge or specific hernial defect is not clinically appreciable. Ultrasound can sometimes demonstrate the hernia defect. Physicians caring for the pregnant woman, must be aware that all abdominal conditions can occur despite the pregnant condition. The manage-

ment of bowel obstruction in pregnancy is essentially no different from treatment of nonpregnant patients and include decompression, intravenous hydration, and timely surgery.[26-28,29,30]

Splenic Artery Aneurysms

Splenic artery aneurysms are quite rare, but they are more common in women. Rupture of a splenic artery aneurysm is a catastrophic event, most commonly associated with pregnancy and usually presents as sudden unexpected shock or death. Half of the cases of rupture occur in patients less than 45 years of age and a quarter of all cases are in pregnant women usually in the third trimester or during labor. They are usually symptomless until rupture in most cases although occasionally they are recognized by vague symptoms such as left upper quadrant or epigastic pain. In some cases, an audible bruit over the left hypochondrium can be appreciated or the aneurysm can be seen on plain x-ray of the upper abdomen as a calcified ring with a central lucent area to the left of the first lumbar vertebra. They can also be identified on ultrasound or abdominal CT scan. If found, splenic artery aneurysms should be treated electively to avoid rupture, with splenectomy and resection of the artery, exclusion of the aneurysm or angiographic embolization.[31] If rupture is suspected, immediate laparotomy should be undertaken with ligation of the splenic artery and resection of the aneurysm and splenectomy. As in the nonpregnant patient, pneumococcal vaccine should be given 2 weeks prior to elective splenectomy or immediately following emergent splenectomy.

Hepatic Lesions

Pregnancy is associated with increased growth and risk of rupture of hepatic adenomas. Hepatic adenomas are usually solitary but multiple lesions have been reported. The association between oral contraceptives or other hormone therapies and the development of adenomas is well established. The risk of rupture during pregnancy probably relates to the expanded blood volume, and an increase in venous blood pressure. Liver hemangiomas are also related to estrogen and pregnancy may stimulate enlargement or increase the risk of rupture. Most patients can be treated conservatively with frequent sonographic monitoring of the fetus and the hemangioma.

Acute fatty liver of pregnancy and the syndrome of hemolysis, elevated liver enzyme levels, and low platelet count (HELLP) are rare but major disorders of pregnancy.

Acute fatty liver of pregnancy and the syndrome of hemolysis, elevated liver enzyme levels, and low platelet count (HELLP) are rare but major disorders of pregnancy. Both are associated with a history of pre-eclampsia and are generally seen in the third trimester.[32] Subcapsular hemorrhage and hepatic rupture are unusual and potentially fatal complications of the HELLP syndrome. A high index of suspicion and prompt recognition are keys to proper diagnosis and management of affected patients. An aggressive multidisciplinary approach is called for in these high risk situations.[33] Surgical principles for control of bleeding are followed and techniques such as packing of the liver, deep mattress sutures or omentoplasty can be employed. In severe cases, liver transplantation has been successfully performed.[34,35]

Hemorrhoids

Hemorrhoids in pregnancy are due to increased circulating volume, increased venous congestion caused by compression of the superior rectal veins by the pregnant uterus as well as the relaxing effect of progesterone on the smooth muscle in the walls of the veins.[5] Hemorrhoids can present with bleeding, prolapse, mucoid discharge, pruritus and rectal discomfort. It is important to rule out other causes of these symptoms such as inflammatory bowel disease, anal

fissure, and carcinoma of the colon, rectum or anus. Sigmoidoscopy can be done safely in pregnancy.[21,36] Treatment is non-operative in most cases and includes dietary fiber, psyllium, stool softeners, increased fluid intake, avoidance of straining and hemorrhoidal analgesics. Rubber band ligation can be performed for internal hemorrhoids. If the hemorrhoids are severely prolapsed or associated ulceration, severe bleeding, fissure, or fistula and symptoms fail to respond to conservative measures, hemorrhoidectomy should be considered. Thrombosed external hemorrhoids can be treated with simple clot extraction.

