Gastrointestinal and Liver Disorders in Women's Health

A Point of Care Clinical Guide

Poonam Beniwal-Patel
Reza Shaker
Editors

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Preface

Several gastrointestinal and liver disorders have increased predilection in women and, as such, require a personalized approach to diagnosis and management. Furthermore, gastrointestinal and liver disorders during pregnancy can present a significant clinical challenge and require a multidisciplinary approach to ensure a healthy pregnancy and good fetal outcomes.

Women of childbearing age frequently contemplate whether their gastrointestinal or liver disease will be a barrier to a healthy pregnancy. Pregnant patients often have many questions for their providers regarding the effect of diagnostic and therapeutic interventions on their babies and themselves. Patients with active disease despite medical therapy and those who have experienced side effects or complications of therapies require even more complex care during pregnancy.

Every provider has been faced with the questions: "If I get pregnant, will my chronic condition impact my baby? "What impact will the medications I am on have on my baby?" "Are there alternative therapies during pregnancy can I try?

These questions, while seemingly straightforward, require the provider to boil down a complex and large volume of literature into a simple answer the patient can comprehend

This book will focus on answers to the patient questions that are frequently posed to providers who care for pregnant patients with GI and liver disorders. *The purpose of this book is to be a point-of-care reference for busy clinicians who need the best evidence-based answers to patient questions at their fingertips.*

Each chapter is predicated on a real patient question that has been encountered in our clinics at the Medical College of Wisconsin. Every clinician in his/her early training has frequently struggled to answer patients in a simple and coherent manner. This requires spending a great deal of time researching and evaluating the literature to provide patients with the most understandable and comprehensive answers. In speaking with other gastroenterologists and hepatologists, it was found that many have shared this same experience and delivered many of the same answers to the same patient questions. This shared experience was the origin of the concept for this handbook: put the expert's answers to common patient questions in the hands of busy providers right at the point of care.

Each chapter starts with a patient question, which leads to a much wider topic. Following the suggested response is a brief review of the literature as it pertains to the patient question and the chapter topic. These reviews are designed to be read in a few minutes and provide high yield information. This information will further enable the provider to formulate their response to any follow-up questions patients may have. It is hoped that clinicians in different clinical settings will benefit from this review of the literature: students, midlevel providers, GI fellows, and busy general gastroenterologists alike.

We hope you will find *Gastrointestinal and Liver Disorders in Women's Health: A Point of Care Clinical Guide* to be a valuable clinical tool in your busy practice.

Milwaukee, WI, USA

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Part I
Gender-Based Differences in Gastrointestinal Disorders

Chapter 1
Differential Diagnoses Between Primary Eating Disorders and Disordered Eating Secondary to a Primary Gastrointestinal Disorder

Jennifer Heinemann and Courtney Barry

"When is disordered eating considered an eating disorder in GI patients? How do I know if my changes in eating behaviors are from my GI issue or if they are from an eating disorder?" – Patient Question

Physician Response: "There is considerable symptom overlap among eating disorders and gastrointestinal (GI) disorders; therefore a thorough assessment to ensure accurate diagnosis is crucial in providing the most effective treatment. Eating disorders are psychiatric disorders, which means they are influenced by thoughts and behaviors and can be treated with cognitive-behavioral therapy and pharmacotherapy [1]. Conversely gastrointestinal (GI) disorders are physiological disorders, meaning they are caused by impaired function of your GI tract. It is possible to have symptoms of both an eating disorder and a GI disorder at the same time. Our thoughts and behaviors affect how we experience our physical symptoms and can help to alleviate or exacerbate those symptoms. At the same time, our physical symptoms can influence our thoughts and behaviors and can lead to changes in our mood. Therefore, it can be difficult to determine if the root causes of a symptom are thoughts, behaviors, physical issues, or a combination of these factors.

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Research in Disordered Eating with GI patients

Neglecting to address psychological issues that impact GI symptoms can lead to a delay in effective treatment [2]. Addressing maladaptive cognitive, behavioral, and emotional factors can reduce disordered eating and improve success in treatment of GI disorders [3, 4]. The mind-body connection's influence on the GI system is well documented. In addition, the connection between disordered eating (the mind) and the GI system (the body) is also well established [2, 5]. Many patients with disordered eating, such as anorexia nervosa or bulimia, will present with GI symptoms or complaints such as failure to gain weight or weight loss, restricted eating, bloating, nausea, purging, constipation or diarrhea, early satiety, abdominal discomfort, and gastroesophageal reflux. In fact, GI specialists may be the first provider to whom an eating disordered patient presents with GI symptoms [6]. It is often difficult to differentiate a primary eating disorder from a GI diagnosis such as food-related GI disorders such as celiac disease, inflammatory bowel disease, cyclical vomiting syndrome, or peptic ulcer disease. GI patients often present with symptoms such as weight loss, vomiting, malnutrition, anemia, or selective eating that may suggest eating disordered behavior, but is not primarily from having an eating disorder diagnosis.

It is imperative to rule out a primary eating disorder when addressing GI symptoms, as most food-related symptoms in eating disordered patients are functional, and there is no evidence in the literature that eating disordered patients have a higher prevalence of GI disorders than the general population [6]. A primary eating disordered patient should be referred to mental health professionals who specialize in eating disorders. Without proper psychological and often psychiatric treatment, these patients are unlikely to improve.

Making the Diagnosis of Eating Disorder

The DSM-V characterizes a primary eating disorder as "a persistent disturbance of eating or eating-related behavior that results in the altered consumption or absorption of food and that significantly impairs physical health or psychosocial functioning" [7]. More specifically, anorexia nervosa entails a restriction of energy intake resulting in significantly lower body weight than expected for one's age, height, and so forth along with an intense fear of gaining weight or becoming fat. This fear can be manifested in verbalizing maladaptive cognition or behavior that persistently interferes with weight gain, even though already at a significantly low body weight. Overall, there is a disturbance in the manner that the person perceives their own body weight, size, or shape with a significant influence on body image on self-evaluation or a continued lack of recognition of the low body weight. Anorexia can be demonstrated in either just restricting behavior or with also binge eating and purging behavior. A diagnosis of bulimia nervosa requires recurrent episodes of eating a large amount of food in a discrete time period while also having a feeling of loss of control over that food

intake as well as the use of inappropriate compensatory behaviors repeatedly to prevent weight gain (such as vomiting, diuretics, laxatives, fasting, or excessive exercise). One would have to meet the threshold of these episodes occurring at least once a week for 3 months. Like patients with anorexia, patients with bulimia have poor body image, significantly influenced by their body weight, shape, or size.

Distinguishing between a primary eating disorder and disordered eating as a result of a GI disorder requires a thorough assessment of reported symptoms and physical exam findings prior to considering a primary psychiatric diagnosis. It is not unusual for a patient who has poor communication skills or presents in a confrontative manner that makes assessment difficult to be more likely to label a psychiatric case before considering a more extensive physical examination. Bern et al. [5] suggest trying nutritional rehabilitation first and only conducting more extensive diagnostics if educational and therapeutic intervention for nutritional behavioral changes fails [5]. In a primary eating disorder, nutritional rehabilitation can significantly reduce GI symptoms, thus ruling out a primary gastrointestinal disease. However, this still entails attention to the whole person and what information somatic symptoms may be conveying. Patients exhibiting psychiatric symptoms may have difficulty conveying a detailed history, which can lead to a delayed or missed diagnosis.

Eating disorders that are often diagnosed with patients with nonspecific GI complaints such as vomiting or nausea, restricted eating or early satiety, and abdominal fullness or abdominal pain include anorexia nervosa (AN) and bulimia nervosa (BN) but can also include other specified feeding or eating disorders such as atypical anorexia nervosa, bulimia nervosa of low frequency and/or limited duration, binge eating disorder, or purging disorder [6]. Elimination disorders are another class of psychiatric diagnoses that can complicate differential diagnosis with GI disorders, but will not be addressed in this chapter. The most common eating disorders that may mimic disordered eating from a GI disorder are AN and BN. AN is typified by a restriction in energy intake relative to the needs of the individual which results in significantly lower body weight than expected for that individual as well as a fear of gaining weight or becoming fat or persistent behavior that interferes with weight gain. In addition, the patient would indicate a distorted body image. BN is indicated by recurrent episodes of binge eating as well as recurrent inappropriate compensatory behaviors in order to prevent weight gain. These patients also have a poor body image.

Physicians should be aware that a presentation of nonspecific GI complaints may be not a primary eating disorder but a primary GI disorder with a secondary, reactive eating disorder which may result in additional secondary GI complaints [5]. It's a case of which came first and can be extremely difficult to parse out, but an accurate understanding is essential of appropriate and effective treatment. The layers of possibilities can be convoluted and take time and patience to sort through. Besides lab work and physical examination including a full discussion with the patient regarding their history, timeline of symptoms, day-to-day life, and stressors, clinicians can determine which symptoms the patient has and if these are likely to be attributed to a GI disorder or an eating disorder (Table 1.2).

Prevalence of Eating Disorders

Eating disorders can occur in either gender. Previously in the *Diagnostic and Statistical Manual of Mental Disorders* – Fourth Edition – Text Revision (DSM-IV-TR), there were gender-based diagnostic criteria for eating disorders [8]. This included for AN, amenorrhea [8]. The National Institute of Mental Health gave the National Comorbidity Survey Replication to over 9000 individuals in 2001–2003 [9]. The survey consisted of questions based on DSM-IV mental disorders [9]. The results demonstrated a 1.2% overall prevalence of binge eating disorder in adults, with a lifetime prevalence of 2.8% [9]. In adults, the overall prevalence of BN was 0.3%, while the lifetime prevalence was 1.0% [9]. The lifetime prevalence for AN was 0.6%, based on National Comorbidity Survey Replication [9].

With the change in the diagnostic criteria for eating disorders, the *Diagnostic and Statistical Manual of Mental Disorders* – Fifth Version – (DSM-V) has removed some of the gender-biased criteria and expanded the severity ratings [8]. With the removal, there is an increase in the number of males being diagnosed with eating disorders [8]. In examining the prevalence of eating disorders, a systematic review of 19 studies using the DSM-V diagnostic criteria found a higher prevalence of BED in females than males, and the prevalence increased with age [10]. Further literature discusses epidemiological studies, in which females are diagnosed with AN and BN more than males [11, 12].

In examining various symptoms and help-seeking behaviors for eating disorders, there is a gender difference in symptom-reporting and treatment behaviors. Women are more likely to be focused on their weight and physical appearance [12, 13]. An article by Striegel-Moore et al. (2009) reported that more women have difficulty controlling how much and type of food they consume, while males tend to engage in overeating [12]. To manage their weight, men are more likely to engage in binge eating and utilize exercise to reduce their weight, while females are more likely to use purging behaviors [12]. Several studies also identified that women are more likely to seek treatment than males [11, 14]. Females were more likely to seek treatment for their eating disorder, if they recognized their eating disordered behaviors [14]. Although there might be differences in symptoms among males and females, it is imperative for physicians to recognize the symptoms of eating disorders and be able to recommend treatment appropriately.

Differential Diagnoses Between Eating Disorders and GI Disorders

When evaluating a patient, it is important to recognize that symptoms can potentially indicate either an eating disorder or a GI disorder. It is also essential to be knowledgeable about disordered eating behaviors that often occur as a result of a GI disorder and are not necessarily indicative of an eating disorder but rather a behavioral reaction to underlying physical issues. And finally, as stated above, these

behavioral reactions may also meet the threshold for an independent diagnosis of eating disorder, even if these disordered eating symptoms are a result only of the primary GI disorder. Table 1.1 indicates disordered eating behaviors or symptoms and which eating disorders they typically present in and the degree to which a healthcare professional would expect to see that symptom in the particular eating

Table 1.1 Symptoms of most prevalent eating disorders

Eating disorder	Symptoms
Anorexia nervosa	Undernutrition/restrictive eating
	Underweight
	Fear of gaining weight
	Poor body image
	Epigastric discomfort
	Constipation
	Early satiety
	Bloating
	Diarrhea
Bulimia nervosa	Eating significantly larger amount of food
	Sense of loss of control
	Self-induced vomiting
	Misuse of laxatives or diuretics
	Fasting or excessive exercise
	Poor body image
	Bloating
	Diarrhea
	Dental Erosion
	Esophagitis
	Chronic vomiting/nausea
	Epigastric discomfort
	Reflux
Binge eating disorder	Eating significantly larger amount of food
	Sense of loss of control over eating
	Rapid eating
	Eating until uncomfortably full
	Eating large amounts when not hungry
	Eating alone due to embarrassment
	Feelings of disgust, depression or guilt
	Epigastric discomfort
	Nausea
	Bloating
	Sporadic fasting
Purging disorder	Self-induced vomiting
	Misuse of laxatives or diuretics
	Dental erosion
	Esophagitis
	Chronic vomiting/nausea
	Reflux

Table 1.2 Differentiating prevalent eating disorders

Eating disorder	Differential medical diagnosis
Anorexia nervosa	Irritable bowel disorder
	Celiac disease
	Peptic ulcer disease
	GERD
	Eosinophilic esophagitis
	Primary ED with secondary GI dysmotility
	Malignancy
Bulimia nervosa	Cyclic vomiting syndrome
	Achalasia
	Gastritis
	GERD
	Diverticulitis
	Celiac disease
	Peptic ulcer disease
Binge eating disorder	GERD
	Prader-Willi syndrome
	Irritable bowel disorder
Purging disorder	Cyclic vomiting syndrome
	Achalasia
	Gastritis
	GERD
	Diverticulitis
	Celiac disease
	Peptic ulcer disease
	Liver/gallbladder disease

disorder diagnosis. While there is overlap in symptomatology among the various eating disorders, there is always at least one distinguishing difference that should help make the diagnosis clear. Table 1.2 indicates suggested differential diagnoses to rule out for various disordered eating behaviors.

Understanding the Impact of General Psychological Issues on GI Symptoms

The mind-body connection between disordered eating and GI symptoms, but more generally GI symptoms and overall psychological symptoms, is well documented [1, 3]. Even people without a clinical diagnosis may notice GI symptoms when experiencing every day anxiety, stress, or grief. Prior to giving an important presentation, one might note "butterflies" and indigestion. During a particularly stressful stretch at work, one might note increases in reflux and changes in bowel movements. After the loss of a loved one, one might note a decrease in

appetite or even some nausea. All of these are common somatic responses to psychological issues that are not considered clinically diagnosable. However, for patients who have clinical levels of anxiety or depression, GI symptoms can be quite prevalent, including exacerbation of existing medical disorders. Patients with anxiety disorders can exhibit a range of GI symptoms such as feelings of choking, nausea, abdominal distress, restriction of food intake, or avoidance of specific foods. A specific example of a GI symptom brought on by psychiatric symptoms alone would be constipation and other changes in bowel symptoms secondary to a patient with obsessive compulsive disorder and contamination concerns in public situations avoiding public restrooms. Patients with mood disorders can exhibit a range of GI symptoms such as weight changes, changes in appetite, specific food cravings, and abdominal pain. Another specific example of a GI symptom brought on by psychiatric symptoms – this time mood-related – would be cramping and changes in bowel movements due to the gut-mind axis connection.

The influence of the mind-body connection goes both ways. Not only do psychological factors influence somatic symptoms, but physical disorders can adversely influence psychological symptoms. For instance, patients with irritable bowel syndrome (IBS) tend to have psychological symptoms such as depression [3], and depression appears to increase the severity of GI symptoms in IBS patients [15, 16].

Ruling Out Somatic Symptom and Related Disorders

Because GI symptomatology can be rather nonspecific and difficult to rule out physical causality, it is not infrequent that GI symptoms are involved when a factitious disorder presents itself [16]. Factitious disorders differ from other somatic symptom disorders in that they include a conscious decision to deceive by exaggerating, falsifying, mimicking, or creating somatic symptoms that do not exist. Factitious disorders can include falsification of physical or psychological symptoms by one's own self or by another, typically a parent or guardian. The former was previously known as Munchausen's and the latter as Munchausen's by proxy. A person diagnosed with factitious disorder differs from a person who is reporting symptoms for primary gain such as financial gain from a lawsuit or other obvious external rewards, which is referred to as malingering. Instead, a person with factitious disorder is manifesting their psychological distress deliberately as a somatic issue does not have any clear primary reward and can create significant psychological distress as well as potential functional impairment by creating harm to oneself. This is an even higher risk for factitious disorder by proxy. This disorder is mentioned here as a potential rule out diagnosis to consider if there are no obvious primary gains, no physical symptoms can be found, and other diagnoses do not fit. If factitious disorder is suspected, a referral to a health psychologist should occur to confirm. Factitious disorders are rare but can cause great cost to the patient and the medical system when one does occur.

A GI patient is more likely to present with a somatic symptom disorder. Somatic symptom disorder presents as one or more somatic symptoms that significantly adversely impact the patient either psychologically or in their day-to-day functioning. These symptoms lead to obsessive thoughts or anxiety or excessive time or energy spent on the symptom. These symptoms are not consciously or intentionally created by the patient. GI professionals are likely to see somatic symptom disorder as a result of significant stress as it is common for people to experience stress somatically with abdominal discomfort, changes in bowel movements, changes in hunger, nausea, or even vomiting. Understanding the psychology of somatic symptom disorders helps one understand the mind-body connection between disordered eating and GI disorders [16]. For instance, a patient may experience severe nausea related to a stressful event. Rather than addressing the underlying psychological stress, the patient focuses on the nausea, becoming anxious about any potential nausea, thus creating the likelihood of experiencing or noticing any nausea in the future. And so the cycle begins.

Somatic symptom disorders, factitious disorders, and eating disorders are important to rule out because these disorders can lead to excessive and potentially harmful – or at best, not helpful – medical intervention. This is not to say that the GI professional cannot be helpful to this patient. Instead, the GI professional may be the most important team member to lead the patient to a successful recovery. When a patient is experiencing a physical symptom, it is essential to have physical causes considered and ruled out as appropriate. A kind, supportive, and informative bedside manner can help the patient appreciate the lack of physical cause as well as understand that the lack of a physical diagnosis does not mean they are not experiencing physical symptoms. The GI physician has great credence from the patient's perspective, and by explaining the mind-body connection and providing positive support for psychological intervention, the GI physician can give the gifts of acceptance and start the patient on the road to recovery.

