I'm going to be talking about gastroenterology and women's health, a very broad topic that I'm going to try to go through as much as possible. I'm going to quickly start with a background talk a little bit about irritable bowel syndrome, pelvic floor dysfunction, some of the liver diseases that are more common in females, gallstones and pregnancy. Hopefully we'll have time.

Women are higher utilizers of healthcare than men. Some GI disorders affect women more than they do to men. Functional disorders is an example of that such as irritable bowel syndrome, gastroesophageal reflux disease, biliary and autoimmune liver diseases such as gallstones, autoimmune hepatitis, primary biliary cirrhosis amongst many others.

Variations in disease development or expression may be based on physiological differences including genetic factors, hormonal factors, and developmental factors as well as environmental and social factors which is health care seeking behavior.

We're going to move to talk about irritable bowel syndrome. IBS is the most common functional GI disorder, it is the most common diagnosis in GI practices in the United States, and it accounts for approximately 30% of all referrals to GI clinics. In addition IBS is one of the most common reasons for a primary care physician visit. How do we diagnose IBS? There is several criteria we tend to follow around 3 criteria for IBS, the most important thing is for a patient to have the occurrence of abdominal pain and/or discomfort for at least 3 days per month during last 3 months and those symptoms have to occur for at least 6 months prior to presentation. In addition to abdominal pain

and discomfort, patients should have 2 of the 3 following; either symptom improvement after defecation, change in stool frequency, or change in stool appearance or form. It's always important to make sure a patient does not have red flags or alarm symptoms such as pain or diarrhea that awakens them up from sleep, blood in the stool, weight loss, fever or an abnormal physical exam. However, it's always important to know that alarm symptoms do suggest a structural abnormality however it does not negate the presence of irritable bowel syndrome.

So IBS as we all know is split into IBS-C which is constipation predominance, IBS-D which is diarrhea predominance and a mixed pattern or an alternating pattern where patients have diarrhea alternating with constipation.

So what causes IBS? Pathophysiology is still unclear, it is a diagnosis of exclusion unfortunately there's no identifiable cause. However, there's different hypotheses people say maybe it's an altered GI motility, some studies show that it's due to visceral hypersensitivity, dysfunction in the psychosocial aspect, dysregulation of the autonomic nervous system, and most more recently there's been controversial results however looking at bacterial overgrowth, food sensitivity, alterations in fecal flora and a small role for inflammation as a contributor.

IBS in the health care seeking western population is more common in women as compared to men with a ratio of 3:1. Although IBS patients are predominantly female, there is a greater sex difference in the sub group of IBS-C constipation predominance. I'm going to quote 2 studies here one of them

was conducted in Japan where they looked at 2,495 university students. Of these students 268 had irritable bowel syndrome, and IBS-C was associated with the female sex with an odd ration of 6.4. There was really no sex difference in the IBS-D subgroup. Again there's another study which confirms the predominance of IBS of females in IBS-C patients.

Females with IBS not only have pain related symptoms they also have non pain related symptoms. There was a study by Lee et al. in 2001 which recruited only IBS patients. They had a total of 714 of these patients 477 were females. Both males and females had similar GI levels of symptoms severity and psychological problems. But when they sub grouped these patients, abdominal distention and constipation was more commonly reported by females. In addition, female patients more often reported nausea, alterations of tastes and smells, unpleasant sensation on the tongue, morning muscle stiffness and greater food sensitivity.

Although 40% of female patients reported menstrual cycle related worsening of symptoms, few symptom differences were found between the pre and post menopausal women, making it unlikely that most of the gender difference was directly related to the menstrual cycle. So Lee et al. concluded that female patients report higher levels of a variety of intestinal and non intestinal sensory symptoms despite similar levels of IBS severity, abdominal pain, and psychological symptoms.

So why is IBS more common in females? Again multi-factorial, there is a component of hormones, social factors and psychological factors. For a woman bowel functioning may be perceived as a source of embarrassment or shame so younger girls and women and taught that bodily functions should be kept private, so is this contributing to this predominance, we still don't know. Society focuses on thinness, there's been studies showing that bloating and constipation may actually result in psychological stress rather than physical discomfort.

Psychological factors influence seeking health care. IBS patients have been shown to have higher levels of psychological disturbances compared to IBS non patients who are patients with IBS who do not seek medical attention, and to controls. Female IBS patients have been noticed to have higher scores of depression, lower scores for energy as compared to the male IBS patient, and they also demonstrated higher scores on the hysteria scale which suggests greater somatization or fear of pain. Despite this, Axis I psychiatric disorders were not more prevalent in females.