Inflammatory Bowel Disease

Most pregnant women with a history of inflammatory bowel disease have uneventful pregnancies and exacerbations of disease can be controlled with medical therapy. It is rare for the new onset of inflammatory bowel disease to be diagnosed during pregnancy.[37]

When relapses of Crohn's disease do occur during pregnancy, they usually present during the first trimester. Abscess is less well controlled in pregnancy and there is a higher frequency of free perforation. For this reason, patients presenting with peritoneal signs should undergo operation without delay. Resection of the source of the sepsis and exteriorization of the bowel ends rather than anastomosis is recommended as an anastomotic leak can prove catastrophic in a pregnant woman, putting both the mother and fetus at increased risk.[38]

The new diagnosis of Crohn's disease in pregnancy is difficult as the symptoms are often nonspecific and are similar to those seen in normal pregnancy.[37] There is often a delay in diagnosis and treatment, which contributes to a poor prognosis.

A minority of pregnant women with ulcerative colitis will need surgery for toxic megacolon. In such cases, a limited surgical procedure may be desirable to reduce the risk of maternal and fetal mortality. The "blow-hole" colostomy and loop ileostomy (Turnbull procedure) has been used successfully in the management of toxic dilation of the colon complicating ulcerative colitis in pregnancy. Completion proctocolectomy and ileal pouch-anal anastomosis can be completed after delivery.[39]

Colorectal Malignancy

Colon cancer during pregnancy is very rare as these tumors are uncommon before age 40.[40,41] The majority of cases of colorectal carcinomas in pregnant women arise from the rectum.[42] This may simply reflect a detection bias by a tendency toward rectal examinations during prenatal care.[43] Delayed diagnosis is common because of similarity between GI complaints common in pregnancy and early signs and symptoms of colon cancer. Digital rectal examination, tests for occult blood, and flexible sigmoidoscopy followed by colonoscopy should be performed for complaints consistent with colonic disease. Treatment of colorectal cancer follows the same general guidelines as for non-pregnant patients.[44] Primary surgical treatment should be performed whenever it is indicated.

The majority of cases of colorectal carcinomas in pregnant women arise from the rectum.

In the first 20 weeks of gestation, hysterectomy is not necessary to safely perform colon or rectal resection so that therapeutic abortion is not mandated.[44] Later in pregnancy, it is preferable to delay surgery to allow fetal maturation and delivery although cancer complications such as hemorrhage, obstruction or perforation may necessitate surgical intervention.[44] Rectal tumors below the pelvic brim may interfere with vaginal delivery and necessitate caesarean section. Stage for stage the survival data are the same for pregnant patients and non-pregnant controls, however diagnosis is often delayed due to pregnancy-associated gastrointestinal symptoms masking cancer symptoms.[44]

Chemotherapy for colorectal cancer does not offer sufficient benefit to the mother to warrant the risk to the fetus.[43] Carcinoembryonic antigen (CEA), a useful tumor marker for colon cancer, may be elevated during pregnancy and therefore is of little value.[42]

A cancer diagnosis during pregnancy is a challenging and potentially devastating situation for the pregnant woman and her family, who are faced with simultaneous life-giving and life-threatening processes.[45] In these situations, close attention to the psychological needs of the patient and her family is as important as meticulous medical care. An interdisciplinary team approach is recommended with close collaboration between the obstetrician, surgeon, oncologist, neonatologist and pediatrician. Involvement of the nursing staff, social worker, chaplain and an ethicist may be useful as well.[45]

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Pregnancy in Inflammatory Bowel Disease

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Crohn's disease and Ulcerative Colitis are two chronic inflammatory conditions involving the gastrointestinal tract. While many aspects in the management of these diseases is identical for all patients, there are some issues that are specific to women that are not necessarily part of routine care. Certain gender-specific issues such as menses, fertility, pregnancy and menopause are often overlooked and mismanaged. Women have different psychological concerns as compared to men with regards to their self-image and impact of disease.

The incidence of Crohn's disease (CD) in women has been increasing over the past few decades.[1] It is not clear whether this is due to improved diagnostic techniques, an increase in smoking habits by young women (patients with CD tend to be smokers compared to people without CD[2]) or other factors not yet identified. However, the consequence of this trend is a growing population of patients with gender specific needs and concerns related to their medical care. Every component of the reproductive cycle can potentially affect disease course or symptoms. Because the diagnosis of CD or Ulcerative Colitis (UC) is often made in the childbearing years, fertility and pregnancy are important issues that previously have been handled exclusively by gynecologists. Health care providers caring for women with Inflammatory Bowel Disease (IBD) should be aware of these issues and their appropriate management. The aim of this paper is to review some clinically relevant gender specific issues in IBD.