Specific Case Studies

While the above sections have discussed the general relation between psychological and GI symptoms and how this can lead to the relation between disordered eating and GI symptoms, it is helpful to note a few particular rare cases to highlight the complexities of this clinical intersection and the importance of a thorough exam and history and the use of mental health consultants.

Kirkcaldy et al. [17] identify a case in which obsessive compulsive disorder presented with the somatic symptom of persistent vomiting [17]. In this case, the somatic symptomatology is completely explained by the psychiatric diagnosis [17].

Demaria et al. [18] identify a case in which the patient presented with an apparent case of anorexia nervosa that was later diagnosed to be mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). In other words, the psychiatric symptomatology was completely explained by a medical diagnosis [18]. The

18-year-old patient described had been experiencing symptoms, starting at age 6, of periodic episodes of diarrhea, abdominal pain, postprandial emesis, and persistent weight loss. Initial medical investigation ruled out several malabsorption conditions or GI diseases. A neuropsychiatric evaluation ruled out disordered eating. Further testing as recommended by a multidisciplinary team, including brain MRI, spectroscopic study, nerve conduction studies, and urine chromatography led to the sequence analysis of the TYMP gene and thus the eventual diagnosis of MNGIE.

Making a Referral

When making a referral to mental health, there is a variety of specialists you can use. Your best option is to have one clinic or one psychologist to whom you trust sending referrals. You can contact that provider or clinic about cases that may need to be referred elsewhere, and they can help you determine where to refer. In general, it would be recommended that GI providers have an established relationship with a health psychologist. Health psychologists are specialists in developing strategies that help medical patients achieve improvements in both emotional and physical health. Health psychologists address social, cognitive, and psychological issues alongside medical and biological issues to treat the whole person and work closely with physicians to determine best approach to helping each patient achieve optimal health. It would also be helpful to have a referring relationship with an eating disorder specialist. While health psychologists can address and diagnose disordered deating, eating disorder specialists are best trained to treat eating disorders.

It can be difficult for many nonmental health providers to finesse an approach to suggesting a referral to mental health in a way that the provider feels comfortable and the patient feels supported. Patient can often feel that they are being dismissed by a provider who doesn't want to help them or who doesn't understand them. They may feel the provider feels it's "all in their head." However, a mental health referral can be not only an opportunity to connect a patient with much needed care but also an opportunity to demonstrate that you as a provider have truly heard and connected with them and want to treat them as a whole person, finding them every resource to maximize their health. Approaching a referral suggestion of mental health with an attitude of respect, caring, and support can lead a patient to feel like someone is finally listening to how hard this has been for them. One should use caution to not dismiss the patient while making a referral. Even if you do not plan to follow up with the patient, you might state that you are willing to talk to the mental health professional directly to discuss their case if they would desire and if the other provider would find that helpful. You might also state that you hope that that provider will keep you in the loop, cc'ing at least the initial note to you because you believe that this follow-up will be very helpful for the patient and you want to make sure that they are able to connect with the new provider and not fall through the cracks. You may ask if you, or one of your staff, could follow up by phone to make sure that they have no difficulty getting in and making appointments with the new provider

and that a good fit has been found. You can reassure that if, for some reason, the new provider doesn't work out (insurance, personality fit, schedules, etc.), that you want the patient to call your office, and that you will provide an alternate referral. The main points are to demonstrate caring, your belief that this referral will be helpful, even essential, for the patient's health and that, by referring to someone else, you are not abandoning them but getting them the care they need. With this approach, patients tend to not take offensive but instead feel supported and believe that the referring provider is going above and beyond by looking out for their needs.

"How can a health psychologist help a GI patient with disordered eating?" – Patient Question
Physician Response: "A health psychologist is a licensed doctoral-level psychologist who addresses physical, psychological/emotional, and social factors that might affect a person's wellness and health. A health psychologist can also help you improve coping with health issues to ensure that your emotional health does not suffer. The health psychologist is a member of the treatment team and works with physicians and other healthcare providers in the patient's treatment. The health psychologist can help the physicians understand other factors that might be contributing to or exacerbating GI disorders and work with the team to develop a plan to address the underlying causes of these behaviors. The health psychologist can work with the patient and help them identify any behavioral changes they could make as well as assisting in addressing the social or psychological complications from the illness. There are several empirically validated approaches to treating a GI patient with disordered eating. Clinical research has demonstrated that these treatment options are very successful in achieving the goal of helping improve wellness and overall health for the GI patient. Having a health psychologist as part of your team can improve your coping as well as hopefully improve your physical symptoms."

The Health Psychologist

The health psychologist is a licensed doctoral-level clinical psychologist, with a specialization in focusing on factors that might contribute to a person's overall health and wellness. The health psychologist receives formalized training to work with patients who have co-occurring medical and psychological conditions. The health psychologist can be an integral member of the treatment team and assist physicians and other providers in identifying and addressing the underlying cause of disordered eating in patients because of their background and education in the complexities of the mind-body connections and how psychological factors impact somatic symptoms. This can be essential in patients with recurring symptoms that do not seem to decrease, such as the example of stress and severe nausea discussed earlier in the chapter. The health psychologist can work with the identified patient to identify other effective ways to manage their stress, which can then reduce the instances of severe nausea, as well as how to cope with the stress of the somatic

symptoms themselves. The health psychologist utilizes a variety of different therapeutic approaches based on the patient's need and serves as a conduit between the patient and the physician regarding the role of psychological issues.

The health psychologist is aware of the patient's need for treatment and to identify, not only the current behavioral symptom of the patient but also the strengths of the patient. In an article by Reid et al., [19] discusses some of the common themes that qualitative studies of individuals with an eating disorder have found including support, control, ambivalence, and addressing the psychological concern, instead of the food intake [19]. Individuals, who experience eating disorders, may feel situations are out of control, which would exasperate negative thoughts and feelings [19]. In order to gain a sense of control, patients may feel that they need to control their eating behaviors [19]. Through this control of their eating, patients may feel that they can gain control over stressful or negative experiences that arise [19]. It is imperative for the health psychologist to be addressing not only their eating behaviors but also the negative or stressful experiences that are occurring outside of treatment and helping the patient identify other healthy coping mechanisms when feeling those negative or stressful thoughts and/or feelings. The health psychologist can help address these issues, help the patient increase self-awareness and self-efficacy regarding these issues, as well as help the physician and medical team understand the specific issues of each patient and how these issues may impact their medical care and treatment plan.

In working with an interdisciplinary team, it is important for the physician to be aware of the link between the GI symptoms and possible psychological disorders, including anxiety and depression. When placing a referral, the GI physician should communicate the severity of symptoms, the interventions already completed to the health psychologist, and what concerns the GI physician has in regard to this patient. These concerns could include lack of expected progress, symptoms that are inconsistent with known medical issues, expressed psychological symptoms or noncompliance. It is important for the physician to not dismiss the patient's symptoms and to explain to the patient how certain psychological disorders, such as anxiety, can exasperate GI symptoms. The physician's understanding of the mind-body connection is crucial to normalize for the patient that certain emotions can worsen GI symptoms. The GI physician would benefit from having a conversation with the patient about psychological treatment in conjunction with continued medical treatment.

After the GI physician has begun the conversation with the patient, the health psychologist can then provide more information on the relationship between mind and body. The health psychologist can work with the patient to identify difficult emotions/thoughts/situations that might exasperate the GI symptoms. They can then develop a treatment plan that meets the needs of the patient and complete interventions that allow for symptom reduction. It is important for the health psychologist and the GI physician to communicate to the patient that the psychological interventions can assist in symptom management but are not a cure for the GI disorder. In knowing and understanding the role of a health psychologist, the GI physician can communicate this information to the patient.

In working with patients with GI disorders, the health psychologist can assist in developing a biopsychosocial treatment plan with the treating physician. Although the treating physician may not be able to change their medical regimen – due to trying all options and still no improvement in symptoms – the health psychologist can assist in the development of the treatment plan to address psychological and social concerns that may be contributing to the symptoms. By taking this role, the health psychologist can help facilitate communications between the patient and treatment team, by sharing if any of the psychological interventions were effective in symptom management and even be an advocate for the patient in helping the GI physician be aware of how the patient is currently feeling. This can lead to reduction in the patient's anxiety and improved compliance with treatment and follow-up.

In transitioning the patient back to the GI physician, the health psychologist will identify what has been effective for the patient, such as deep breathing, relaxation techniques, and to follow up with (1) if the patient is still utilizing the interventions and (2) their effectiveness. The health psychologist will be willing to train or educate the GI team in any interventions they may be able to use with the patient to improve care, including informing the GI physician what the patient might need, for instance, encouraging more frequent follow-ups when a stressful event may be occurring, such as a move or other life event. The health psychologist relays to the GI physician if support is needed by another family/friend during the appointment and how to provide information to the patient in the form to which they will best respond (handouts, verbal, etc.). By integrating the interventions and recommendations of the health psychologist with the GI physician's treatment recommendations, the GI symptoms may be managed using an interdisciplinary treatment team approach. The types of empirically validated therapeutic interventions a health psychologist may use are detailed next.

Therapeutic Intervention: Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) is an empirically based therapeutic approach that examines the individual's thoughts, usually maladaptive and cause negative affective states, such as anxiety and depression. To alleviate these feelings and thoughts, individuals may resort to negative and unhealthy behaviors [20]. The treatment focuses on assisting the individual patient in increasing awareness of the negative thoughts, in order to ultimately change an individual's negative behaviors [20]. Therapy can be individualized or in group format and may consist of tasks that focus on building awareness of the triggering event (stressor), the thoughts that arise and the physical behaviors that occur [20]. Some common examples of techniques include changing automatic thoughts; problem-solving stressors that evoke a physical response, such as severe nausea; and learning healthy coping mechanisms to manage negative or troublesome situations that might arise in the patient's life [20].

Cognitive-behavioral therapy is an empirically validated treatment for eating disorders, including bulimia nervosa and gastrointestinal-related disorders. In a

meta-analysis conducted by Linardon et al. [21], therapist-guided CBT for bulimia nervosa and binge eating disorder was more effective in addressing any behavioral or cognitive symptoms, compared to other psychological therapies [21]. In fact, in long-term studies, CBT demonstrated effectiveness of eliminating negative behavioral symptoms [21]. This demonstrates that even after treatment, CBT can be beneficial in reducing behavioral symptoms for eating disorders. A component of CBT could consist of increasing relaxation when experiencing stress or negative emotional responses [20]. Relaxation techniques can be taught by the health psychologist to help cease a physiological stress response, which can be useful when patients are experiencing a negative stress response. The relaxation training has been found to be helpful in patients experiencing IBS [20].

In examining CBT as an effective treatment for AN, there has been some mixed evidence. A systematic review that CBT is an effective shorter-term treatment for AN, including addressing adherence, eating disorder symptoms, and some psychological symptoms (depression, maladaptive thoughts), however was not considered to be better than other psychological therapies [22]. Further research on longitudinal effectiveness is needed. This demonstrates that CBT can be effective treatment intervention for AN and can assist the patient in not only treating the underlying psychological concerns but also physical wellness.

Therapeutic Intervention: Interpersonal Therapy (IPT)

Interpersonal therapy is a type of therapy that was originally developed for depression but has been empirically validated on treatment for eating disorders (BN, BED, AN). The treatment consists of three phases: identifying the interpersonal context of how the eating disorder evolved and was sustained [23]. This highlights the various interpersonal problem areas within the patient's life and allows them to make changes within these areas (phase 2) [23]. Finally, the last phase consists of identifying future interpersonal problems that may arise and effective ways to manage them [23]. This approach does not target the eating behaviors nor the maladaptive thoughts and behaviors, unlike CBT. There have been several articles that discuss the effectiveness of IPT on BN, AN, and BED, compared to other approaches [23–25]. It has demonstrated an improvement in eating disordered symptoms.

In choosing a treatment approach, it is beneficial to have a clear referral question, in order to identify if there are underlying psychological symptoms that need to be addressed, and that the patient is ready to address these symptoms, or if the goal of treatment is to improve GI symptoms. This can be done by explaining how psychological factors can contribute physical GI symptoms, developing a therapeutic alliance, providing empathy to the patient, and engaging and encouraging patient to monitor symptoms and treatment progress. The health psychologist can play an important role in helping the patient receive the necessary treatment, as long as the physician and their treatment team also have an understanding – and more importantly, an appreciation – of the role of psychological factors on eating behaviors and GI symptoms.

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Chapter 2
Functional Swallowing Disorders

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Abbreviations

CBT	Cognitive behavioral therapy
EHYP	Esophageal-directed hypnotherapy
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
IBS	Irritable bowel syndrome
PPI	Proton pump inhibitor

Introduction

Functional swallowing disorders are increasingly recognized as a source of esophageal symptoms. In a recent study, three out of four patients with esophageal symptoms not responsive to acid suppression were found to have a functional swallowing disorder [1]. As opposed to other esophageal conditions, symptoms in functional swallowing disorders are not due to mechanical obstruction, esophageal dysmotility, or gastroesophageal reflux. Instead, symptoms in functional swallowing disorders are considered a function of esophageal hypersensitivity, a heighted perception to physiologic stimuli, and hypervigilance, an enhanced awareness of

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symptoms [2]. As such, the general management of functional swallowing disorders hinges on pharmacologic neuromodulation, behavioral interventions, and reassurance. However, the pathophysiologic understanding, and therefore effective therapies for functional swallowing disorders, remains in its infancy. Consequently, clinicians often struggle with diagnosis and management of these conditions, and functional swallowing disorders are associated with a reduced quality of life and high health-care utilization [3].

It is particularly important to consider the diagnosis and treatment of functional swallowing disorders in the context of women's health. Several factors, such sex-related differences in central pain processing and heightened esophageal sensitivity may influence the onset and maintenance of functional swallowing disorders. Moreover, female patients may have questions related to symptom course and medication use during pregnancy, or the impact symptoms may have on their children. The objective of this review is to provide clinicians with a framework to address common clinical questions regarding functional swallowing disorders broadly, as well as specific to women's health.

What Is the Role of the Esophagus in Swallowing?

A general understanding of normal esophageal anatomy and function is imperative to understanding the pathogenesis of functional swallowing disorders. The primary functions of the esophagus are to propel food or fluid into the stomach and to prevent gastroesophageal reflux. Though a seemingly simple role, a highly coordinated and complex array of sensory pathways, neural reflexes and motor responses are required to adequately accomplish these tasks.

Esophageal Anatomy

Anatomically, the esophagus is a tubular organ approximately 18–26 cm in length in adults. The upper esophageal sphincter marks the proximal border of the esophagus, and the lower esophageal sphincter is the distal border of the esophagus, which is normally anchored to the crural diaphragm [4]. The esophageal lumen is surrounded by an esophageal wall consisting of mucosa, submucosa, and muscularis propria. The muscularis propria is composed of a circular muscle layer that is surrounded by a longitudinal muscle layer. Composition of the muscle fibers in the esophagus varies along the length of the esophagus. The proximal esophagus is composed of striated muscle, the distal esophagus is composed of smooth muscle, and the segment between the two, the transition zone, is a mix of striated and smooth muscle fibers [5].

Esophageal Motility

Motor innervation of the esophagus is primarily controlled by the vagus nerve. The nerve fibers in the striated muscle originate from lower motor neurons in the nucleus ambiguous in the brainstem whereas in the smooth muscle originate in the dorsal motor nucleus of the vagus [6]. Primary peristalsis is the predominant coordinated motor pattern to clear esophageal contents into the stomach. Swallowing initiates primary peristalsis and deglutitive inhibition of the distal esophagus and lower esophageal sphincter. Rebound excitation occurs after the sequential termination of deglutitive inhibition. The intricate balance between inhibition and excitation is regulated by cholinergic excitatory input and nitrergic inhibitory input [7].

How Are Esophageal Symptoms Generated?

When caring for patients with functional swallowing disorders clinicians should educate patients on the brain-gut axis, particularly the neural relationship between the densely innervated esophagus and centrally mediated psychology and cognition. Vagal afferents in the esophageal mucosa are sensitive to a multitude of stimuli including chemical, thermal, and mechanical. Physiologic stimuli are transmitted via spinal afferents in the dorsal root ganglia to the brain [7]. Furthermore, vagal afferents in the esophageal smooth muscle layer are sensitive to muscle stretch.

Common esophageal symptoms include heartburn, chest pain, dysphagia, and globus sensation. Acidification and mechanical distension from gastroesophageal reflux can provoke symptoms of heartburn and chest pain. Spastic esophageal motor disorders with abnormal contraction and shortening of the longitudinal muscle layer may also be associated with chest pain. Dysphagia can be perceived in response to discoordinated motility in the esophageal body (e.g., ineffective esophageal motility or distal esophageal spasm), mucosal inflammation (e.g., gastroesophageal reflux disease or eosinophilic esophagitis), or a mechanical obstruction (e.g., peptic stricture) [7].

What Is a Functional Swallowing Disorder?

In contrast to the esophageal disorders described above, functional swallowing disorders are characterized by the experience of symptoms such as heartburn, chest pain, or dysphagia that are not attributed to a mechanical obstruction, motility disturbance, or reflux disease [2]. Thus, it provokes the question from patients, “How did I get this?”. The exact pathophysiological mechanism behind the development of a functional esophageal disorder is unclear. However, research indicates that a

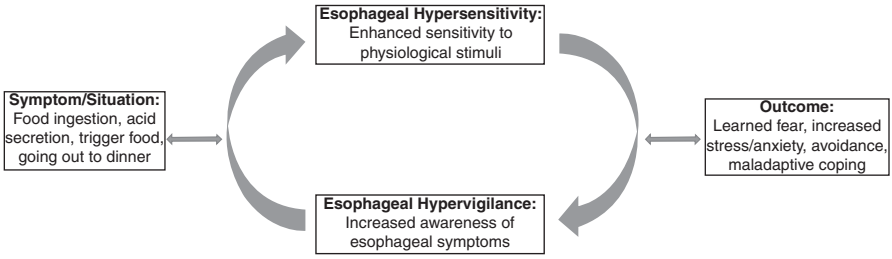

Fig. 2.1 Pathway to development of functional swallowing disorders. Specific symptoms and/or situations may trigger esophageal hypersensitivity and/or hypervigilance and result in poor outcomes. Maladaptive coping and psychosocial factors will perpetuate and amplify this cyclical relationship between symptoms/situations and outcomes

combination of two processes – esophageal hypersensitivity and esophageal hypervigilance – contributes to the development and maintenance of these disorders (Fig. 2.1). For instance, dysphagia can be perceived in the absence of an identifiable abnormality, likely due to hypersensitivity and hypervigilance to bolus movement during physiologic peristalsis.