I know we mentioned the menstrual cycle in IBS earlier but that was the second to the end point of that study. Heitkemper et al. conducted a study focusing on if menstrual cycle worsened IBS or not so they asked the question whose symptoms differ, between IBS females on oral contraceptives versus IBS females not taking oral contraceptive, versus controls. And when they compared IBS with controls, IBS females had more severe symptoms of all types both GI symptoms and non GI symptoms such as sleep, cognitive, anxiety, depressive and anger symptoms. So there was no evidence that the pattern of change over menstrual cycle phase, it's different between both groups.

Comparing IBS with oral contraceptive pills versus IBS patients with no oral contraceptive pills, again there was no significant difference for most symptoms of IBS, using OCPs however patients had lower cognitive anxiety and depression, which may be improving their PMS symptoms but not really their IBS symptoms. Menstrual cycle and rectal sensitivity however has been, there has been a link seen. Women with IBS are more sensitive to the rectal sigmoid distention as compared to women with no IBS and compared to males with IBS. During menses rectal distention was associated with increased abdominal pain, bloating, and rectal sensitivity as compared to other phases of the menstrual cycle. So in conclusion IBS is one of the most common GI disorders, it's a diagnosis of exclusion and female predominance is seen particularly in the western countries. And the reasons for this are multifactorial.

Pelvic floor dysfunction is the second topic that we're going to move to. I'm just going to go over normal defecation with you guys. It's a complex series of events related to neuromuscular activity and transit in the GI tract. It also relates to the pelvic floor muscles, form and function and other factors including sensory and dietary issues. The anal sphincters and the pelvic floor regulate storage and evacuation of both stool and urine. Pelvic floor in women is a dome shaped striated composite of muscles that encloses the bladder, uterus and rectum. Stool is transferred from the sigmoid colon to the rectum by high amplitude colonic contractions. This tends to occur in the morning upon awakening and after meals. Rectal distention then occurs when the stool is pushed from the sigmoid colon to the rectum. And when this distention occurs what happens then induces

reflex relaxation of the internal anal sphincter which allows the stool now to drop into the anal canal until voluntary defecation is desired. When voluntary defecation occurs what happens is that people increase their intraabdominal pressure, relax the puborectalis muscle which is this sling that is around the rectum and there is descent of the pelvic floor which widens the angle between the rectum and the anal canal. This whole thing in addition to inhibition of the external anal sphincter allows people to have a normal defecation.

Paradoxical contractions or failure of relaxation of the pelvic floor muscles with bearing down causes a functional obstruction which manifests with symptoms of constipation; so usually when we see patients with constipation we try to categorize them into one of three groups, either that they have functional constipation related to IBS-C or chronic or idiopathic constipation, this is the most prevalent condition that we see; slow transit constipation due to a problem with motility, this is the least prevalent and defecation disorder which encompasses the pelvic floor dysfunction, dyssynergia.

It's extremely important to conduct a detailed physical exam in those patients, you have to examine their abdomen, neurologic exams evaluating for signs of neuropathy and a rectal exam both looking at the anal area and digital rectal exam. When we look at the anal area we check for excoriations, skin tags which may tell us if a patient had a fistula before or not, fissures, hemorrhoids and scars from prior episiotomies. Digital exam we assess for anal stricture, stool in the rectal vault, sphincter tone at rest, this assesses for the internal anal sphincter, sphincter tone during a squeeze which assesses for the external anal sphincter and we also check for pelvic descent by asking patients to

bear down and assess the strength of pelvic floor muscles. In the absence of alarm signs and symptoms studies have shown that there is no evidence to support the use of extra lab testing, x-rays or endoscopy. The only thing we usually you know perform is anal manometry to help us confirm the diagnosis and, you know, know which type of dyssynergia the patient has.

So the prevalence of pelvic floor dyssynergia ranges between 20 to 81% at tertiary referral centers and this actually depends on the expertise and availability at certain centers. So if it's a pelvic floor dysfunction center people will have a higher – the prevalence will be higher. Prevalence is 3 times higher in women versus men and this is believed – and this disease is believed to be an acquired behavioral disorder. Two-thirds of patients learn to relax their external anal sphincter and puborectalis muscle appropriately with biofeedback training. Increased muscle tension may also result from symptoms of anxiety and/or psychological stress. Sexual abuse has been reported in 22% of women with functional defecation disorders. Older women tend to have pelvic floor dysfunction and the main reason is failure of the anorectal angle to open and excessive perineal descent from any prolapse that is present.

Manometry, I'm not going to go over the details but what we usually assess is the intrarectal pressure and the anal sphincter pressure and depending on if it's high, if the anal sphincter fails to relax we make the diagnosis.

In conclusion pelvic floor dysfunction accounts for 33% of constipation in the community and up to 70% of cases seen in tertiary centers. There is a female predominance and biofeedback is a very effective treatment.