Fertility

Overall, the fertility rates for women with IBD are essentially the same as those of the normal population.[3] The major caveat to this rule is in the woman who has undergone ileal pouch-anal anastomosis (IPAA) for ulcerative colitis.[4,5] Fecundity (the physiological ability to reproduce) decreases by upwards of 80% in women who have undergone this procedure; the true etiology of this finding is unclear, but presumed extensive adhesion formation in the pelvis which impairs normal tubal function is thought to play an important role. In the setting where a woman is facing a total colectomy for refractory disease, the possibility of an ileorectal anastomosis should also be discussed. Early studies suggesting lower fertility rates had not taken into account an increased voluntary childlessness rate in women with IBD.

Active Crohn's disease, however, can reduce fertility in several ways, depend-

ing upon the location of inflammation. Active inflammation in the colon has been shown to decrease fertility[6] as well as any inflammation or scarring directly involving the fallopian tubes or ovaries. Women who have had any surgical resection are at risk for adhesions, which can also impair tubal function.

None of the medications used to treat IBD has an effect on female fertility, but it is important to remember that sulfasalazine therapy reduces sperm motility and count in males. While there is no minimum required time period for quiescent disease prior to a planned conception, at least three months is recommended. Open discussions between patient and physician are the best way to ensure the best outcome of a pregnancy. If a woman is doing well and in remission, there is every reason to expect the pregnancy to proceed smoothly. If active disease is present, it is likely to continue through pregnancy and will place the pregnancy at greater risk for a complication.[7] This risk appears to be higher in CD than in UC.

The main priority is to establish and maintain remission before the patient conceives. One of the problems in Crohn's disease is the accurate definition of remission. In CD, a patient may feel fine even though she has an elevated C-reactive protein (CRP), an abnormal colonoscopy and/or x-ray.

Some women remain childless for fear of disease transmission to their offspring. Current data suggests that this risk is low; 7% if one parent has CD and less if one parent has UC.[8] However, the risk of IBD increases as high as 37% if both parents have the disease. The risk of inheriting IBD is higher in Jewish (7.8%) than in non-Jewish (5.8%) families.[9] It is important to remember that IBD is not a "genetic" disorder in the truest sense. Even with genetic predisposition, that other factors are necessary to produce expression of either disease.

Effect of IBD on Pregnancy

Women with inactive IBD appear no more likely to experience spontaneous abortion, still birth, or children born with a congenital abnormality.[9] Figure 1 summarizes results of 24 published reports comparing outcomes in women with IBD versus the normal population. Some work has suggested that babies born to women with IBD, regardless of disease activity, are of smaller birth weight.[10] This appears to be particularly in those women with Crohn's disease. Women with active disease run a greater risk for premature birth.[11]

Some work has suggested that babies born to women with IBD, regardless of disease activity, are of smaller birth weight.

The presence of IBD does not appear to have an impact on maternal complications related to pregnancy, including hypertension or proteinuria.[12] However, active perianal disease may worsen after a vaginal delivery. One retrospective a study of women with CD found that 18% of those without previous perianal disease developed such disease after delivery, usually involving an extensive episiotomy.[13] Otherwise, the presence of IBD does not have a significant impact on the method of delivery, nor is it an indication for Cesarean Section.

Effect of Pregnancy on IBD

For women with quiescent UC, the rate of relapse is approximately the same in pregnant versus non-pregnant patients.[7] This is in contrast to the presence of active disease at the time of conception, which is associated with continued or worsening disease activity in approximately 70% of women. Comparable observations are seen in Crohn's disease. Figures 2 and 3 illustrate pregnancy-related disease activity as reported by Miller and colleagues. The older literature suggested a trend for disease to flare in the first trimester, but this was documented prior to the accepted practice of maintenance therapy, continued even during

pregnancy. A possible explanation for these findings was investigated by Kane et al.[14] They demonstrated that the degree of disparity between mother and fetus in key HLA types predicted disease course throughout pregnancy. Disparity at specific alleles leads to a down-regulation of the mother's innate immune system so as to not "reject" this foreign entity within. A consequence of this down-regulation is a self-induced immunesuppression and a clinical improvement.