Esophageal Hypersensitivity

Esophageal hypersensitivity is a two-pronged physiological process consisting of allodynia, the perception of normal stimuli as painful and discomforting, and hyperalgesia, the amplification of already painful stimuli [8]. Thus, individuals with a hypersensitive esophagus may perceive benign sensations, such as a normal amount of acid reflux or bolus moving down the esophagus, as painful. In addition, already painful sensations are amplified and felt as more painful than they otherwise would be for someone without hypersensitivity. The mechanisms involve both peripheral and central sensitization. Peripheral sensitization occurs from repeated exposure to noxious stimuli at the level of the esophagus, while central sensitization results from maladaptive central nervous system processing such as increased nerve excitability in the spinal cord [8, 9]. Symptoms can emerge from one or a combination of mechanical (e.g., esophageal distention), chemical (e.g., acid), or emotional (e.g., stress) triggers [10]. Research suggests there are potential sex-related differences in central pain processing, specifically as it relates to the esophageal pain and symptom perception. A number of studies indicate hormonal women have increased esophageal sensitivity and reduced thresholds for pain compared to men, which is likely attributed to hormonal differences [11, 12]. Therefore, despite similar prevalence rates of esophageal disorders between men and women [2], women may be at risk for experiencing more frequent or painful symptoms compared to men.

Esophageal Hypervigilance

Esophageal hypervigilance is the increased awareness of esophageal symptoms [13]. It is a psychological process consisting of cognitive-affective, behavioral, and physiological reactions that are out of proportion to the threat of the symptom. Enhanced attention to esophageal sensations can activate the body's threat system, resulting in learned fear and avoidance of symptoms and situations that may provoke symptoms (e.g., eating). Hypervigilance is cyclical – as symptoms persist, the patient becomes more hypervigilant and avoidant, interpreting even normal or benign sensations as potential threats [14]. In addition, when symptoms do not occur as expected, the lack of symptoms is attributed to the hypervigilance and avoidance, which reinforces the cycle and further exacerbates symptoms [15]. Esophageal hypervigilance can contribute to anxiety, maladaptive coping, and social isolation [15]. Research in a variety of esophageal conditions has demonstrated that increased hypervigilance is associated with greater symptom severity and decreased quality of life [14, 16].

Taken together, esophageal hypersensitivity and hypervigilance are underlying drivers in the symptom experience of patients with functional swallowing disorders. Maladaptive cognitive-affective processes such as excessive worry, catastrophizing (i.e., escalating the severity of symptoms while minimizing one's ability to cope), and symptom-specific anxiety can also impact one's ability to effectively cope with illness, which may perpetuate symptoms [17]. It is also important to note that the factors contributing to symptom onset may or may not be the same factors maintaining the disorder. For example, some patients can identify an initial trigger or event that prompted the symptoms, such as a spicy meal that produced an episode of intense heartburn or minor choking episode that resulted in injury to the esophagus. While the trigger subsided and esophagus healed, the symptoms are maintained through the cycle of hypersensitivity and hypervigilance. In the event a trigger is not identified, it is likely that hypersensitivity developed and is being further exacerbated by hypervigilance and other psychosocial factors (e.g., symptom-specific anxiety, environmental stress). It is important that these concepts are understood and applied throughout diagnosis and treatment of functional swallowing disorders. Patients may feel unheard and overlooked from previous providers, family, and friends. Therefore, validating that functional swallowing disorders are real disorders and explaining the physiological and psychological mechanisms behind them can help facilitate a positive physician-patient relationship and understanding of these disorders.

What Are the Different Types of Functional Swallowing Disorders?

Functional swallowing disorders represent a group of chronic diseases, which according to Rome IV criteria of functional esophageal disorders require the presence of symptoms for at least 3 months with symptom onset at least 6 months prior

to diagnosis. In general they cannot be explained on the basis of gastroesophageal reflux disease, mucosal abnormality, or motor dysfunction. Therefore, prior to arriving at a diagnosis of a functional swallowing disorder, patients will typically fail a trial of proton pump inhibitor (PPI) therapy, have absence of erosive findings on upper gastrointestinal (GI) endoscopy and possibly lack of esophageal eosinophilia on histopathology, have normal reflux monitoring, and have absence of a major motor disorder on esophageal manometry. The order of testing may differ depending on presenting symptom [2].

Functional Chest Pain

Functional chest pain presents with recurring retrosternal chest pain of presumed esophageal origin, without associated esophageal symptoms such as heartburn and dysphagia. Functional chest pain is a subset of noncardiac chest pain and thereby requires that a cardiac source of chest pain has been excluded. Among patients with noncardiac chest pain, approximately 30% will have true functional chest pain. The prevalence of noncardiac chest pain appears to be gender-equal and higher in younger patients and well-developed countries [18]. Up to 75% of patients with noncardiac chest pain will have coexisting psychiatric diagnoses such as anxiety disorders, depression, and somatization disorders.

Functional Heartburn

Function heartburn presents with retrosternal burning discomfort or pain and is seen in approximately 50% of patients with lack of response to PPI therapy [19]. Interestingly, patients with a proven diagnosis of gastroesophageal reflux disease (GERD) and adequate acid control with PPI therapy may also present with an overlapping component of functional heartburn [20].

Reflux Hypersensitivity

Reflux hypersensitivity presents with heartburn and/or chest pain in the context of a normal endoscopy and normal acid burden on reflux monitoring. However, in contrast to functional heartburn or functional chest pain, patients with reflux hypersensitivity will have a positive association between symptoms and physiologic reflux. Therefore, while reflux hypersensitivity shares the same pathophysiologic mechanism as other functional swallowing disorders, it is unique in that symptoms are actually triggered by physiologic chemical or mechanical stimulus from reflux [2]. Similar to functional heartburn, persistent symptoms in a patient with baseline GERD adequately controlled with PPI therapy may arise from an overlap with reflux hypersensitivity [20].

Globus

Globus sensation is the persistent or intermittent nonpainful sensation of a lump in the throat. While globus sensation is common and equally prevalent among men and women, women are more likely to seek health care for symptoms. In addition to the aforementioned general clinical evaluation for functional swallowing disorders, an evaluation for a gastric inlet patch should be performed in patients with globus sensation. In prior studies, mild esophageal balloon distension reproduced globus sensation, supporting a role of esophageal hypersensitivity. In particular, globus sensation symptoms may be driven or exacerbated by increased life stress [2].

Functional Dysphagia

Functional dysphagia is the sensation of solid and/or liquid bolus sticking or passing abnormally throughout the esophageal body. In addition to the general clinical evaluation for functional swallowing disorders, the diagnosis of functional dysphagia requires exclusion of oropharyngeal sources of dysphagia. Barium contrast studies with a tablet or solid bolus may be useful to evaluate for subtle mechanical sources of dysphagia [2].

What Are Treatment Options for My Functional Swallowing Disorder?

It is important for patients to understand that a variety of centrally and peripherally directed treatment options are available to manage functional swallowing disorders (Table 2.1). These include pharmacologic neuromodulation and behavioral interventions. Across disorders, clinicians should provide reassurance and avoid repetitive testing or escalation of unneeded therapy.

Pharmacotherapy

Antidepressants

Antidepressants modulate central and peripheral hyperalgesia and are the first-line pharmacologic treatment options for functional swallowing disorders. Different categories of antidepressants can be used including tricyclic antidepressants, serotonin reuptake inhibitors, serotonin noradrenergic reuptake inhibitors, and trazodone [21]. A randomized, double-blind, placebo-controlled trial comparing clonidine,

Table 2.1 Management options for functional swallowing disorders

Pharmacologic therapy	**Starting dose**
Tricyclic antidepressants	Amitriptyline 25 mg daily; imipramine 50 mg daily
Selective serotonin reuptake inhibitors	Sertraline 50 mg daily; paroxetine 50 mg daily; citalopram 20 mg daily
Serotonin norepinephrine reuptake inhibitors	Venlafaxine 75 mg daily
Behavioral intervention	**Intervention**
Cognitive behavioral therapy	Identify and change maladaptive thoughts, feelings, and behaviors related to symptoms
Esophageal-directed hypnotherapy	Deep state of relaxation with targeted suggestions to modify esophageal sensations and symptoms
Relaxation strategies	Aimed to reduce stress and improve self-efficacy (e.g., diaphragmatic breathing, progressive muscle relaxation)
Disorder-specific treatment	**Intervention**
Acid suppression (reflux hypersensitivity)	Single-dose proton pump inhibitor or H2 receptor antagonist
Dietary modification (functional dysphagia)	Eat in the upright position, avoid trigger food items, carefully chew food, chase food with liquids
Empiric endoscopic dilation (Functional dysphagia)	Bougie dilation 50–54 French to treat subtle rings or strictures

imipramine, and placebo among patients with noncardiac chest pain reported a 52% reduction with imipramine 50 mg nightly in chest pain episodes compared to placebo [22]. In a randomized open-label trial of patients with functional chest pain not responsive to PPI therapy, the addition of amitriptyline 10 mg at bedtime compared to double-dose PPI therapy, patients in the amitriptyline + PPI arm derived a significantly higher proportion (70.6%) of symptom improvement. Similarly, several observational and randomized controlled trials comparing imipramine, amitriptyline, sertraline, paroxetine, and venlafaxine to placebo report greater than 50% symptom response in patients with noncardiac chest pain [21]. Though not as well studied in other functional swallowing disorders, neuromodulation is reportedly effective in treating globus sensation and reflux hypersensitivity. In a trial of 30 patients with globus pharyngeus randomized to amitriptyline 25 mg at bedtime compared to PPI, patients in the amitriptyline group reported a significantly greater response (75%) compared to PPI (36%) [23]. Therefore, neuromodulatory options are available, and the choice of antidepressant will depend on symptom presentation, side effect profile, and patient preference.

Acid Suppression

Acid suppression is generally not indicated for most functional swallowing disorders. However, theoretically patients with reflux hypersensitivity, particularly those with sensitivity to acidic reflux, may derive benefit from acid suppression.

Behavioral Interventions

With the recognition of the role of esophageal hypersensitivity, hypervigilance, and other psychosocial factors in the onset and maintenance of functional swallowing disorders, behavioral interventions that target these underlying mechanisms are becoming increasingly popular [24]. The most researched behavioral interventions for esophageal disorders include cognitive behavioral therapy (CBT) and esophageal-directed hypnotherapy (EHYP) [25, 26]. Treatments are typically administered by clinical health psychologists or other mental health professionals that have specialized training in treating a variety of chronic GI disorders.

Cognitive Behavioral Therapy

CBT is a short-term, skills-based therapy that was initially developed in the 1960s to treat depression [27] and has since been adapted for use in various psychiatric and medical populations, including GI disorders. The goal of GI-focused CBT is to evaluate and modify dysfunctional cognitions (e.g., maladaptive thoughts or beliefs) and behaviors (e.g., avoidance) specifically related to GI symptoms or situations that may cause symptoms. The components of CBT include psychoeducation, relaxation strategies, cognitive restructuring, and behavioral exposure techniques [28]. Most research in GI-focused CBT has been in the irritable bowel syndrome (IBS) population, which has demonstrated decreased symptom severity and improvements in quality of life and psychological functioning [29, 30]. GI-focused CBT has also been adapted for functional esophageal conditions, such as functional dysphagia, functional heartburn, globus sensation, functional chest pain, rumination syndrome, and supragastric belching, although research is limited and primarily anecdotal [25, 26]. Therapeutic targets include building insight into the brain-gut axis and the role of stress in symptom exacerbation, restructuring maladaptive thoughts and beliefs around esophageal symptoms (e.g., catastrophizing), and changing unhealthy behaviors or habits by teaching adaptive coping strategies to effectively manage symptoms and symptom-related stress [25, 26].

Esophageal-Directed Hypnotherapy

Hypnotherapy is a different form of behavioral therapy that has also been traditionally applied to the IBS population, but adapted for application in esophageal disorders. Similar to CBT, EHYP is a short-term therapy that can be completed in 5–7 weekly or biweekly sessions. The goal of EHYP is for the patient to maintain a relaxed state with focused attention on therapeutic suggestions and paired visual imagery specifically targeting the esophagus. Riehl and Keefer [15] provide a detailed review of EHYP for esophageal disorders, including general EHYP structure as well as applications for a range of esophageal conditions including

dysphagia, functional heartburn, globus sensation, noncardiac chest pain, and dyspepsia [15]. A typical EHYP session begins with a series of relaxation techniques, including an eye-closure induction, progressive muscle relaxation, and further deepening through guided imagery (e.g., imagining walking down a staircase). Following this, the therapist provides the targeted suggestions that focus on improving esophageal functioning, as well as decreasing esophageal hypervigilance, and normalizing hypersensitivity [15]. Hypnotherapy is believed to directly impact the brain-gut axis through changes in gut functioning and sensory processing in the brain [31]. While the majority of studies in hypnotherapy for GI disorders have focused on IBS, there is promising research supporting its adapted use in a variety of esophageal disorders. Early evidence suggests EHYP can be effective in reducing symptom severity, anxiety, and catastrophic thinking as well as improvements in quality of life [15, 32]. In addition, because EHYP targets the underlying mechanisms, studies have also found normalized esophageal sensitivity and reduced esophageal hypervigilance [32].

Others

Other behavioral modifications such as eating in the upright position, avoiding trigger food items, careful chewing of food, and chasing food with liquids should be recommended for functional dysphagia. Furthermore, anecdotal reports suggest a benefit from relaxation therapy and acupuncture for functional swallowing disorders [2].

Endoscopic Therapy

In patients with functional dysphagia, empiric bougie dilation to 50–54 French can also be considered to treat subtle rings or strictures.

What if I Don't Want Any Therapy?

There is no need for a patient to undergo treatment if he or she is reporting little to no symptoms, especially in the event that the patient is not interested in pursuing treatment. Given that functional swallowing disorders are absent of mechanical obstruction, motility disturbance, or reflux disease, there is no medical necessity to undergo treatment. Furthermore, functional swallowing disorders can regress independently over time. The patient's gastroenterologist or primary clinician should ensure the patient has a good understanding of the mechanisms behind functional swallowing disorders and provide reassurance that there are no foreseeable negative consequences to continuing without treatment. Additionally, it may be helpful to

inform the patient that if symptoms or decisions change, the option to re-evaluate treatment is always available.

The gastroenterologist should also make sure to assess all potential aspects of the disorder, including impairments in quality of life. Even minor symptoms can impact quality of life and should be assessed. For example, a patient may limit or avoid certain types of foods in an effort to self-manage. While this approach may result in decreased symptoms and "feeling fine," it can also have a significant impairment on quality of life. Quality of life can be assessed during a routine clinic visit, either through face-to-face conversation or with a questionnaire such as the Northwestern Esophageal Quality of Life Scale, which assesses esophageal illness health-related quality of life and can be administered to patients across a variety of esophageal conditions [33]. While a patient may still ultimately decide against pursuing treatment, it is important to inquire and routinely check in on a patient's reported quality of life.

Will My Swallowing Disorder Worsen if I Get Pregnant?

GI complaints, specifically in the upper GI tract, are a common occurrence throughout the course of pregnancy. Some of the most frequently reported pregnancy symptoms include nausea, vomiting, and heartburn, which occur in roughly 40–80% of women [34]. Heartburn is particularly important to consider, as it can manifest as a new onset of GERD in women who were not symptomatic prior to pregnancy, or exacerbate symptoms for women with pre-existing GERD [34, 35]. The onset of these additional upper GI symptoms may be distressing, particularly for women with functional swallowing disorders. It is important to note that the patient's swallowing disorder, in theory, should not be affected by pregnancy, as symptoms are not attributed to mechanical obstruction, motility disturbance, or reflux disease. However, symptoms of nausea, vomiting, and heartburn that occur during pregnancy may exacerbate already existing symptoms as well as stress related to symptoms. This is particularly true when considering the implications of esophageal hypersensitivity and hypervigilance. A patient with esophageal hypersensitivity who develops acid reflux during her pregnancy may experience more pain or discomfort in response to the abnormal levels of acid than someone who does not have hypersensitivity. In addition, a patient that is already hypervigilant toward the sensations in her esophagus may become further escalated with the onset of these pregnancy-related esophageal symptoms.

Stress and the subsequent consequences are also important to consider in the context of pregnancy and functional swallowing disorders. For some women, pregnancy can be a challenging time and may result in stress and anxiety. Functional esophageal disorders are stress-sensitive disorders. Although stress and anxiety does not necessarily *cause* a functional swallowing disorder, it can certainly contribute to the onset, maintenance, and exacerbation of symptoms [36]. Stress can influence the underlying mechanisms of functional swallowing disorders, includ-

ing esophageal hypervigilance and hypersensitivity. For example, research has demonstrated that lab-induced acute stress increases perceptual and emotional responses to intraesophageal acid stimuli in patients with GERD [37]. Further, stress can negatively impact an individual's mood, cognitions, and coping behaviors which in turn can influence reactions to esophageal symptoms. An open patient-provider communication is important to discuss these issues. A patient who feels invalidated or unheard may be reluctant to discuss her feelings with her provider due to potential feeling of shame or embarrassment. Providing an open, nonjudgmental space for these types of discussions is imperative in providing ideal patient-centered care. Patients may benefit from relaxation strategies, such as diaphragmatic breathing or progressive muscle relaxation, which can be taught in a routine visit and practiced at home. If available, a referral to see a health psychologist is an excellent resource for women experiencing stress-related esophageal symptoms during pregnancy. The health psychologist can work with her on identifying the connection between stress and symptoms and provide effective tools for managing stress [25].