I'm going to shift gears and move to liver diseases. Women are at a significantly higher risk of developing more serious liver disease than men even after adjusting for body weight. Women are also more likely to develop alcohol induced liver disease with less alcohol consumption. Autoimmune hepatitis is – was initially described as disease of young girls because more frequently seen in younger females. As with any autoimmune condition it is more common in females. Prevalence of autoimmune hepatitis in the U.S. is approximately 50 per million and the female predominance is in a 3 to 1 ratio.

Primary biliary cirrhosis primarily affects women and only 5% of PBC patients are men. The pathogenesis of PBC is unclear but it is characterized by T lymphocyte mediated attack on small intralobular bile ducts. Antimitochondrial antibody has a high sensitivity and specificity for PBC so this is something that we frequently check. Pruritus and fatigue are common presenting symptoms of this condition.

I'm not going to go over the details but focal nodular hyperplasia, hepatic adenomas and hemangiomas are liver lesions that are more commonly seen in female patients.

Gallstones, highly prevalent affecting more than 20 million Americans, the majority are fortunately asymptomatic. Two major types of gallstones exist, pigmented gallstones and cholesterol gallstones. What happens is that bile becomes increasingly lithogenic with age, with increased cholesterol secretion and with decreased bile secretion. Female gender increases the incidence of having gallstones up to 4 times until the age of 50, that's because of the effect of estrogen. What estrogen does is that it increases cholesterol secretion in bile and decreases the concentration of bile acids. Both these together supersaturate bile which makes it more prone to forming sludge and stones.

Another very broad topic, GI diseases and pregnancy, so there is 4 conditions that we usually worry about and see in patients who are pregnant, they are pertaining to the liver: hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, HELLP syndrome and acute fatty liver of pregnancy. For this part I decided to change the format of the presentation and make it in a question and answer format just because I think it's extremely helpful to compare different cases because we'll be able to tell the differences between these conditions more easily.

So a 19 year old healthy primigravida at 10 weeks of gestation has had intractable vomiting for 2 weeks. She is dehydrated, has lost weight and is jaundiced. Labs include an AST of 346, ALT of 675 and an elevated bilirubin of 5. So which of the following is the most likely diagnosis? Is it acute viral hepatitis, acute fatty liver of pregnancy, hyperemesis gravidarum, gastric outlet obstruction or cholecystitis?

So I'm hearing a lot of Cs, and that is correct. Hyperemesis gravidarum is when patients have – pregnant female patients have intractable vomiting in the first trimester it usually resolves by week 20 so that was one of the tip offs as to why this is hyperemesis gravidarum. It affects .3% of all pregnancies. Risk factors include hyperthyroidism, psych illnesses, multiparity, diabetes mellitus. On labs high transaminase levels can occur in up to 20-fold above normal limits and jaundice is not uncommon. It's imperative to exclude viral hepatitis and what we treat those patients with, we admit them, we make sure they are – we rehydrate them, give them IV fluids and antiemetics to support them through their pregnancy, through the first trimester because hopefully this is supposed to resolve during the second and third trimesters.

Now question number 2, a 32 year old woman is 24 weeks pregnant, sorry 24 weeks into her second pregnancy and has had 2 weeks of pruritus. She has had a history of gallstones, currently she feels well and denies any pain or fever. Physical exam reveals a gravid abdomen. Labs include an elevated AST at 277, elevated ALT at 655 and a bilirubin of 2.5. A right upper quadrant ultrasound is performed and reveals no ductal dilatation. So what is the next best steps?

I'd take a look at your answers and why don't you ask those that are in favor of A to raise their hands?

Okay A? B? C? D? And then E? Okay. So it's not E, it's actually D. And I'll explain to you why. So intrahepatic cholestasis of pregnancy is most likely what this patient has. This is a disease

entity due to elevation of bile acids from abnormal biliary transport across bile canalicular membranes. It's a variable prevalence, usually in U.S. pregnancy it's approximately 0.1, it affects 0.1% of U.S. pregnancies. There is a geographic variation with a high incidence in Chile and Sweden, and we don't know why. And it seems to have a seasonal variation peaking in November, again we don't know why. There is a genetic predisposition which affects the transporter protein mutation. It usually appears in the second half of pregnancy and disappears after delivery. Pruritus is a very common presentation and there has been reports of suicide because pruritus is so intense that these people tend to kill themselves. Jaundice is present in 20% of cases, and the labs shows transaminases with mild elevation but can be increased up to 10 to 20 times of upper limit of normal. Alkaline phosphatase is elevated 2 to 3 times upper limit of normal but looking at alkaline phosphatase is not so helpful because alkaline phosphatase is elevated in pregnancy because of the placenta. Bilirubin typically is less than 5 and the key thing is serum bile acid levels, we usually measure them and if they are elevated that's what gives us the diagnosis. Treatment is controlling the pruritus, we give Ursodiol and Cholestyramine. The good thing is fetal complications is less than 2% in this case.