It is important to remember that hemoglobin and albumin levels decrease and ESR increase during pregnancy. Because of these normal physiologic changes, disease assessment during pregnancy should rely more on clinical symptoms than laboratory parameters. Ultrasound exams are clearly safe, and there is no evidence that if indicated, that a sigmoidoscopy will induce premature labor.[15] Colonoscopy should only be performed when extent and severity of disease specifically need to be ascertained.

There is data that suggests that a history of child bearing changes the natural history of Crohn's disease.[16] Women having been pregnant had fewer resections or longer intervals between resections as compared to women who had not had children but otherwise similar disease. One theory proposed by the authors is the inhibition of macrophage function by relaxin. Relaxin is a hormone produced exclusively during pregnancy which may result in less fibrosis and stricture formation by this inhibition of macrophages.

Treatment of IBD During Pregnancy

The key principle to management is to remember that the greatest risk to pregnancy is active disease, not active therapy.[17] Since there are limited definitive data available on the safety of IBD medications in pregnancy, the focus therefore should be on establishing remission before conception and maintaining remission during pregnancy.

Sulfasalazine readily crosses the placenta but has not been associated with any fetal abnormalities. However, patients taking sulfasalazine should also be supplemented with folic acid before conceiving to decrease the risk of neural tube defects. A dose of one milligram bid would be appropriate.

The safety of mesalamine during pregnancy has been demonstrated in a number of trials.[3,18] In two separate studies, women taking 2-3g/day had no increased incidence of fetal abnormalities than that in normal healthy women. Topical 5-ASA agents are likewise safe during pregnancy.[19]

The data regarding immunomodulator therapy (azathioprine, 6-MP) is more conflicting. There are no large studies on the use of these medications during pregnancy in women with IBD. To date, our information comes from the transplantation literature[20] and from small retrospective series in IBD.[21,22] It is generally believed by the most experienced IBD clinicians that immunosuppressives such as 6-MP, azathioprine and cyclosporine can be used safely during pregnancy if the mother's health mandates therapy. Methotrexate, another immunomodulatory medication, is contraindicated in pregnancy.

The key principle to management is to remember that the greatest risk to pregnancy is active disease, not active therapy.

Corticosteroids have not been associated with teratogenicity in humans and can be used as required to control disease activity.[11] Prednisone crosses the placenta less efficiently than other steroid formulations such as betamethasone or dexamethasone. Budesonide, while having a high first pass metabolism, has a high binding affinity and not recommended over prednisone. Only limited data is available regarding the safety of antibiotics as treatment for CD. Currently, ampicillin, cephalosporins and erythromycin are believed safe, while ciprofloxacin is relatively contraindicated be-

cause of the potential for arthropathogenecity in the fetus. Metronidazole has been used to treat vaginitis in women during the first trimester of pregnancy but no controlled trials have definitively shown its safety.[23] Table 1 details the safety of those medications used in IBD.

Infliximab is the first biologic therapy approved for use in Crohn's disease. It has been given an FDA Category B safety rating. Post-marketing data suggests it is not associated with an increased risk for congenital anomalies or infectious complications in those children born to mothers receiving this therapy.[24,25]

The medications known to be safe for breastfeeding include sulfasalazine, the mesalamine preparations (Asacol®, Pentasa®, Rowasa®) and steroids. Mothers planning on nursing should discontinue the use of cyclosporine, metronidazole, ciprofloxacin and methotrexate. No data is available regarding the thiopurines and should be discussed on a case by case basis. Table 2 summarizes the safety data regarding medications and their use during breastfeeding. Current studies are underway medication levels in breast milk, to assess for any increased risk of immunosuppression of the infant.

Surgery and Pregnancy

The indications for surgery during pregnancy are identical to that of non-pregnant patients. These include obstruction, perforation, abscess and hemorrhage. Pregnancy has not been shown to complicate stoma function. Women may experience some prolapse due to abdominal pressure, but no increased risk to the pregnancy is encountered.

For those women who have had ileal pouch anal anastomosis procedures, an increase in the number of bowel movements during pregnancy has been reported, but no increased risk for pouchitis or delivery complications has been reported.[26]

Conclusion

The management of women with IBD often presents special challenges to the health care provider. The different phases of the reproductive cycle in a woman's life can lead to significant medication changes and management decisions. While infertility rates are not usually increased, having an ileal pouch is associated with decreased rates of fecundity and patients should be counseled prior to surgery regarding fertility. Management of the pregnant IBD patient has the same goals as for the non-pregnant patient — induce remission in those who are sick, and maintain remission in those who are well. The risk: benefit ratio for the majority of the medications we use to treat IBD weighs heavily in favor of the benefit of a healthy mother. Mode of delivery and breastfeeding decisions should be individualized, based on a patient's surgical history, the presence of perianal disease, and the mother's preferences and obstetric indications.