Another potential issue to consider for pregnant women with functional esophageal disorders is ensuring they receive adequate nutrition for themselves and the developing fetus. As previously described, the pain or discomfort associated with a functional swallowing disorder can lead to hypervigilance, learned fear, and avoidance of symptoms and potential triggers. It is not uncommon that patients will identify specific food triggers and avoid them in an attempt to reduce symptoms. Examples of common foods avoided in individuals with functional swallowing disorders include carbohydrates (e.g., bread, pasta), "tough" meats, foods high in sugar, and carbonated beverages. The avoidance of a significant amount of foods can significantly impact caloric and nutritional intake, which is especially detrimental for pregnant women. Thus, clinicians should screen for food avoidance behaviors that may impact food intake during pregnancy and provide appropriate referrals.

As discussed earlier in the chapter, some pharmacological options exist for patients with functional esophageal conditions, including PPIs and antidepressant neuromodulators. It should be stated that anytime a woman becomes pregnant, the patient, gastroenterologist, and obstetrician/primary pre- and postnatal clinician should discuss the risks and benefits to GI-related pharmacotherapy during pregnancy. Evidence to date suggests that most PPIs are safe to use during pregnancy [38–41] and the American College of Gastroenterology guidelines for managing GERD recommend the use of PPIs during pregnancy [42]. In addition, a 2017 consensus review of over-the-counter PPI use also indicated there is no contraindication of category B over-the-counter PPI use in pregnancy, although they recommend a "step-up" approach consisting of lifestyle modifications, antacids, and H2 blockers before prescribing a PPI [40]. Low-dose antidepressants may also be used in treatment of functional esophageal disorders to modulate hypersensitivity. Antidepressant therapy may have to be discontinued due to conflicting evidence regarding the risks of antidepressant use during pregnancy and should be discussed with patient's pre- and postnatal clinical team [43, 44].

Are My Kids at an Increased Risk of Developing a Swallowing Disorder?

Pediatric data on functional swallowing disorders is extremely limited. Rome IV criteria for child and adolescent functional GI disorders provide an overview and guidelines on the various pediatric diagnoses [45]. They are grouped into three major categories based on the type and location of the disorder along the GI tract and include functional nausea and vomiting disorders, functional abdominal pain disorders, and functional defecation disorders. Functional nausea and vomiting disorders are primarily focused in the upper GI tract and are comprised of cyclic vomiting syndrome, functional nausea and functional vomiting, rumination syndrome, and aerophagia. Functional swallowing disorders that may be present in adults are rarely discussed in pediatric literature potentially due to lack of awareness and research and low prevalence.

To date, there is no compelling evidence to indicate a genetic component to the development of functional swallowing disorders. Family and twin studies in other disorders of gut-brain interaction, such as IBS, have indicated a potential role of genetics in illness predisposition and development [46]. However, it is important to recognize that genetic composition alone does not reflect the full picture. Rather, illness development is complex and comprised of multimodal genetic interaction and differences in genetic expression (i.e., epigenetics), as well as environmental and lifestyle factors, such as early childhood life experiences and stress [46]. In sum, a child whose parent has a functional swallowing disorder is at no greater genetic risk of developing one themselves.

While the genetic influence is still largely unknown, childhood environmental factors have been widely implicated in the development of chronic GI conditions. One of the most salient is learned illness behavior. From a social learning perspective, children can learn illness behaviors through modeling and reinforcement [47, 48]. The way a parent responds to his or her own symptoms can influence how a child behaves when he or she becomes sick, and research indicates it may be even more important to consider than genetics [49]. For example, a parent displaying excessive worry, catastrophizing, and increased attention or preoccupation to symptoms may intentionally or unintentionally encourage similar illness behavior in their child [17]. Research in IBS has demonstrated that children of adult mothers with IBS report more frequent stomachaches, have more school absences, and display increased health-care utilization than children of mothers without IBS [50]. Reinforcement can also encourage future illness behavior. Examples include parents providing reward (e.g., increased attention, gifts) or taking away adverse consequences (e.g., allowing child to stay home from school) in response to a child's complaints.

There are several ways in which parents with functional swallowing disorders can foster an environment of positive health behaviors. Healthy communication involving open, honest, and developmentally appropriate conversations about their disorder can normalize illness and provide the space for the child to feel comfort-

able asking questions or expressing emotion [51]. In addition, reassurance that a functional swallowing disorder is not fatal may help to reduce stress or anxiety for the child. Modeling adaptive illness behaviors can also teach the child to self-manage symptoms and may protect against the development of unhelpful behaviors such as excessive worry and catastrophizing.

Summary

In summary, functional swallowing disorders are common and associated with a significant health-care burden. Clinicians must recognize that esophageal symptoms such as heartburn, chest pain, and dysphagia not attributable to mechanical or physiologic disturbances may be a function of esophageal hypersensitivity and esophageal hypervigilance. Furthermore, health-care teams need to be equipped to effectively manage functional swallowing disorders. A multidisciplinary treatment approach is optimal and includes pharmacologic neuromodulation, psychogastroenterology-based behavioral interventions, education, and reassurance. A strong patient-clinician communication is important to ensure all aspects of the patient's symptom experience are being properly assessed.

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Chapter 3
Gastroesophageal Reflux Disease

Rena Yadlapati and Abraham Khan

Abbreviations

GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
H2RAs	Histamine-2 receptor antagonists
IBS	Irritable bowel syndrome
LES	Lower esophageal sphincter
P-CABs	Potassium-competitive acid blockers
PPI	Proton pump inhibitor
TIF	Transoral incisionless fundoplication
TLESRs	Transient lower esophageal sphincter relaxations
TRIM	The reflux improvement monitoring

Introduction

Gastroesophageal reflux disease (GERD) is among the most common conditions seen in ambulatory gastroenterology clinics [1]. The estimated worldwide prevalence is 8–33% across all age-groups and genders. Disease burden of GERD

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continues to rise, and according to recent population-based studies, the prevalence of GERD in North America ranges from 18% to 28% [1, 2].

GERD arises when retrograde reflux of gastric contents into the esophagus results in troublesome symptoms and/or erosive complications [3]. Generally, the clinical diagnosis of GERD is based on patient-reported symptom burden. Objective diagnostic evaluations are typically reserved for the evaluation of warning signs or symptoms. The primary management for GERD hinges on lifestyle modifications and acid suppression. Approximately half of patients with suspected GERD will derive symptom relief with acid suppression. In the cases of symptom non-response, a diagnostic evaluation for GERD is recommended with endoscopy and reflux monitoring. The choice of reflux monitoring modality, and whether to perform testing on or off acid suppression, is guided by the pretest likelihood of GERD [4]. Management options for non-response to proton pump inhibitor (PPI) therapy include behavioral interventions, adjunctive pharmacologic therapy, and invasive anti-reflux treatments. The treatment of choice will depend on a multitude of factors [5].

Given the complex diagnostic and treatment considerations, patients often seek guidance regarding diagnostic modalities, complications of disease progression, risks associated with long-term PPI therapy, management options, and the role of the brain-gut axis in symptom generation. For women being evaluated for GERD, treatment decisions surrounding pregnancy are common, and many women with GERD are concerned about the side effects of GERD treatments on other female-predominant conditions such as osteoporosis. This review aims to address questions patients commonly ask regarding GERD.

Definition and Diagnosis of Gastroesophageal Reflux Disease

How Is Gastroesophageal Reflux Disease Defined?

The current clinical definition of GERD derives from the 2006 Montreal Definition and Classification of GERD. According to the global Montreal Definition, “GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications.” GERD commonly presents as a symptomatic esophageal syndrome without the presence of esophageal mucosal injury, referred to as nonerosive GERD. GERD can also lead to esophageal mucosal injury such as erosive esophagitis, peptic stricture, intestinal metaplasia, and esophageal adenocarcinoma. In GERD syndromes with esophageal mucosal injury, patients may or may not experience troublesome symptoms [3] (Fig. 3.1).

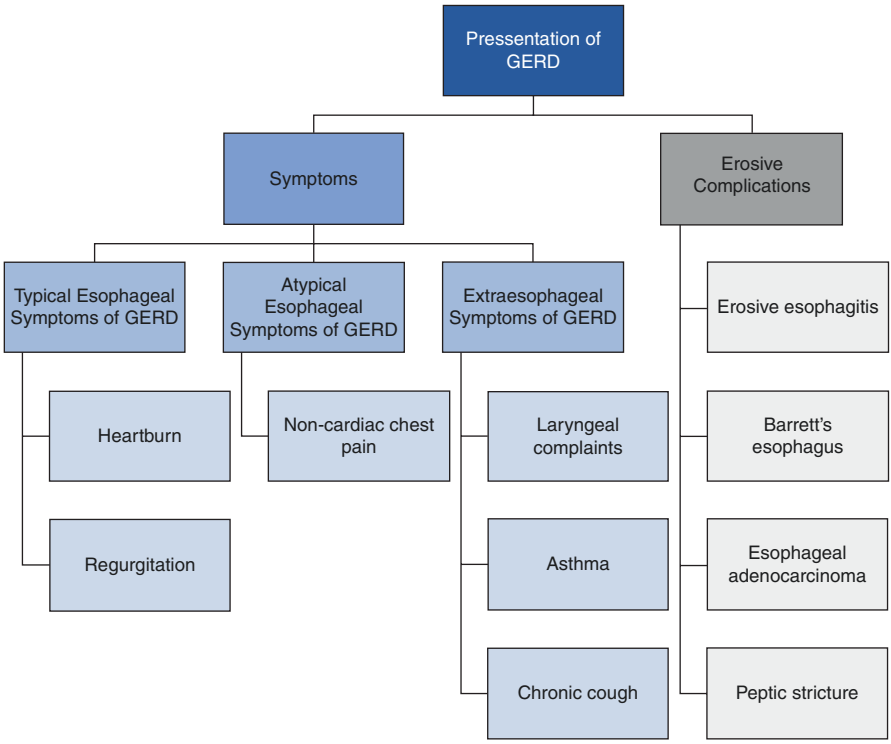

Fig. 3.1 Presentations of GERD. GERD may present with symptoms and/or erosive complications

What Symptoms Does GERD Cause?

Esophageal Symptomatic Syndromes of GERD

An esophageal symptomatic syndrome of GERD requires patients to experience troublesome GERD symptoms defined as mild symptoms occurring 2 or more days a week or moderate/severe symptoms occurring more than once a week. Heartburn and regurgitation are the characteristic typical symptoms of GERD. Heartburn is a retrosternal burning sensation, and regurgitation is a perceived flow of gastric contents refluxed proximal to the upper esophageal sphincter. GERD can be clinically diagnosed based on symptom presentation without invasive diagnostic testing. In addition to typical symptoms, episodic chest pain resembling ischemic cardiac pain is considered to be an atypical symptom presentation of GERD [3]. In the case of troublesome chest pain, cardiac sources of chest pain must be considered prior to embarking on a diagnosis and treatment of GERD.

GERD Syndromes with Esophageal Injury

Potential GERD complications in the esophagus include erosive esophagitis, Barrett's esophagus, esophageal adenocarcinoma, and peptic stricture. Erosive esophagitis is assessed on endoscopy, with the Los Angeles classification scheme grading esophageal erosions from mild to severe (A, B, C, D) being most widely adopted in practice [6, 7]. Significant esophagitis has the potential of increasing the risk of developing Barrett's esophagus, a change of the normal squamous epithelium of the esophagus to a columnar-lined intestinal metaplasia with malignant potential. In one study of over 700 patients, Barrett's esophagus was found in 11% of endoscopies for GERD [8]. A minimum of 8 weeks of PPI therapy has been recommended in patients with Grade C and D esophagitis while also considered in lower grades, and a repeat endoscopy is recommended after this course to exclude Barrett's esophagus and to document healing of erosions [6, 9]. Barrett's esophagus is a premalignant condition that may result in progression to esophageal adenocarcinoma. Identifying individuals who are more likely to develop Barrett's esophagus as well as individuals who may be at higher risk of malignant transformation with Barrett's esophagus is important to combat the rising incidence of esophageal adenocarcinoma in the last several decades, especially in the Western world [10]. An estimated 40% of patients with esophageal adenocarcinoma report no prior history of GERD symptoms, further emphasizing the need for improvement in the ability to detect patients at risk [11]. Accepted risk factors for Barrett's esophagus include increasing age, male gender, Caucasian ethnicity, obesity, central obesity, tobacco use, family history of Barrett's esophagus, and duration of GERD symptoms. As women are at significantly less risk of Barrett's esophagus than men, screening women for Barrett's esophagus is generally not recommended in the absence of multiple other risk factors [9].

Peptic strictures from GERD have become less common over time with the widespread use of aggressive acid suppressive therapy. Peptic strictures can cause dysphagia and typically need an endoscopy to confirm a benign etiology, dilation therapy to improve dysphagia, and PPI therapy to decrease the overall need for endoscopic treatment [12].

How Do I Know if I Have GERD?

GERD is empirically diagnosed based on patient history and experience of troublesome symptoms. Women commonly experience troublesome GERD symptoms. In a large scale study of over 10,000 women, 22% complained of at least weekly symptoms to suggest GERD [13].

What Objective Tests Are Available to Diagnose GERD?

Indications for objective diagnostic testing include the presence of warning signs or symptoms (e.g., unintentional weight loss, dysphagia, gastrointestinal bleeding, iron deficiency anemia), treatment failure, and diagnostic uncertainty.

Upper GI Endoscopy

Diagnostic testing for GERD begins with an upper gastrointestinal (GI) endoscopy to evaluate for erosive complications from GERD and assess for potential alternative diagnoses. Confirmatory erosive findings of GERD on endoscopy include high-grade esophagitis (Los Angeles Grades C or D), long-segment Barrett's esophagus (≥3 cm length), or peptic stricture. However, erosive disease is found in less than 20% of patients with a clinical suspicion of GERD. In addition, lower grades of esophagitis can be found in asymptomatic controls and are not conclusive for GERD [14]. Therefore, while upper GI endoscopy remains a first-line objective evaluation for GERD, it has a low sensitivity for GERD diagnosis. During an endoscopic assessment for GERD, an evaluation of the esophagogastric junction flap valve and vertical length of hiatal hernia should also be performed. Esophageal biopsies to evaluate for GERD are not recommended since histopathological findings are not conclusive for GERD. However, for patients also experiencing dysphagia without any visible source of dysphagia on upper GI endoscopy, esophageal biopsies from the proximal and distal esophagus are recommended to assess for eosinophilic esophagitis [6].

Ambulatory Reflux Monitoring

Ambulatory reflux monitoring is the current standard to confirm or exclude pathologic GERD. Reflux monitoring assesses for excessive esophageal acid exposure, reflux episodes, and the relationship between reflux episode and symptom perception. Ambulatory reflux monitoring is available as a catheter- or wireless-based system. Transnasal catheter pH monitoring systems provide 24-h monitoring and can be combined with impedance sensors to provide combined impedance-pH monitoring. Since pH-impedance detects all reflux episodes regardless of acidity as well as the directionality of the flow, it is considered the gold standard. Limitations of pH-impedance monitoring include patient intolerance, limited availability, and complexity in interpretation. Reflux monitoring is also available as a wireless capsule-based pH monitoring system. Wireless reflux monitoring can assess for acidic GERD over extended periods (up to 96 h) and is better tolerated by patients. Limitations of wireless reflux monitoring include expense, variability in day-to-day esophageal acid exposure, and inability to measure non-acidic reflux or directionality of flow [4, 15].

Ambulatory reflux monitoring can be performed on or off acid suppression to evaluate different properties. According to the Lyon Consensus, reflux monitoring should be performed off of PPI for patients with unproven GERD (i.e., absence of high-grade erosive findings on endoscopy and no prior positive reflux monitoring) in order to assess for baseline pathologic GERD. On the other hand, in patients with previously proven GERD (i.e., presence of high-grade erosive findings on endoscopy or a prior positive reflux monitoring), reflux monitoring should be performed on double-dose PPI therapy to assess for PPI refractory GERD and exclude inadequate acid suppression as the mechanism of persistent symptoms. Combined pH-impedance testing is recommended when reflux monitoring is performed on PPI therapy in order to assess for weakly acidic and non-acidic reflux episodes (Fig. 3.2). According to the Lyon Consensus, an acid exposure time less than 4% is physiologic (normal), and acid exposure time greater than 6% is definitively abnormal. Furthermore, more than 80 reflux episodes over 24 h are definitely abnormal, whereas less than 40 reflux episodes over 24 h are physiologic (normal). Reflux monitoring also assesses for symptom-reflux association with both a positive symptom index (>50%) and a positive symptom association probability (>95%) providing the best support for a positive symptom-reflux association. The symptom index is a proportion of the number of symptoms occurring within a 2-min window of an objective reflux event and is a measure of effect size. The symptom-reflux association is a statistical measure of probability [16].

A positive acid exposure time on reflux monitoring is consistent with pathologic GERD, a positive symptom-reflux association without a positive acid exposure time is consistent with reflux hypersensitivity, and both a negative symptom-reflux association and negative acid exposure time are consistent with a negative study [16].

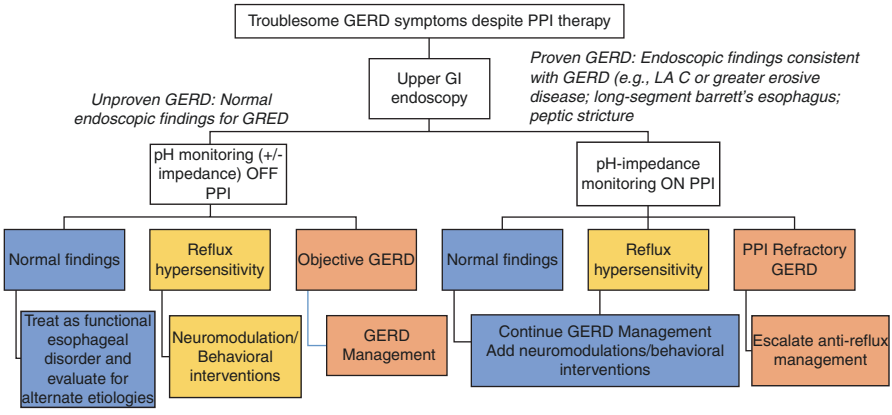

Fig. 3.2 Role of ambulatory reflux monitoring in diagnosis of PPI nonresponsive GERD symptoms

I don't Have Heartburn or Regurgitation, But I Was Told That My Other Symptoms Are Related to GERD: Is This True?