Question 3. A 23 year old primigravida with twin gestation at 32 weeks presents for hypertension evaluation. She is currently taking Methyldopa, despite treatment she continues to have systolic blood pressures in the 160s. Exam reveals 1+ low extremity edema. Labs show a hemoglobin of 8.5, AST 95, ALT 85, mildly elevated, and low platelet count of 90,000. Her bilirubin is 1.5, INR is 1 and her creatinine is normal at .7. Her albumen is mildly decreased at 3.1. So a right upper

quadrant ultrasound is performed and that's normal. So what's the next best step in management? A, switch her antihypertensive to Labetalol and send her home and tell her to come back later. B, admit patient, switch Methyldopa to Labetalol and give Corticosteroids to promote fetal lung maturity, the babies are 32 weeks. C is admit patient for observation, just watch her. And D is liver biopsy. E is immediate delivery. So there is – it's between B and E and I think both of them correct. B is the right answer just because you know the baby is still 32 weeks rather than a little more mature.

So this patient has HELLP syndrome which develops in .2 to .6% of pregnancies. Diagnosis and management still controversial, however what we do is stabilize the patient, treat her hypertension and DIC, give her seizure prophylaxis and deliver her. We usually try to wait until 34 weeks and we tend to give steroids if she presents sooner for fetal lung maturity. On labs patients have microangiopathic hemolytic anemia, elevated liver enzymes, AST and ALT are low and low platelets. Most patients present between 27 and 36 weeks with variable symptoms. Pain is the most common.

Last question. A 36 year old primigravida presents at 34 weeks gestation with 2 day history of nausea and abdominal pain. She appears ill with jaundice, tachycardia and blood pressure of 140/95. Her exam reveals a distended abdomen without hepatosplenomegaly or ascites. She has mild peripheral edema and is very drowsy. Lab tests show the following: her bili is high at 13.6, AST, ALT are high 580 and 753 respectively. Hemoglobin not so bad, 10.5. White count extremely high

at 27,000. Platelets are low but not very low at 105,000. INR is 3.2, creatinine is 1.6 and glucose is 85. The most likely diagnosis is?

So HELLP Syndrome? Not really because her – she does not have anemia. No hemolytic anemia. B, fulminant viral hepatitis? Maybe but this is a pregnancy question so less likely. C, intrahepatic cholestasis of pregnancy? No because this patient is actually in liver failure, she is drowsy, her INR is 3.2, she basically has hepatic encephalopathy so she has acute fatty liver of pregnancy, which is an emergency. So she's in liver failure secondary to microvesicular fatty infiltration which surprisingly reverses after delivery. It leads to hepatic encephalopathy and liver failure. It affects 0.005 to 0.01% of pregnancies and maternal mortality is 7 to 18% and fetal mortality 9 to 23%. It's a sudden catastrophic illness of the third trimester.

Symptoms include nausea, vomiting, pain, jaundice, anorexia and sometimes fulminant liver failure. Labs as we saw, transaminase levels between 300 and 500 but can range as high as 1,000. Bilirubin is typically less than 5 mg/dl. Patients have normocytic anemia but not as bad as the HELLP Syndrome and they also coagulopathy. Liver biopsy is diagnostic and prompt delivery following maternal stabilization is what is recommended. Most patients recover, however this condition unfortunately can recur.

Just one or two more slides. Like we all know chronic GI illnesses such as inflammatory bowel disease require patients to continue their medications during pregnancy and there is always a concern

and a question can we continue this medicine, can we not? Patients are on immunomodulators for their IBD, anti-TNF agents and both physicians and patients are concerned about this. However it's extremely important to maintain IBD intermission during pregnancy because it decreases complications later for both the mom and the baby.

Also we have diseases that we – symptoms that we need to manage in pregnant women like GERD and constipation so it's really important to know which medications are compatible with pregnancy or not. I couldn't go through everything but this here is the FDA has developed a system to categorize drugs according to their safety, A being very like safe because controlled studies in animals and humans showed no risk; and then they increase in risk A, B, C, D, and X. X is studies that showed that really the drug is contraindicated because it's going to cause severe fetal abnormalities.

This is the last slide, I just put some of the medications we use and I'm just going to go over the ones that are X category. Methotrexate particularly in younger people, younger people with IBD who are on Methotrexate we stop this if they have any interest in conceiving. We even stop it around 9 months before they even start trying to get pregnant. Thalidomide, Bismuth, sodium bicarb containing antacids because of the metabolic alkalosis fluid overload potential, Tetracyclines and Ribavirins. And by this I'm going to end the talk. Thank you.