Figure 1 Effect of IBD on Pregnancy Outcomes in 24 Published Reports

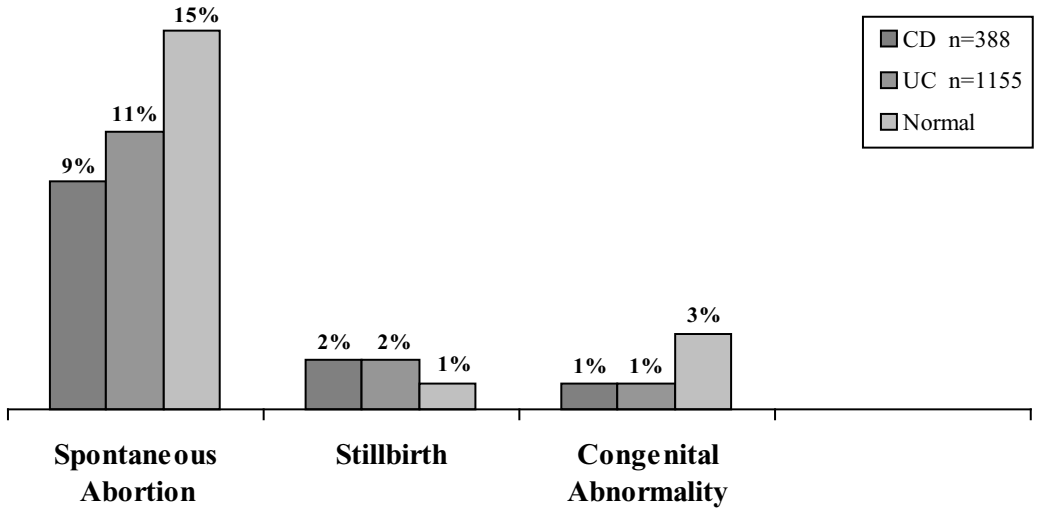

Figure 2 Effect of Pregnancy on UC – Disease Activity at Conception

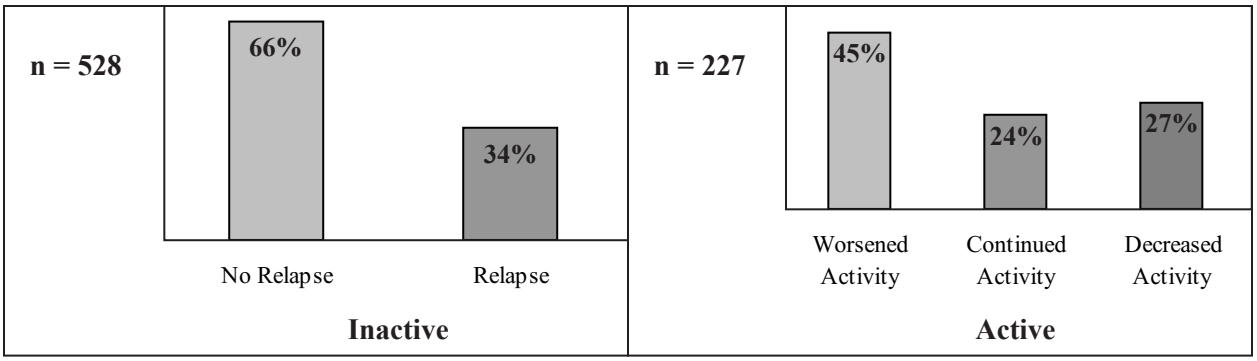

Figure 3 Effect of Pregnancy on CD – Disease Activity at Conception

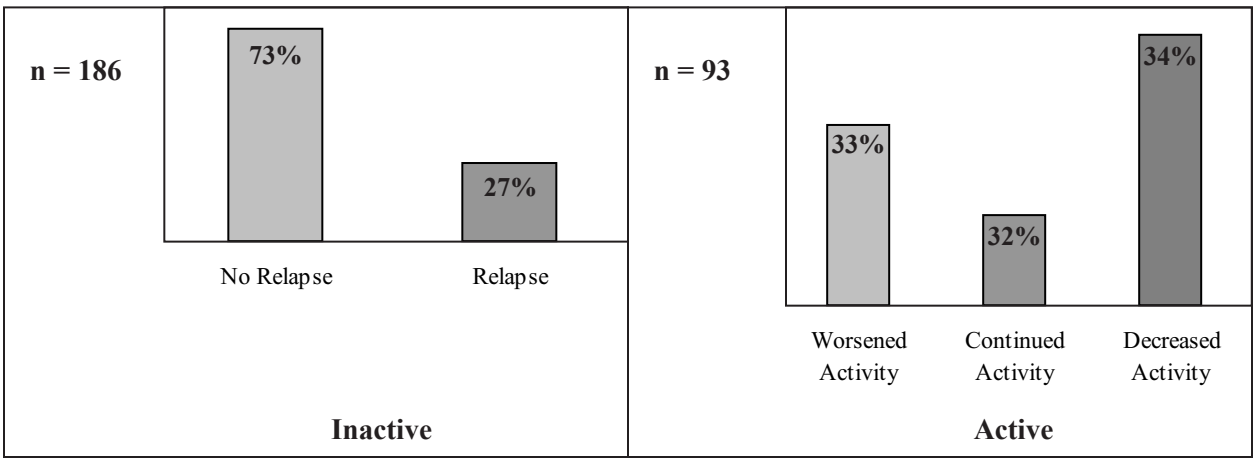

Table 1 Safety of IBD Medications During Pregnancy

Safe to Use When Indicated	Limited Data	Contraindicated
Oral mesalamine, balsalazide	Olsalazine	Methotrexate
Topical mesalamine	Azathioprine/6MP	Thalidomide
Sulfasalazine	Infliximab	
Corticosteroids	Cyclosporine	
Ciprofloxacin (after first trimester)	Metronidazole	

Table 2 Safety of IBD Medications During Breastfeeding

Safe to Use When Indicated	Limited Data	Contraindicated
Oral mesalamine, balsalazide	Olsalazine	Methotrexate
Topical mesalamine	Azathioprine/6MP	Thalidomide
Sulfasalazine	Infliximab	
Corticosteroids	Cyclosporine	
Ciprofloxacin (after first trimester)	Metronidazole	

Table 3 Medications Used in the Treatment of Inflammatory Bowel Disease

Drug	FDA Class	Recommendations for Pregnancy	Recommendations for Breastfeeding[2]
Adalimumab	B	Limited human data: Low risk	No human data: probably compatible
Amoxicillin/ Clavulinic Acid	B	Low risk	Probably compatible
Azathioprine/ 6- mercaptopurine	D	Data in IBD, transplant literature suggest low risk	No human data: potential toxicity
Balsalazide	B	Low risk	No human data: potential diarrhea
Ciprofloxacin	C	Avoid: Potential toxicity to cartilage	Limited human data; probably compatible