While the typical GERD symptoms are heartburn and regurgitation, the aforementioned and accepted Montreal Definition of GERD does not delineate that a patient must have heartburn or regurgitation to have GERD [3]. Upper abdominal, atypical chest, laryngeal, and respiratory symptoms also may be caused by GERD in individual patients. These symptoms, however, are less responsive to treatment [17]. Furthermore, making a GERD diagnosis based on nontypical symptoms is challenging, as even an expert history has limited accuracy, and commonly used questionnaires also have limitations when compared to physiologic diagnostic testing [18, 19].

A clinical presentation attributed to GERD emanating from the larynx, pharynx, or respiratory system is often called extraesophageal or supraesophageal reflux disease. Although GERD may be associated with conditions such as asthma, chronic cough, and laryngitis in individual patients, gastroesophageal reflux is not always the cause of these symptom presentations. Routine diagnostic testing can also be challenging in patients to ascertain the influence of GERD with atypical symptoms, for example, an otolaryngologist assessment of GERD on laryngoscopy cannot be made accurately with this testing alone [20]. Consensus and guideline recommendations suggest that ambulatory reflux testing be done in patients with extraesophageal symptoms of GERD with no clear response to treatment, and practically this testing has the best potential in deciphering the influence of GERD in these common clinical dilemmas [6, 16, 21].

Other clinical presentations, such as belching and vomiting disorders, are often initially assessed as having GERD as a primary etiology, though advances in diagnostic testing such as esophageal manometry and impedance technology can assess these symptoms directly in order to understand if behavioral syndromes such as aerophagia or rumination are bearing a role [22]. Furthermore, the severity of symptoms in GERD can vary widely in patients, as a multitude of mechanisms can account for symptom genesis in individuals, such as peripheral and/or central hypersensitivity, psychological factors, and mucosal barrier function [23].

As diagnostic technology improves over time to confidently relate atypical symptoms to GERD, the future recommended approach in a patient with GERD is to phenotype the patient by mechanism and confidently relate individual symptoms to the underlying refluxate, in order to identify a more tailored individual approach of treatment [16].

I Have IBS and Was Recently Diagnosed with GERD: Is There an Overlap Between the Two?

Irritable bowel syndrome (IBS) and functional dyspepsia are considered the most common functional gastrointestinal disorders, and there is a common overlap between these syndromes and GERD [24, 25]. IBS is characterized by Rome IV

criteria as recurrent abdominal pain, at least 1 day per week on average over a 3-month period, associated with two or more of the following: relationship to defecation, relationship with the frequency of stool, and/or relationship with a change in form of stool [26]. Overlap between GERD and IBS ranges between 5 and 30% in community studies depending on the symptom criteria used [27]. Women may also experience IBS differently than men, as one study revealed that women more frequently report less than three bowel movements per week, changes in the number of bowel movements before abdominal discomfort overall, as well as abdominal fullness and bloating than men [28].

However, it remains unclear whether GERD or IBS always has independent pathophysiology or if there can be a shared underlying series of mechanisms resulting in two different pathologies. Many studies have undertaken a goal in assessing the true overlap of GERD and IBS, but few have been performed according to pathophysiologic criteria, and more recent data suggest that functional esophageal disorders overlap more frequently with IBS than true GERD [29].

Pathophysiology

How Did I Get Gastroesophageal Reflux Disease?

Reflux of gastric contents into the esophagus is a normal physiologic occurrence to vent the stomach of air and liquid. Normally this occurs through relaxation of the lower esophageal sphincter (LES) and inhibition of the crural diaphragm in response to gastric distention. Transient LES relaxations (TLESRs) are the primary mechanism of reflux episodes in GERD [30–33].

An excess of gastroesophageal reflux leading to symptom burden and/or mucosal disruption results in pathologic GERD. Pathologic GERD typically requires compromise to one or more protective anatomic and physiologic mechanisms which exist to prevent pathologic GERD in the setting of an enhanced reflux physiology.

Dysfunction in the Anti-reflux Barrier

Several anatomic and physiologic defense mechanisms exist to prevent GERD. The anti-reflux barrier is composed of the LES tethered to the extrinsic crural diaphragm by way of phrenoesophageal ligaments. The orientation of these structures forms the gastroesophageal flap valve, a two-way valve to accommodate bolus emptying and enable gastric venting [34]. The anti-reflux barrier is therefore situated between the intrathoracic and intra-abdominal cavity to serve as a high-pressure barrier zone between the stomach and the esophagus. The anti-reflux barrier is a complex dynamic structure exposed to a myriad of mechanical and anatomical stresses. Dysfunction of the anti-reflux barrier can occur through laxity of extrinsic

structures or the intrinsic LES to result in a hypotensive LES and/or separation between the LES and the crural diaphragm. The latter would represent a hiatal hernia where the stomach is anatomically proximal to the crural diaphragm in the intrathoracic cavity [35]. When the anti-reflux barrier is disrupted, gastroesophageal reflux is more likely to occur with rises in intragastric pressure or even freely.

Impaired Clearance of Refluxate from the Esophagus

One function of the esophagus is to propagate bolus from the esophagus into the stomach. The esophagus predominantly clears bolus through swallow-induced primary peristalsis. Mechanical distension of the esophageal lumen can also induce secondary peristalsis. Furthermore, salivary and esophageal gland secretions neutralize acid in the esophagus. In cases of esophageal dysmotility, impaired salivation, or a hiatal hernia with re-refluxing of bolus, the esophagus may inadequately clear gastroesophageal reflux from the esophagus [36].

Disrupted Structural Integrity of the Esophageal Epithelial Barrier

The esophageal epithelium functions as a structural barrier to noxious exposure from gastric contents via a complex of apical junction proteins. Acid and bile exposure to the esophageal epithelium has been shown to reduce the barrier function of the epithelium through effects on structural proteins such as claudin-1 and claudin-4. As a result, the spaces between epithelial cells widen to permit increased exposure to gastric contents. Therefore, chronic bolus stasis or exposure to noxious contents can lead to erosive mucosal injury. Since mechano- and chemonerve fiber endings are present within intercellular spaces, a reduced integrity of the epithelial barrier may also lead to heightened nociception to esophageal stimuli [37–41].

Visceral Hypersensitivity and Hypervigilance

Esophageal symptoms commonly attributed to GERD may also develop without mechanical dysfunction, esophageal dysmotility, or evidence of pathologic burden of reflux and thus meet criteria for functional esophageal disorders. The pathophysiology of functional esophageal disorders is believed to arise from alterations in neural processing between peripheral triggering and central perception of esophageal symptoms. Functional esophageal disorders as they relate to GERD symptoms may present as functional chest pain, functional heartburn, reflux hypersensitivity, and/or globus pharyngeus. Diagnosis of a functional esophageal disorder according to the Rome IV criteria requires at least 3 months of symptoms with an onset of at least 6 months [42].

Management

What Lifestyle Modifications Can I Make to Manage My GERD?

I Was Just Diagnosed with GERD, What Natural Changes Can I Make to Manage My Symptoms?

Lifestyle modifications to reduce GERD symptoms are recommended in all patients [6, 43] (Table 3.1). Typical recommendations include maintaining a healthy weight, elevating the head of the bed, avoiding late-night eating, tobacco and alcohol limitation, and avoidance of common dietary triggers of symptoms. Each of these recommendations has been assessed in the literature.

Obesity is a known significant risk factor for erosive esophagitis and Barrett's esophagus [44]. The relationship between obesity and GERD has specifically been observed in women. In the Nurses' Health Study, women with a BMI of 35.0 kg/m^2 had 2.9 times increased odds of experiencing frequent GERD symptoms compared to women with a BMI of 20 to 22.4 kg/m^2 [13]. In this study even among women with a normal BMI, weight gain was associated with a new onset of GERD symptoms [13]. Thus, weight loss and reduction of central obesity are important recommendations for patients with GERD. Recently, an electronic clinical decision support tool (The Reflux Improvement Monitoring (TRIM) Program) was developed to identify and enroll patients with obesity and GERD into a patient education and weight monitoring program. Enrollment in TRIM was associated with significant improvement in symptoms, significant reduction in weight, and overall positive patient engagement. Tools such as TRIM may be effective generalizable methods to promote weight management and healthy lifestyles in the current era of electronic health records [45].

Patients having difficulty with GERD therapy often report nighttime symptoms [46]. Sleeping with the head of the bed elevated using a wedge or bed risers has

Table 3.1 Lifestyle interventions for GERD

Lifestyle intervention	Description
Weight management	Maintain healthy weight; minimize central obesity
Elevate head of the bed	For patients with nighttime symptoms and/or known large hiatal hernias, elevate the head of the bed by 6–8 in. with risers/wedges
Avoid late-night eating	For patients with nighttime symptoms and/or known large hiatal hernias, avoid meals within 2–3 h of lying down, and avoid larger meals at nighttime
Tobacco limitation	
Alcohol limitation	
Avoid dietary triggers	If a dietary trigger is identified for an individual patient, try avoiding the specific dietary trigger
Physical exercise modification	For patients with symptoms during exercise, modify exercises involving intra-abdominal pressure

been shown to improve GERD [47, 48], and lying on the left side may also decrease esophageal acid exposure time at night due to the esophagogastric junction being more superior to the potential refluxate in this position [49, 50]. While it is logical to associate late-night meals with an increased risk of GERD at night while supine, no conclusive evidence exists thus far in proving this association [51].

An extensive systematic review of studies between 1975 and 2004 showed an overall increase in esophageal acid exposure times with tobacco and alcohol consumption; however cessation of tobacco and alcohol did not show an improvement of GERD based on symptoms or ambulatory reflux monitoring [52]. To this date, there remains a lack of conclusive evidence that recommending alcohol and tobacco cessation can improve an esophageal reflux burden. However, with the known benefit of reducing neoplastic progression of Barrett's esophagus and risk of esophageal adenocarcinoma, this recommendation remains compelling [43].

A decision to treat GERD symptoms more aggressively must be made in conjunction with an individual patient's risk of GERD complications such as erosive esophagitis and Barrett's esophagus. Warning signs such as unintentional weight loss, dysphagia, and gastrointestinal bleeding necessitate an upper endoscopy to exclude a GERD complication. If a GERD complication is found, more aggressive medical management is typically needed to improve outcomes [9].

Are There Certain Foods That I Should Avoid for My GERD?

Broad dietary restrictions of many foods for all patients with GERD is of limited value in reducing GERD symptoms [52]. Common foods that induce GERD symptoms are chocolate, fatty foods, citrus, spicy food, carbonated beverages, and caffeine, and avoiding specific triggers is recommended for individual patients [43]. There has been evidence to support that chocolate and carbonated beverages can lower the pressure of the LES, while chocolate and fatty foods can increase esophageal acid exposure time [52]. However, the same studies do not show physiologic effects with other common triggers, and no studies have shown improvement in GERD symptoms or complications when avoiding specific dietary choices. There remains a role for ambulatory reflux monitoring in detailing symptom associations with GERD and understanding if specific dietary triggers enhance a particular patient's reflux burden. Ultimately, avoidance of clear dietary triggers of symptoms, or dietary triggers of reflux on ambulatory reflux testing, can more confidently lead to improvement of GERD individually in patients.

I Have Noticed That My GERD Is Worse When I Exercise: Should I Stop Exercising?

There have been several studies supporting that gastroesophageal reflux symptoms are common during exercise, even with otherwise asymptomatic subjects, as more intense exercise can result in more significant reflux events [53, 54]. One study also

suggested that dysfunction of the anti-reflux barrier at the esophagogastric junction is the mechanistic culprit in the increase of esophageal acid exposure during exercise in both controls and GERD patients [55]. Allowing the stomach to empty by prolonging the period between finishing a meal and the onset of exercise may prevent symptoms in some patients. With exercise fundamentally having many other health benefits, the ultimate decision to vary an exercise routine if it predisposes to more GERD should be made between an individual patient and practitioner while factoring in the likelihood of GERD complications and need for GERD treatment.

What Pharmacologic Options Are Available to Treat My GERD?

The mainstay pharmacologic treatment for GERD is acid suppression with PPI therapy. PPIs are highly efficacious in suppressing gastric acid secretion and function by binding to the H+/K+ ATPase pump to inhibit gastric acid secretion. PPIs have been available since the 1990s and are increasingly used. To assess for symptom response to PPI therapy, patients should be advised to take their PPI 30 to 60 minutes prior to a meal for a minimum of 8 weeks.

I Am Concerned About the Risks of Proton Pump Inhibitors: What Are the Real Risks?

Many millions of patients have now had exposure PPIs, and in recent years, there has been increasing attention to potential side effects of these drugs, both in the scientific literature and the media. Associations with gastrointestinal and pulmonary infections, osteoporosis and bone fractures, dementia, heart disease, kidney disease, and several micronutrient deficiencies have been published. However, there is a lack of high-quality randomized controlled trials to evaluate the true cause and effect of these proposed associations [43].

There have been several updated reviews detailing the evidence behind the potential adverse effects of PPIs and assessing the risks for an individual patient [56–58]. For instance, certain risks are biologically plausible with PPIs; however the risks are low, and the conditions are treatable. These risks include iron and vitamin B12 deficiency, *Clostridium difficile* colitis, complications in cirrhosis, and the development of small intestinal bacterial overgrowth. The low-quality evidence surrounding the other potential risks, such as vascular disease, chronic kidney disease, bone fracture, and dementia currently should not alter a decision to give a PPI to a patient for an evidence-based indication [59]. For example, postmenopausal women at risk of osteoporosis are frequently concerned about the possibility of worsening bone disease with chronic PPIs, as there has been some association in the literature between PPIs and osteoporotic fractures. However, a recently prospective, double-blinded study of postmenopausal women to 26 weeks did not show a change in bone

homeostasis with PPIs [60]. As most of the potential risks of chronic PPIs remain theoretical, women on chronic PPI should continue to be assessed by a practitioner with a contemporary knowledge of the evidence behind risks of PPIs.

What if I Don't Want to Start Medications?

For patients without erosive reflux disease on endoscopy, the decision to start medications requires a discussion with the healthcare team regarding the patient's quality of life, preferences, ability to tolerate symptoms, and individual risk of long-term disease progression. Patients with significant erosive reflux disease or Barrett's esophagus have an increased risk of progression to esophageal adenocarcinoma. Current guidelines recommend at least once-daily PPI therapy in patients with Barrett's esophagus [9].

What if I Start Proton Pump Inhibitors and Feel Fine?

Most patients will note an adequate symptom improvement with PPI therapy. In these cases of PPI response, it is reasonable to reduce the PPI dose to the lowest effective dose tolerated or completely discontinue the PPI therapy [61]. Previous studies have demonstrated that step-down therapy, or the reduction in PPI dose, is tolerated by up to 90% of patients with uncomplicated GERD [62]. There is no one particular method to discontinue PPI therapy. Given the potential of a rebound acid hypersecretion following abrupt PPI cessation, some authorities will recommend a gradual taper [63]. During and following the PPI taper, patients may use over-the-counter antacids as needed for intermittent symptom relief.

I Am Willing to Start Medications Aside from Proton Pump Inhibitors: What Are My Options?

Acid Suppression

Prior to the availability of PPI therapy, histamine-2 receptor antagonists (H2RAs) were the mainstay of acid suppression. H2RAs can be considered as a first-line for acid suppression in nonerosive reflux disease. Although there is controversy regarding whether H2RAs help to decrease nocturnal acid breakthrough, studies have shown that in patients on both double-dose PPI and nightly H2RAs, nighttime reflux symptoms are improved, and sleep is less disturbed [64]. Tolerance to H2RAs has been suggested, however, and the benefit of adding H2RAs may wane over time [65]. Compared with PPIs, H2RAs are less effective at gastric acid suppression. Studies demonstrate that H2RAs are inferior in healing and maintaining healing in erosive disease. Therefore, H2RAs should not be recommended as the primary acid suppression in erosive reflux disease [33, 64].

Alginate Antacid

Alginate antacid is an oral pharmacologic that when exposed to gastric acid precipitates to form a floating raft to function as a physical barrier between gastric contents and the LES. It is typically taken with meals and at bedtime [66, 67]. While not extensively studied, some data exists to support its role in patients with PPI nonresponse in terms of reducing the number of acid reflux events and symptom burden, particularly in controlling postprandial heartburn and regurgitation [43, 68]. The low side effect profile and unique mechanism of action make alginate antacids a potentially useful and intriguing adjunct to PPI therapy [67]. For patients with nonerosive reflux disease reluctant to take long-term PPI therapy, alginate antacid may be considered as a potential alternative.

GABA Agonist

GABA agonists target LES relaxation and in studies have been shown to decrease the number of TLESR events and reduce heartburn and regurgitation symptoms in PPI refractory GERD when compared to placebo [69]. It is reasonable to trial GABA agonists in patients with a presumed TLESR mechanism of reflux. Serious potential side effects of GABA agonists, including CNS depression, should be discussed with patients prior to starting therapy.

Neuromodulation

Pharmacologic neuromodulation may be an effective treatment option across the spectrum of GERD. In fact, the majority of patients diagnosed with GERD based on symptoms that do not respond to PPI therapy will have a functional esophageal disorder [70]. Antidepressant therapy such as tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin noradrenergic reuptake inhibitors may be effective in modulating central and peripheral hyperalgesia in these cases [70].