Corticosteroids	C	Low risk: possible increased risk: cleft palate, adrenal insufficiency, premature rupture of membranes	Compatible
Cyclosporine	C	Low risk	Limited human data: potential toxicity
Fish Oil Supplements	—	Safe. Possible beneficial.	No human data
Infliximab	B	Low risk	No human data: probably compatible
Mesalamine	B	Low risk	Limited human data: potential diarrhea
Methotrexate	X	Contraindicated: Teratogenic	Contraindicated
Metronidazole	B	Given limited efficacy in IBD, risk of cleft palate, would avoid	Limited human data: potential toxicity
Olsalazine	C	Low risk	Limited human data: potential diarrhea
Rifaximin	C	Animal teratogen. No human data.	No human data: probably compatible
Sulfasalazine	B	Considered safe. Give folate 2 mg daily	Limited human data: potential diarrhea
Tacrolimus	C	Use if mother's health mandates	Limited human data: potential toxicity
Thalidomide	X	Contraindicated: Teratogenic	No human data: potential toxicity

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Appendix

FDA Use-In-Pregnancy Ratings*

Category	Description
A	Adequate, well controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women. Or Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. Or No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate, well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate, well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

*U.S. Food and Drug Administration, FDA Consumer Magazine, Volume 35, #3, May-June 2001.

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