Future Pharmacologic Treatment Options

Studies investigating novel treatment options for GERD are underway. Potassium-competitive acid blockers (P-CABs), such as vonoprazan, competitively inhibit proton pumps and are currently approved in Japan for the treatment of peptic ulcer disease, healing of reflux esophagitis, and eradication of *Helicobacter pylori* infection [71, 72]. Compared to PPIs, P-CABs have a higher potency, longer duration of action, and ability to block both inactive and active proton pumps [33]. Multiple retrospective studies have shown a symptom improvement in PPI-refractory GERD [73], and vonoprazan was found to be non-inferior to lansoprazole for treatment of erosive esophagitis [74]. At present P-CABs are not available for clinical use in the

United States. IW-3718 is a novel investigational bile acid sequestrant currently under study. In a phase 2A randomized double-blind placebo-controlled trial, the percentage of heartburn-free days increased in patients taking IW-3718 compared with placebo [43].

Can You Tell Me About Surgical and Endoluminal Treatment Options for My GERD?

My Doctor Suggested I See a Surgeon for Anti-reflux Surgery: What Are My Options and What Are the Risks?

Anti-reflux surgeries are surgical options to anatomically restore the anti-reflux barrier. According to professional gastroenterology societies, anti-reflux surgery is indicated for PPI refractory GERD or in the uncommon scenario of PPI intolerance (6). Whether anti-reflux surgery is appropriate as an alternative to PPI therapy is unclear.

Laparoscopic Fundoplication

The current standard for anti-reflux surgery is laparoscopic fundoplication. Laparoscopic fundoplication returns the esophagogastric junction to an intra-abdominal location, repairs the crural defect, and wraps the gastric fundus around the distal esophagus to create a one-way valve. Nissen fundoplication is a complete 360° wrap. Partial wraps such as a Toupet fundoplication (posterior 270° wrap) are more commonly performed in an effort to reduce risk of post-fundoplication complications. Success rates of fundoplication vary between 67 and 95% reported in the literature, and postoperative outcomes are highly dependent on appropriate patient selection, surgical expertise, and adequate preoperative evaluation [35]. The preoperative evaluation for anti-reflux surgery requires diagnostic evaluation with an upper GI endoscopy and esophageal manometry. When erosive disease is not evident on endoscopy, reflux monitoring is a requisite to confirm an objective diagnosis of GERD prior to anti-reflux surgery.

Laparoscopic fundoplication is a complex surgery and complications may arise. The perioperative mortality is reported to be 0.1–0.2%. In the acute postoperative period, up to 30% of patients may experience dysphagia, likely as a result of postoperative edema and inflammation which should subside over time. Postoperatively the fundoplication wrap is at risk of disruption in the form of a slipped wrap and/or herniation above the wrap, as well as obstructive complications from narrowing or angling at gastroesophageal transition. Furthermore, up to 30% of patients may experience long-term complications which include gas-bloat syndrome, functional chest pain, an inability to belch or vomit, and diarrhea. Therefore, it is essential to select the appropriate patient and set long-term expectations with the patient prior to embarking on laparoscopic fundoplication [35].

Magnetic Sphincter Augmentation

The magnetic sphincter augmentation device is an FDA-approved device for management of GERD (LINX Reflux Management System). It works via biomechanical augmentation of the LES by use of a magnetic reinforcing appliance [75, 76]. Advantages of magnetic sphincter augmentation include that it is a reversible, reproducible, and technically simple anti-reflux intervention that does not alter gastric anatomy [77–81]. To date, there are no reports of perioperative deaths or life-threatening complications following magnetic sphincter augmentation implantation. The most feared complication of magnetic sphincter augmentation is device migration and erosion into the esophagus, reported in up to 0.15% of cases [82–84]. A meta-analysis comparing magnetic sphincter augmentation to laparoscopic fundoplication reported a significantly reduced risk of gas-bloat with the magnetic sphincter augmentation [85].

What Nonsurgical Interventions Are Available to Treat My GERD?

Several methods of treating GERD on endoscopy have been assessed in recent decades in order to decrease the reflux burden ascending through the esophagogastric junction. Many of the initial techniques have been withdrawn due to complications or a lack of consistent treatment benefit. Of the treatments available, studies have focused on GERD patients without significant erosive esophagitis, Barrett's esophagus, or larger hiatal hernias.

Transoral Incisionless Fundoplication

Transoral incisionless fundoplication (TIF) is fundamentally an endoscopic attempt at surgical reconstruction of the LES, by creating a wrap and a 270° or greater fundoplication [86]. A multicenter study comparing TIF to PPI and sham therapy showed an improvement in esophageal acid exposure and regurgitation at 6 months [87], but in a randomized study comparing TIF to PPIs, there was no significant reduction of esophageal acid exposure, and most patients had resumed PPI therapy at 12 months [88]. A meta-analysis also showed that most patients resume PPI over time after TIF, and there is only a limited amount of evidence supporting improvement in reflux episodes and esophageal acid exposure on follow-up [89].

Radio-Frequency Application

Radio-frequency application to the esophagogastric junction is designed to cause hypertrophy and scarring in the area to increase LES-resting pressure and reduce TLESRs [86]. Currently there are conflicting data regarding its utility in treating GERD. One meta-analysis of only randomized controlled trials did not show a benefit in normalizing esophageal acid exposure time, improving quality of life, or leading to

cessation of PPI therapy [90]. A later meta-analysis of randomized controlled trials along with prospective cohort studies did show an improvement in quality of life and significant reductions in PPI therapy and esophageal acid exposure [91].

Endoluminal treatment of GERD is an evolving field, and techniques to target the LES are being studied beyond TIF and radio-frequency application. Practically, patients considering an anti-reflux procedure, whether endoscopic or surgical, are those that often do not have consistent benefit to PPI therapy. In a recent recommendation from an expert panel on how to approach and treat these patients after categorizing them by physiologic parameters, no endoscopic therapy was recommended in any patient who fit this clinical scenario [5]. This highlights the further work needed to determine whether endoscopic therapies for GERD can have a sustained benefit and improve outcomes.

What to Expect

Will My GERD Get Worse During Pregnancy?

GERD is common during pregnancy, with one study finding it can have an onset of 52% in the first trimester, 40% in the second, and 8% in the third [92]. An increased intra-abdominal pressure is the plausible mechanism, but the cause may be multifactorial for an individual patient, with another proposed factor being decreased LES pressure caused by progesterone [93]. One study of 607 women, of which 14% had mild heartburn before pregnancy, showed that 72% of these women ultimately had heartburn in the third trimester, and the severity increased throughout pregnancy [94]. Predictors of heartburn during pregnancy include increasing gestational age and heartburn before pregnancy [95].

Fortunately, invasive testing for GERD during pregnancy is rarely needed, and heartburn frequently resolves after delivery [95]. However, pregnancy has also been shown to be a risk factor for frequent GERD symptoms 1 year postdelivery when compared to a control group [96]. Treatments should focus on the aforementioned GERD lifestyle modifications to prevent heartburn. If needed to control symptoms, PPIs are considered safe in pregnancy. In a large cohort of over 5000 births with exposure to PPIs in the first trimester, there was not an increased risk of birth defects. Sucralfate may also be an option though it has limited efficacy for GERD overall [6, 97].

If I Have GERD, Are My Children at Increased Risk?

A genetic predisposition for GERD has not been established. However, children with similar environmental and dietary risks, such as a predilection for obesity, may also have a risk of GERD. Furthermore, there is a well-established risk of Barrett's esophagus and esophageal adenocarcinoma in patients with a first or second degree

relative with one of these complications arising from GERD [98]. Thus, practitioners caring for children of parents with significant GERD should assess risk factors and be cognizant of potential GERD development in these individuals.

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Chapter 4
Cyclic Vomiting Syndrome: Does Gender Matter? How Does It Affect the Health of Women?

Vishnu Charan Suresh Kumar and Thangam Venkatesan

What Is Cyclic Vomiting Syndrome (CVS)? Are Women More Predisposed to CVS than Men?

Suggested Response to the Patient

Cyclic vomiting syndrome (CVS) is a chronic functional GI disorder (FGID) with a prevalence of 2% in the USA [1]. Patients experience recurrent episodes of intense nausea, vomiting, and abdominal pain. Other symptoms can include a migraine headache, sensitivity to light, hot and cold flashes, and diarrhea. CVS consists of four phases: the inter-episodic phase, the prodromal phase, the emetic phase, and the recovery phase as described by Fleisher et al. (Fig. 4.1) [2]. Both positive (birthdays, graduation parties, or holidays) and negative stresses (exams, death, or divorce) can trigger an episode. In women, episodes can also be triggered by menses, a phenomenon known as *catamenial CVS* [3]. The exact cause of CVS is not known. It is considered an FGID, which means that is a problem with the communication between the brain and the gut (malfunction of the brain-gut axis). CVS is diagnosed using the internationally accepted criteria, called the Rome IV criteria [4]. There are no specific blood tests or x-ray tests (biomarkers) to make the diagnosis.

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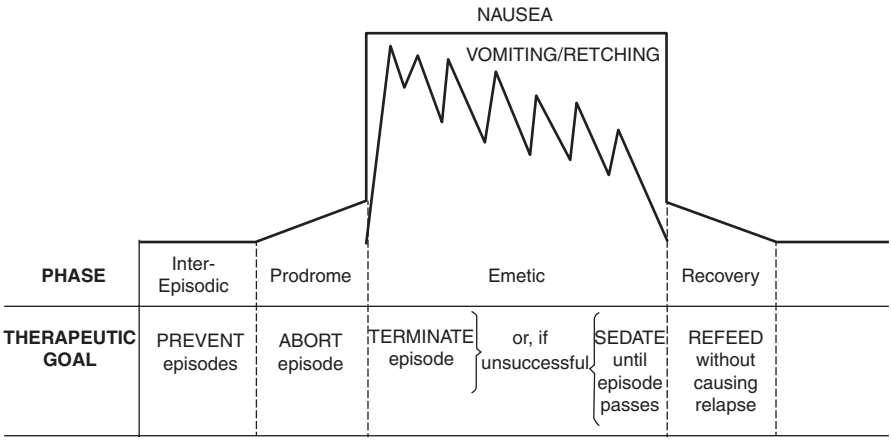

Fig. 4.1 Phases of cyclic vomiting syndrome. (Reproduced from BMC Medicine, Vol 3, 2005. "Cyclic Vomiting Syndrome in 41 adults: the illness, the patients, and problems of management")

Some patients (about 40%) with CVS use cannabis and report relief from symptoms associated with CVS such as nausea and vomiting. However, paradoxically, chronic cannabis use has been associated with hyperemesis. Cyclic vomiting in the context of heavy cannabis use is called cannabinoid hyperemesis syndrome (CHS). CVS and CHS have similar symptomatology except for the chronic cannabis use that is thought to lead to hyperemesis in CHS. There is limited data on CHS, and it is unclear if this is a separate entity or if it is actually CVS triggered by excessive cannabis use. This may occur because cannabis products that are now available have very high proportions of Δ9-tetrahydrocannabinol (THC), compared to several years ago [5]. THC is the main psychoactive ingredient in cannabis and is thought to be responsible for adverse effects associated with its use, such as anxiety and early-onset psychosis, particularly in young adults. It is best to avoid heavy cannabis use, until more is known about how this affects human health.

Some studies have shown that CVS affects women more, but results have been inconsistent [6]. There have been mixed results with others showing a male preponderance [7]. However, CVS has a huge medical, social, and economic impact in the life of women and should be addressed.

A Brief Review of the Literature

Cyclic vomiting syndrome is a chronic FGID, which is characterized by recurrent episodes of severe nausea and vomiting interspersed with symptom-free periods. The first reports of CVS were in nine children in 1882 by Samuel Gee, a pediatrician [8]. It was initially thought to be a pediatric disorder, but studies now indicate that it is as common in adults. The prevalence of CVS in adults was 2% in a recent

Table 4.1 Rome IV criteria for the diagnosis of cyclic vomiting syndrome in adults [4]

Stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week)
Episodes abrupt in onset and occurring at least 1 week apart
Three or more discrete episodes in the prior year with two episodes in the past 6 months, with absence of vomiting between episodes. Other milder symptoms can be present between episodes
Supportive criteria include
A personal and/or family history of migraines

population-based study [1]. While the exact pathogenesis of CVS is still unclear, polymorphisms in mitochondrial DNA (mtDNA) and the cannabinoid receptor type 1 (CNR1) genes have been associated with an increased risk of CVS [9, 10]. A study of 74 families of patients with CVS reported a matrilineal inheritance of CVS, with multiple functional disorders affecting family members on the maternal side of the family [11]. CVS has no biomarkers and is diagnosed using Rome IV criteria (Table 4.1) [4]. Repeated endoscopies and CT scans as well as other invasive modalities of testing should be avoided. In our experience, a thorough history combined with a good physical examination and basic laboratory tests along with an EGD and CT abdomen or UGI series with a small bowel follow-through to exclude small bowel obstruction is sufficient to establish the diagnosis in most cases.

The clinical symptoms of CVS are similar in both children and adults. The mean onset of symptoms is 5 years in children and 35 years in adults. Episodes last from a few hours to several days. CVS has four phases as described by Fleischer (Fig. 4.1): the prodromal phase, the emetic phase, the recovery phase, and the inter-episodic or asymptomatic phase. The prodromal phase precedes the emetic phase [2]. During the prodromal phase, patients begin to sense the onset of an episode and may even report an impending sense of doom. Patients may experience symptoms such as nausea, abdominal pain or "pressure," fatigue or weakness, feeling hot or cold, sweating, cramping, urge to defecate, shakiness, insomnia or restless, aversion to food, pounding or irregular heartbeat, irritability, and feelings of panic during this phase. The emetic phase is characterized by intense nausea, vomiting, retching, and abdominal pain. The patient is often listless and prefers to lie in a quiet, dark room. Some patients take very hot showers/baths which they report alleviates symptoms. This is referred to as a "compulsive hot-water bathing pattern," which is unique to this disorder. While this is significantly associated with cannabis use, it occurs in ~50% of patients with CVS who do not use cannabis [12, 13]. During the recovery phase, symptoms begin to subside, and patients will slowly resume oral intake. The inter-episodic phase is a relatively symptom-free period between episodes, although some patients may experience nausea and dyspepsia during this period. A subset of patients can have episodes that lengthen and become more frequent with time. As a result, the typical cyclic nature of episodes is lost with, and patients do not return to normalcy in between episodes. This pattern has been referred to as "*coalescent CVS*," where the diagnosis may not be readily apparent [2]. A careful history must

be sought to make a diagnosis in these instances. Patients with coalescent symptoms should be treated with prophylactic agents such as amitriptyline, which can greatly reduce symptoms.

The prevalence of CVS is ~2% in adults and is similar to the pediatric age group [1]. A study in Ireland showed that the incidence CVS was 3.15 per 100,000 children per year [14]. In a recent study, the prevalence of CVS in a tertiary outpatient gastroenterology setting was found to be 10.8%. The diagnosis of CVS was considered in only 4% of patients with typical symptoms and reflects the lack of awareness of CVS even among specialists [15]. Adults experience a significant delay in diagnosis due to the prevailing notion among clinicians that CVS is a pediatric disorder [16].

CVS affects both males and females. Studies so far about predilection of CVS based on gender have yielded mixed results. A study of 101 patients with CVS revealed that patients were more likely to be female [6]. Data from a recent study of 99 patients with CVS corroborated these findings where 74% of patients with CVS were women [15]. Other studies have shown a greater proportion of men being affected [6, 7]. Two studies of 132 and 31 patients with CVS, respectively, showed a slight male preponderance of 55 and 58% [17, 18]. In summary, CVS affects a large proportion of women, and its effects on women's health should be a public health priority.

Will My Cyclic Vomiting Syndrome Get Worse if I Get Pregnant? Can I Pass It onto My Children?

Suggested Response to the Patient

Cyclic vomiting syndrome is affected by hormonal changes that occur during the menstrual cycle [19]. Some women experience symptoms that coincide with the menstrual cycle, and this subset of CVS which is triggered by menses is called "catamenial CVS" [3]. Given this, it is reasonable to speculate that the major hormonal changes that occur during pregnancy also affect CVS. Unfortunately, there is minimal data on the effects of CVS on pregnancy and vice versa. Though we do not have information about this, there is data in a closely related condition, migraine headache. Almost half the patients who suffer from CVS also suffer from migraine or have a close family member with migraine.

It is encouraging to know that approximately 2/3 of patients with migraine headache experience a significant improvement in symptoms during pregnancy. A small percentage suffer from worsening of their disease or develop migraine headache for the first time during pregnancy. Pregnant women who experience an acute episode of migraine are at an increased risk of adverse outcomes such as preterm delivery, low birth weight, and preeclampsia [20].

Though there are no studies evaluating the effects of pregnancy on CVS, we know that a subset experience improvement, while others have a worsening of symptoms. This is based on collective experience of the primary author and other

experts in the field. There do not appear to be any data to indicate that there is any increased risk of birth defects. However, some women who have CVS symptoms during pregnancy seem to be more predisposed to having low-birth-weight babies, akin to those with migraine headache. In general, it is recommended that women with CVS who are contemplating pregnancy or are pregnant be referred to a high-risk obstetric practice.

Family studies and pedigree analysis (detailed family histories) have shown that functional disorders such as CVS, irritable bowel syndrome, migraine, and fibromyalgia congregate in families, affecting members on the maternal side of the family. This suggests that these disorders may be inherited from the mother's side, otherwise called a *matrilineal inheritance pattern* [21]. However, these findings are yet to be replicated or confirmed. In short, children born to mothers with CVS may have an increased risk of developing CVS, but we do not have enough evidence yet to prove that CVS is hereditary. CVS is likely due to a combination of both genetic and environmental factors like early life adversity and stress, which can precipitate attacks of CVS. For now, symptoms should be managed collaboratively with a team that consists of the obstetrician, the gastroenterologist with expertise in CVS/FGIDs, and the primary care physician.

A Brief Review of the Literature

Migraine headaches are significantly influenced by the reproductive cycle in women [19]. As estrogen plays a vital role in migraine, its fluctuation is thought to be the reason behind the variation in severity during different stages of a woman's life. Symptoms of migraine actually improve in 60–70% during pregnancy, particularly from the second trimester onward [19]. However, a small percentage of women might experience worsening of symptoms. A subtype, migraine with aura which presents with transient neurological symptoms (visual, sensory, motor, or language symptoms) that either precedes or accompanies the headache has been observed to worsen during pregnancy [22]. A nationwide population-based study including 4911 women with migraine headache showed that there was 1.16- and 1.24-fold increased risk of having low birth weight and preterm labor [23]. Another study showed that ~55% of pregnant women with migraine who presented to the acute care setting with an acute attack of migraine experienced an adverse event such as preeclampsia, preterm delivery, and low birth weight during pregnancy [20].

As CVS is thought to be a variant of migraine [21], we can only predict that pregnancy would have similar effects on the severity of CVS as in migraine headache. Studies that elucidate the relationship between pregnancy and CVS are needed. Further, the effects of CVS on pregnancy and perinatal outcomes also need to be studied. Collaborative efforts by the medical community with both public and industry support in collaboration with patient and advocacy groups are needed to address these important issues that affect the health of women with CVS.

Genetic factors play a role in the pathophysiology of CVS. Some studies have shown that mtDNA polymorphisms 16519T and 3010A were associated with increased odds of having CVS in children [24]. However, this was not found to be true in adults with CVS, though a matrilineal inheritance pattern of functional GI disorders was seen in a subset of adults with CVS [21]. More recently, polymorphisms in the gene for the cannabinoid receptor (CB1R), a part of the endocannabinoid system, were found to modulate risk for CVS [10]. The CB1R gene is located on chromosome 6q 14–15 and encodes for the CB1 receptor. A study of 263 patients with CVS showed a significantly increased risk of CVS among individuals with the AG and GG genotypes of CB1R at rs806380, whereas the CC genotype of CB1R at rs806368 was associated with a decreased risk of CVS. Of note, rs806380 is associated with cannabis dependence with the G allele having a protective effect [25]. Additionally, the same study by Wasilewski et al. also showed that the CT and CC genotypes of rs2023239 of CB1R were associated with a positive response to therapy with tricyclic antidepressants (TCAs). These findings suggest that there are multiple genetic factors that contribute to the development of CVS. However, there are no data to prove that CVS is hereditary, and the pathophysiology is likely due to a complex interaction between both genetic and environmental factors.

What Are My Treatment Options in General? What Medications Can I Safely Take During Pregnancy?

Suggested Response to the Patient

The treatment of CVS is multifactorial, and a biopsychosocial approach to address psychosocial factors in addition to the standard treatment should improve patient outcomes. Standard therapy consists of preventive or prophylactic medications that are taken daily and abortive or rescue medications that are taken to "stop" or prevent symptoms from progressing to a full-blown episode. Prophylactic medications are indicated in moderate-to-severe CVS. CVS is defined as moderate-to-severe when patients have ≥4 episodes/year, episodes that last longer than 2 days, or when patients are unable to maintain activities of daily living such as work or school [26]. The primary goal of prophylactic treatment is to reduce the frequency and severity of episodes, restore normal functioning, and enable patient to continue with their normal routine. First-line treatment in the prophylaxis of CVS is amitriptyline (AT). AT is a TCA and has been shown to reduce the duration, frequency, and severity of CVS episodes as well as the number of emergency department visits and hospitalizations due to CVS [27]. Other medications used for prophylaxis include antiepileptics such as zonisamide or levetiracetam. Mitochondrial supplements such as coenzyme Q10 and riboflavin, which are helpful in migraine headaches, can also reduce symptoms of CVS. Aprepitant, a newer antiemetic agent that is largely used to prevent chemotherapy-induced nausea and vomiting, has been shown to be

helpful as both prophylactic and abortive treatment in patients with CVS who are refractory to other medications. Of note, aprepitant *can reduce the efficacy of oral contraceptive pills*, and other options for birth control should be considered.

Abortive medications to "stop" an episode are offered to all patients regardless of the severity of the illness. This is usually a combination of medications which includes antiemetics, sedatives, and triptans. Abortive therapy should be initiated in the prodromal phase when they are most effective in preventing an episode. Medications called triptans are effective, and the intranasal route is preferred. These are often combined with antiemetics such as ondansetron and phenothiazines or benzodiazepines which can promote sleep and help abort symptoms. A newer medication called aprepitant may also be used [28]. Management of CVS based on the severity of CVS is shown in Fig. 4.2.

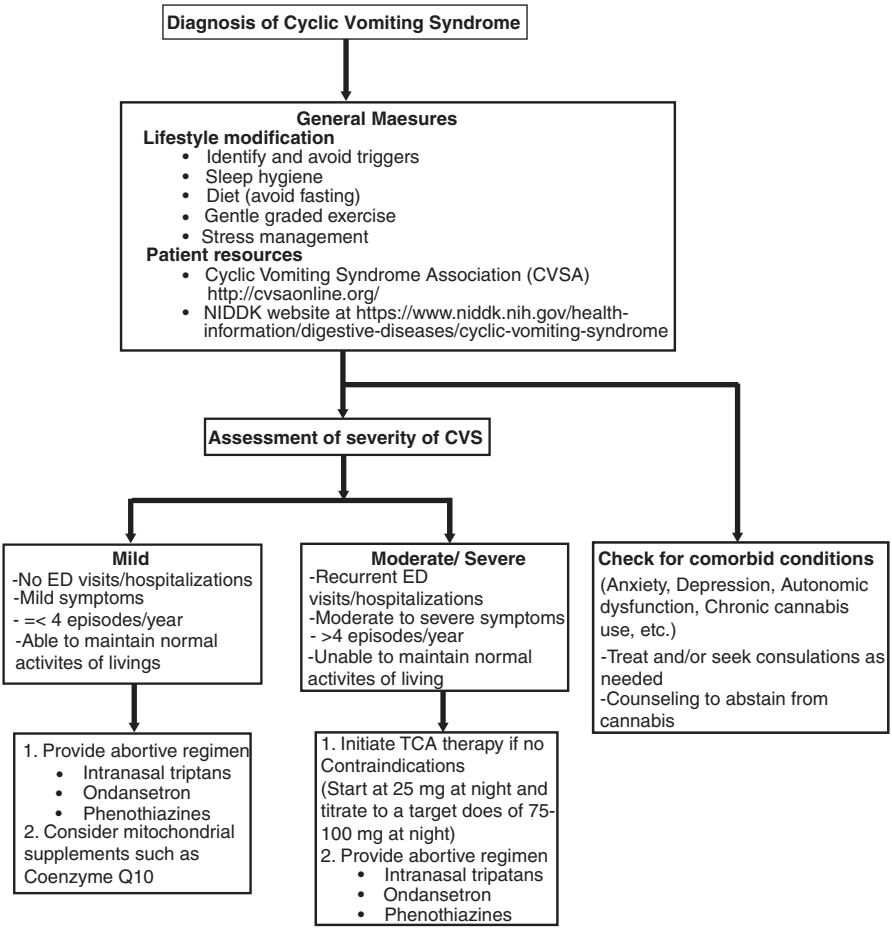

Fig. 4.2 Suggested algorithm for the management of cyclic vomiting syndrome. (Reproduced from Bhandari and Venkatesan [44])

Sometimes neither abortive nor preventative measures work, and patients may need to be seen in an emergency department or admitted to the hospital for further management. Treatment of patients should be expeditious and in general consists of IV fluids, antiemetics, and sedatives such as benzodiazepines. Opioids are best avoided, given the risks of addiction and overdose. If necessary, their use should be individualized and monitored closely by the treating physician. Ondansetron, diphenhydramine, and aprepitant may be used in pregnancy. Finally, lifestyle modification is crucial in the management of CVS. Patient engagement with active participation in their care plan is crucial to achieve good patient outcomes. Some simple tips for patients to manage symptoms of CVS are shown in Table 4.2.

Managing CVS during pregnancy can be challenging. In general, avoiding medications as far as possible, particularly during the first trimester, is recommended. All medications are classified as A, B, C, or D or X, based on the safety profile in pregnancy

Table 4.2 Tips for managing CVS

What Are Things That Can Help Me?	How Can I Identify Common Triggers?
	Try and figure out what brings on your episodes of CVS and do your best to avoid these things This can mean staying well hydrated, avoiding excessive alcohol, and taking your daily prescription medications Regular exercise (avoid overexercising), regular meal schedules (avoid skipping meals), and moderation or avoidance of caffeine may also help If you feel an episode coming, use your prescription *abortive medications at the "first sign"* and do not wait till you start vomiting *Abortive medications are medications that are prescribed by your doctor to "stop" or "abort" an episode*
Foods	Avoid fasting, and be sure to eat regular, balanced meals Figure out which foods may bring on your episodes and avoid those foods. Some people have found cheeses, chocolate, beans, or wine to bring on an episode
Intense excitement	During vacations, birthdays, or other exciting events in your life, take time to relax and breathe when you feel tense Try to avoid excessive energy output Try and get at least 8 h of sleep daily
Try to relax and manage emotional stress	Learn to relax by listening to music, spending quiet time alone, taking a warm bath, meditating, or exercising. Find a quiet place where you will not be disturbed Take off your shoes and turn off your cell phone for 5 min Take deep breaths and focus your mind on one peaceful thought, image, or word, then try to hold that thought When other thoughts enter your mind, relax and refocus Let the invading thoughts fall away When you're done, stretch your arms over your head With practice, this quiet time can help you feel restored You can also visit [a]www.heartfulness.org

[a]This is a website that offers resources to practice meditation and is free of charge

and effects on the fetus. Category A drugs have been studied extensively in humans and have showed no risk to the fetus. Category B denotes drugs that were studied in animals and found to be safe, but no human studies were available. Category C drugs either have no human studies done or have shown adverse effects to the fetus in animal studies. The drug may be used in pregnancy if the potential benefits of the drug outweigh the risks. Category D drugs are best avoided in pregnancy given evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans. Category X drugs showed adverse effects in both human and animal studies and are contraindicated in pregnancy [29]. In general, class A and B medications are considered safe for use in pregnancy. As always, the risks and benefits must be considered before using any medication during pregnancy. A list of medications that are commonly used in pregnancy, their pregnancy category, dosage, and side effects are shown in Table 4.3.

Some medications such as topiramate, lorazepam, and sumatriptan (as well as other triptans) should not be used during pregnancy as they have been shown or reported to cause congenital malformations of the fetus such as oral cleft defects

Table 4.3 Medications used in the treatment of cyclic vomiting syndrome

Medication	Pregnancy category	Dosage	Side effects	Other comments
Prophylactic medications used in CVS				
Amitriptyline	C	Start at 25 mg at night Titrate by 10 mg every 5 days to a target dose of 75–100 mg	Weight gain (less with nortriptyline) Sedation (improves after 8–12 weeks) Constipation Xerostomia Mood changes Serotonin syndrome (rare)	QTc prolongation (monitor with EKG) Obtain baseline EKG and repeat during dose titration and after target dose is reached QTc <470 ms for men and <450 ms for women is ideal
Nortriptyline, desipramine, and imipramine may also be used	C		Xerostomia Urinary retention Blurred vision Bad dreams Mood changes Serotonin syndrome (rare)	Use cautiously in cardiac disease (myocardial infarction or conduction abnormalities) Avoid with concurrent use of monoamine Oxidase inhibitors within 14 days *Black box warning*: Suicidal ideation if the patient has severe depression, usually within 2 weeks of initiation; typically applies to patients <24 years of age (*not reported in CVS*)

(continued)

Table 4.3 (continued)

Medication	Pregnancy category	Dosage	Side effects	Other comments
Antiepileptics				
Topiramate	D	Start at 25 mg at night Increase by 25 mg every week to a target dose of 100 mg May increase further if no response. May check levels to guide therapy	Cognitive dysfunction. Difficulty with memory, speech, language Sedation Renal stones Paresthesias Diarrhea Acidosis	Contraindicated in patients with nephrolithiasis Cautious use in patients with glaucoma, can cause acute myopia, discontinue with a decrease in visual acuity or ocular pain Caution in patients with hepatic disease Check bicarbonate levels every 6 months
Zonisamide	C	Start with 100 mg daily Median effective dose (400 mg/day in divided doses)	Mental confusion	Aggressive behavior may improve with dose reduction Increased suicidal ideation may occur with use
Levetiracetam	C	1000 mg/day in divided doses		May increase risk of kidney stones
Aprepitant (a kit contains a 125 mg pill and two 80 mg pills)	B	One kit weekly 125 mg on day 1 and 80 mg on day 2 and day 3 of each week (as prophylaxis)	Fatigue Alopecia Constipation Headache Hypersensitivity reactions including anaphylaxis have been reported (<0.5%)	Side effects are uncommon High cost; insurance may not cover for off-label use in CVS
Coenzyme Q 10	Not applicable	200 mg twice daily	Abdominal discomfort Headache	Caution in patients with soy allergy
Medications used as abortive therapy in CVS				
Sumatriptan (Intranasal or IM)	C	Single dose of 20 mg intranasally (can be repeated after 2 h), not to exceed 40 mg daily	Dizziness Paresthesia Unpleasant taste Chest discomfort or pressure	Should not be used in pregnancy Contraindicated in ischemic heart disease, stroke, peripheral vascular disease, uncontrolled hypertension
Aprepitant (PO)	B	125 mg day 1, 80 mg day 2 and 3	Fatigue Alopecia Constipation Headache Hypersensitivity reactions including anaphylaxis have been reported (<0.5%)	Very expensive; insurance may not cover for off-label use in CVS

Table 4.3 (continued)

Medication	Pregnancy category	Dosage	Side effects	Other comments
Ondansetron (PO, ODT, or IV)	B	8 mg every 8–12 h	QTc prolongation Headache Malaise Drowsiness Serotonin syndrome when combined with SSRI, SNRI, MAOI	Obtain baseline EKG QTc <470 ms in women and <450 ms in men is recommended. Increased risk of cardiac, orofacial cleft defects and renal agenesis reported in infants with first-trimester exposure
Diphenhydramine (PO or IV)	B	25 mg every 6–8 h	CNS depression (sedation, confusion) Anticholinergic side effects: constipation, xerostomia, urinary retention, blurred vision	Use with caution in patients with glaucoma and benign prostate hypertrophy (BPH), as well as the elderly Use with caution in patients with ischemic heart disease and hypertension
Lorazepam (PO or IV)	D	0.5–2 mg every 4–6 has needed	CNS depression Anterograde amnesia Respiratory depression Hypotension Paradoxical aggression in elderly	Use cautiously as they can result in dependence Chronic use can lead to acute withdrawal symptoms upon discontinuation
Promethazine (PO or IV)	C	12.5–25 mg every 4–6 has needed	CNS Depression Bradycardia Extrapyramidal symptoms Anticholinergic symptoms A rare cause of neuroleptic malignant syndrome QTc prolongation	IV administration can cause severe tissue injury including burning, gangrene, or thrombophlebitis Use cautiously in patients with glaucoma and benign prostate hypertrophy
Prochlorperazine (PO, IV, or suppository	C	5–10 mg PO or IV every 6–8 h not to exceed 40 mg/day 25 mg suppository every 12 h	CNS depression Anticholinergic symptoms (constipation, xerostomia, blurred vision, urinary retention) Leukopenia, agranulocytosis, neutropenia Extrapyramidal symptoms A rare cause of neuroleptic malignant syndrome	Caution in patients with a history of drug-induced leukopenia or neutropenia Caution in patients with dementia, glaucoma, and seizure disorder

[a]While most physicians rely on the FDA classification of drugs, this was abandoned in 2014. The FDA now proposes a seven-narrative structure rather than the previous classification (A–X). The new structure includes information about the potential risks of a drug to the fetus based on human and animal studies [43]. However, many physicians continue to use the old system in practice

and anal atresia, especially after exposure in the first trimester. Ondansetron, diphenhydramine, and aprepitant were found to be safe during pregnancy and are Class B medications. However, recent studies indicate an increased risk of cleft palate and cardiac defects with ondansetron use in the first trimester. This must be taken into consideration while treating patients with CVS during pregnancy [30].

A Brief Review of the Literature

CVS is best managed using a biopsychosocial approach. As with other FGIDs, pharmacotherapy, lifestyle modification, measures to treat comorbid conditions such as anxiety and depression, and addressing social barriers to health are important to achieve good healthcare outcomes. Such an approach has been proposed for other FGIDs such as irritable bowel syndrome and found to be effective [31, 32]. Also, a recent pilot study involving 110 patients with inflammatory bowel disease found that this approach was both feasible and well received by patients [33].

Prophylactic medications are initiated for patients with moderate-to-severe CVS. TCAs are considered first-line prophylactic agents. Although there are no randomized controlled trials, several retrospective studies and open-labeled trials have shown that they are effective to both adults and children. Some of the important studies are highlighted here. Hejazi et al. in an open-label study of 46 patients demonstrated a marked reduction in the number of CVS episodes from 17 to 3, in the duration of a CVS episode from 6 to 2 days, and in the number of ED visits/hospitalizations from 15 to 3.3 with amitriptyline [27]. Another study by the same group showed that chronic opioid use, chronic cannabis use, and psychiatric disorders are predictive of a poor response to TCAs [17]. Another study of 101 patients with CVS showed that the majority of patients (86%) responded to TCAs [6]. Amitriptyline is usually started at a dose of 25 mg and titrated up in increments of 10 mg each week to a target dose of approximately 100 mg nightly. Side effects include dryness of mouth, fatigue, somnolence, constipation, or blurred vision. In such cases, amitriptyline can be switched to other TCAs such as nortriptyline. The QT interval should be checked and monitored during dose titration with amitriptyline as it can cause QT prolongation.

Anticonvulsants such as zonisamide and levetiracetam are considered second-line therapy if standard prophylactic therapy fails. A case series of 20 adults with CVS showed that these medications were effective as prophylactic therapy in 75% of the patients [34]. Topiramate was found to be effective either alone or with a TCA in a retrospective study involving 101 patients [6]. A study using an Internet-based survey showed that 68% of the patients using coenzyme Q10 had a 50% reduction in at least one of the parameters (frequency, duration, severity of nausea, and number episodes of emesis). The study also showed that patients on coenzyme Q10 experienced no side effects as compared to 50% of patients on amitriptyline, though the incidence of side effects was not as high in other studies. A study of 41 children

and adolescents weighing >60 kg showed that aprepitant was effective both as a prophylactic and an abortive agent [28].

Abortive therapy should be used during the prodromal stage. Triptans are effective in aborting episodes in the majority of patients and was more effective in those with a history of migraine headache [35]. A retrospective study of adults with CVS reported that 83% were able to successfully abort their episodes using triptans, and migraine headache was not predictive of a response in these patients [6]. Antiemetics (ondansetron) and anxiolytics (benzodiazepines) are used routinely in combination with triptans. Aprepitant was effective in 76% of children and adolescents with CVS [28].

Triptans should however be avoided in pregnancy and the periconceptual period. A systematic review revealed that there might not be a large increase in risk of congenital malformations with the use of triptans, but there is currently insufficient information to rule out a small increase in risk of adverse effects to the fetus. For this reason, the authors advise against using triptans (pregnancy category C) in pregnant women, though occasional inadvertent exposure is unlikely to have adverse outcomes [36]. A large cohort study reported that TCAs were associated with an increased risk of cardiac, musculoskeletal, craniofacial, digestive, and respiratory defects of the fetus with exposure during pregnancy and nortriptyline to be relatively safe during lactation [37]. A retrospective study done between 1997 and 2011 showed that first-trimester exposure to topiramate increased the prevalence of oral clefts [38]. Lorazepam was associated with fetal malformations in 187 infants among 100,000 births, exposed to during the first trimester. Lorazepam has also been associated with anal atresia [39]. We recommend avoiding lorazepam during pregnancy in CVS. Among anticonvulsants, levetiracetam (1.77% in 817 pregnancies) was associated with the lowest risk, and valproate was associated with the highest risk (10.93% in 2565 pregnancies) of congenital malformations [40]. Again, these category C medications are best avoided, and if used, the risk vs. benefits need to be carefully considered and discussed with both the patient and an obstetrician before an informed decision is made.

Other medications used in CVS such as ondansetron are increasingly used in pregnancy though the American College of Obstetrics and Gynecology does not recommend this as first-line treatment. Off-label use of ondansetron for treatment of nausea and vomiting during pregnancy increased from ~1 to ~22% between 2000 and 2014 [41]. First-trimester exposure to ondansetron was associated with a statistically significant increase in the risk of cardiac (OR: 1.52 95% CI: 1.35–1.70) and orofacial cleft defects (OR: 1.32 95% CI: 0.76–2.28), in a recent large population-based study involving 864,803 mothers [42]. However, the increase in cardiac defects was not seen in a separate study utilizing the National Birth Defects Prevention Study and the Slone Birth Defects Study, though an increased risk of renal agenesis-dysgenesis (adjusted OR 1.8, 95% CI 1.1–3.0) was noted in infants who were exposed to ondansetron during the first trimester [30]. While ondansetron is labeled a category B medication, risks vs. benefits should be considered prior to its use. Patients with CVS would benefit from being seen in a tertiary referral center with expertise during pregnancy.

In summary, a biopsychosocial approach with a multidisciplinary team is recommended for the management of CVS. Along with pharmacological therapy, physicians and patients should work together to address psychosocial issues that affect healthcare outcomes. We suggest a stepwise systematic approach to diagnose and manage CVS. Prophylactic therapy includes TCAs, anticonvulsants, aprepitant, and mitochondrial supplements. Abortive therapy consists of triptans and antiemetics and sedatives. During pregnancy, category A and B drugs can be used safely, whereas category C drugs may be used when benefits outweigh the risks. There are several gaps in our knowledge about the relationship between pregnancy and CVS, and studies to determine the effects of pregnancy on CVS are warranted.

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Chapter 5
Idiopathic Gastroparesis

Dariush Shahsavari and Henry P. Parkman

Commonly Posed Patient Questions

1. **My recent gastric emptying test was normal, though it was delayed in the past and I was told I had gastroparesis. What do I have?** [1–3]
   Gastric emptying testing is needed to diagnose gastroparesis. The standard gastric emptying test is gastric emptying scintigraphy, which uses a radiolabeled isotope bound to solid food to image the meal emptying. However, there is variable methodology used at different centers. Standardization of gastric emptying among different centers has been suggested using the a 4 h imaging protocol with scans taken 0, 1, 2, and 4 h after ingestion of a radioactive Tc-99m-labeled low-fat egg white with jam and two pieces of toast. The shorter duration tests lasting 60–90 min using different meals are not as helpful. Relatively high variability in gastric emptying constitutes another limitation of gastric motor testing. Unfortunately, gastric emptying rates measured by gastric motor testing do not correlate well with symptoms of gastroparesis. Patients can have severe nausea and vomiting with normal gastric emptying. These patients have significant symptoms and are, for the most part, indistinguishable from those with gastroparesis. These findings suggest that factors in addition to slow gastric emptying contribute to symptoms.
2. **My abdominal pain is still present and getting worse. My prior gastroenterologist gave me Percocet for the abdominal pain. What will you do?** [4–6]
   Abdominal pain in gastroparesis is a difficult symptom and a difficult symptom to treat. The classic teaching is to look for other causes of abdominal pain in patients with gastroparesis who have abdominal pain. This can entail evaluation for gallbladder or pancreatic causes of abdominal pain. Other causes may include

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functional dyspepsia, irritable bowel syndrome, and visceral hyperalgesia. Nevertheless, some studies show that moderate to severe abdominal pain is prevalent in gastroparesis (66% of patients), impairs quality of life, and is associated with idiopathic etiology. The abdominal pain does not correlate with the delayed gastric emptying. Pain has largely been ignored in gastroparesis; its cause is unknown. The presence of abdominal pain unfortunately is a poor predictor of a good improvement in overall gastroparesis symptoms. Abdominal pain can be difficult to treat. Narcotic analgesics can delay gastric emptying as well as also provoke symptoms of nausea and vomiting. They are best to be avoided. Symptom modulators, such as low dose tricyclic antidepressants, are often tried.

3. **Can my gastroparesis be cured?** [4, 7, 8]
   Symptoms of gastroparesis may be constant or they may fluctuate with worsening periods. The medications used for gastroparesis are designed to bring the symptoms under better control. Controlling glucose in diabetic gastroparesis may also help improve symptoms. In all patients, dietary management is important and nutritional consultation may be helpful. It has been suggested that idiopathic gastroparesis of acute onset with infectious prodrome could constitute postviral or viral injury to the neural innervation of the stomach or the interstitial cells of Cajal in the stomach. In some series, patients with postviral gastroparesis improve over time, generally several years.
4. **I have joined an online chat room for gastroparesis. Many of the patients have received Botox for their gastroparesis with good results. Is this something that will help me?** [9, 10]
   Several studies have tested the effects of pyloric injection of botulinum toxin in patients with diabetic and idiopathic gastroparesis. Endoscopic treatment entails injection of botulinum toxin (Botox; Allergan, Inc.) into the pyloric sphincter. Initial studies were unblinded in small numbers of patients from single centers and observed mild improvements in gastric emptying and modest reductions in symptoms for several months. Two double-blind studies have been reported; these show an improvement in gastric emptying, but no effect on symptoms compared to placebo. Thus, botulinum toxin injections do not result in sustained improvement in symptoms of gastroparesis. Some patients though do seem to improve. Identifying who these patients are is the subject of current research. If Botox injection helps symptoms, it generally lasts 3–6 months. Other treatments such as pyloromyotomy may be longer lasting.
5. **My doctor told me not to take metoclopramide due to its side effects and referred me to you for treatment. What will you do?** [10–13]
   Metoclopramide (Reglan) is a dopamine type 2 receptor antagonist both in the CNS and in the stomach. Metoclopramide exhibits both prokinetic and antiemetic actions. It has been the mainstay of treatment of gastroparesis. The prokinetic properties of metoclopramide are limited primarily to the stomach. Reglan can cause both acute and chronic CNS side effects in some patients. These side effects should be discussed with the patient prior to treatment and documented in the patient's medical record. In the United States, metoclopramide is approved

for diabetic gastroparesis for up to 12 weeks duration. Patients with gastroparesis have chronic nausea and often need longer periods of treatment. If used, the dose is usually limited to 10 mg four times a day, for several months. Domperidone has similar effects to metoclopramide and has less central side effects than Reglan. Domperidone may well help symptoms of gastroparesis. It does have some cardiac side effects, such as palpitations or irregular heartbeat. For this reason, an EKG is obtained prior to treatment and during treatment. Domperidone is not approved by the Food and Drug Administration in the United States but is approved in several other countries. Since domperidone is not approved, patients need to pay themselves for this medication.

Introduction

Gastroparesis is a chronic symptomatic disorder of the stomach manifested by delayed emptying without evidence of mechanical obstruction [10]. This gastric motility disorder can lead to severe symptoms in patients with poor quality of life. Although in many patients, symptoms can be controlled with medical therapy, some patients remain markedly symptomatic with progressive weight loss. Gastroparesis, whatever the etiology, is much more prevalent in females than in males. This chapter will discuss aspects of gastroparesis, particularly idiopathic gastroparesis, with special emphasis on the gender aspects on gastric motility, gastroparesis, symptoms, and treatment. This chapter updates the present status of our understanding of this disorder and the treatments available.

Epidemiology

Gastroparesis occurs more often in women than men. Interestingly, this is true for each of the three main forms of gastroparesis: idiopathic, diabetic, and even postsurgical. The epidemiology of gastroparesis, however, has not been well systematically studied. This stems from the fact that for proper diagnosis, a gastric emptying test is needed, a test that is difficult to obtain in population studies. Data from the Rochester Epidemiology Project, a database of linked medical records of residents of Olmsted County, Minnesota, show that the age-adjusted incidence of definite gastroparesis per 100,000 person-years for the years 1996 to 2006 was 9.8 for women and 2.4 for men [14]. Definite gastroparesis was defined as diagnosis of delayed gastric emptying by standard scintigraphy and symptoms of nausea and/or vomiting, postprandial fullness, early satiety, bloating, or epigastric pain for more than 3 months. The age-adjusted prevalence of definite gastroparesis per 100,000 persons was 37.8 for women and 9.6 for men. More recent estimates have suggested that this prevalence of gastroparesis was an underestimation and the prevalence is greater, being approximately 1.8% of the general population [15].

The prevalence of gastroparesis might be increasing. Data from the US Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS), a nationally representative sample of five to eight million hospitalizations per year, show that, from 1995 to 2004, hospitalizations with gastroparesis as the primary diagnosis increased by 158% and those with gastroparesis as the secondary diagnosis increased by 136% compared with a 13% increase in all hospitalizations [16]. The increase in hospitalization rate for gastroparesis has occurred since the year 2000 and could reflect increasing prevalence and/or the effects of heightened awareness about and better identification of gastroparesis [16]. This increase in gastroparesis hospitalizations may also be due, in part, to the increasing rate of diabetes leading to more cases of diabetic gastroparesis, withdrawal of some gastroparesis treatments from the market (cisapride, tegaserod) with hospitalizations for symptoms not adequately being treated, and hospitalizations needed for insertion of the gastric electric stimulator.

Symptoms

Common symptoms of gastroparesis include nausea (>90% of patients), vomiting (84% of patients), and early satiety (60% of patients) [17]. Other symptoms include postprandial fullness and abdominal pain [18, 19]. Symptoms can be persistent or can manifest as episodic flares. Weight loss, malnutrition, and dehydration may be prominent in severe cases. Although weight loss is classically described in gastroparesis, some patients can be overweight, especially patients with type 2 diabetes mellitus (T2DM). In diabetics, gastroparesis may adversely affect glycemic control with both hypoglycemia and hyperglycemia.

Woman with gastroparesis tend to be more symptomatic than men [20]. Parkman et al. analyzed 718 patients in NIH gastroparesis consortium, between September 2007 and December 2017, who were followed every 4–6 months. Eighty-four percent of patients were women, and a higher proportion of them had idiopathic gastroparesis compared to men (69%). Female patients showed more severe stomach fullness, early satiety, postprandial fullness, bloating, stomach visibly larger, and upper abdominal pain [21]. A case-control study out of Israel by Dickman et al. showed that females with T2DM had higher BMI and hemoglobin A1C levels, and the prevalence of nausea, early satiety, and loss of appetite was higher in women [22]. In another study, women with idiopathic gastroparesis reported more nausea, stomach fullness, early satiety, bloating, abdominal distention, and constipation compared to men [20]. In women with very severe symptoms, pregnancy is a relative contraindication due to the high risk of maternal morbidity and possibly poor fetal outcome [23].

Symptom profile can be established and symptom severity assessed with the Gastroparesis Cardinal Symptom Index (GCSI), a subset of the Patient Assessment of Upper Gastrointestinal Symptoms (PAGI-SYM) [24]. The GCSI comprises three subscales (nausea and vomiting, postprandial fullness and early satiety, and bloating)

that the patient scores with reference to the preceding 2 weeks [24]. A variant on the GCSI, the GCSI daily diary (GCSI-DD), can be used to record symptoms on a daily basis and may be more accurate in recording symptoms [25]. The daily diary assesses severity of nausea, early satiety, postprandial fullness, and upper abdominal pain as well as records the number of episodes of vomiting. A composite score can be calculated for overall severity of gastroparesis. This GCSI can be used to assess individual symptoms which may then be individually targeted for treatment. Single symptom approaches to treatment may be more feasible than attempts at global symptom improvement for gastroparesis.

Although it has been assumed that the gastrointestinal symptoms in patients with gastroparesis can be attributed to delay in gastric emptying, most investigations have observed only weak correlations between symptom severity and the degree of gastric stasis. In general, the symptoms that appear to be best correlated with a delay in gastric emptying include nausea, vomiting, early satiety, and postprandial fullness [1, 26]. Some symptoms that have been present in patients with gastroparesis such as bloating and upper abdominal pain are not correlated with delayed gastric emptying and might be related to sensory alterations that might also be present in patients with gastroparesis. Improving gastric emptying by itself may not lead to successful treatment of all gastroparesis symptoms.

Abdominal pain is usually not the main symptom in gastroparesis, and other causes of abdominal pain need to be investigated in these patients. The pathophysiology of pain in gastroparesis is poorly understood. The NIDDK Gastroparesis Clinical Research Consortium multicenter studies have shown moderate to severe upper abdominal pain in up to 66% of patients, and in 21% of patients the abdominal pain or discomfort was the predominant symptom. Idiopathic gastroparesis was more likely to be associated with abdominal pain than diabetic gastroparesis [27]. One recent study showed that in gastroparesis patients with abdominal pain, more than one third had a neuropathic component to their pain and two thirds had physical exam findings of somatic pain [28].

Etiology

Major etiologies of gastroparesis are diabetic, postsurgical, and idiopathic [10, 29, 30]. Less common causes of gastroparesis include connective tissue disease, neurologic disease such as Parkinson's disease, eating disorders, metabolic or endocrine conditions (hypothyroidism), critical illness, and medications such as opiates and anticholinergics [29]. In addition, several classes of medications used to treat diabetes, such as GLP-1 analogs, and amylin analogs can delay gastric emptying [10]. Various conditions associated with idiopathic gastroparesis are listed in Table 5.1.

Gastroparesis is a relatively common complication of diabetes: delayed gastric emptying has been found to occur in approximately 40% of patients with longstanding type 1 diabetes and approximately 20% of patients with type 2 diabetes [29, 30]. These estimates, though, are from academic medical centers, and true estimates

Table 5.1 Causes of idiopathic gastroparesis

Medications
Opioids
Tetrahydrocannabinol (THC) derivatives (e.g., marijuana)
Alpha 2-agonists (e.g., clonidine)
Tricyclic antidepressants
Calcium channel blockers
Dopamine agonists
Anticholinergics
Octreotide
Glucagon-like peptide 1 (GLP-1) (e.g., exenatide, liraglutide)
Amylin analogs (e.g., pramlintide)
Phenothiazines
Cyclosporine
Proton pump inhibitors (PPIs)
Progesterone
Infection
CMV
EBV
VZV
Norwalk
Hawaiian virus
Rotavirus
Connective tissue disorders
Systemic sclerosis
Mixed connective tissue disorder
Polymyositis/dermatomyositis
Demyelinating diseases
Multiple sclerosis
Myotonic dystrophy
Paraneoplastic syndrome
Small-cell lung cancer (SCLC)
Pancreatic cancer
Cholangiocarcinoma
Intestinal cancer
Autoimmune
Myasthenia gravis
Sjogren's syndrome
Parkinson disease
Multiple system atrophy
Miscellaneous
Hypothyroidism
Renal failure
Amyloidosis
Mesenteric ischemia
Gastroesophageal reflux disease (GERD)
Celiac plexus injury or compression
Eosinophilic gastroenteritis

appear to be lower in the general population in patients seeing primary care physicians. In the Rochester Epidemiology Project, cumulative incidence of developing gastroparesis was found to be 5.1% in type 1 diabetes mellitus (T1DM) and 1.0% in type 2 diabetes mellitus (T2DM) patients [31].

In the NIH Gastroparesis Consortium Registry, baseline symptoms were similar in T1DM and T2DM patients, even though T1DM patients had worse gastric emptying delays and higher HbA1c [32]. Diabetic gastroparesis is often attributed to chronic hyperglycemia-induced damage to the vagus nerve and is frequently observed in association with other diabetic complications such as neuropathy, retinopathy, and nephropathy. Enteric pathology may also exist in diabetic gastroparesis including loss of interstitial cells of Cajal (the pacemaker cells), loss of nitric oxide containing nerves, and presence of an inflammatory infiltrate. Glucose can modify gastric emptying tests and symptoms: hyperglycemia can delay gastric emptying and worsen symptoms of gastroparesis, whereas hypoglycemia may accelerate gastric emptying.

Idiopathic gastroparesis is a common classification for gastroparesis. Characteristics of 243 patients with idiopathic gastroparesis enrolled in the NIH Gastroparesis Clinical Research Consortium Registry were recently characterized based on medical histories, symptoms questionnaires, and gastric emptying scintigraphy [20]. Patients' mean age was 41 years, and the majority (88%) were female. Half (50%) had acute onset of symptoms. The most common presenting symptoms were nausea (34%), vomiting (19%), and abdominal pain (23%). Severe delay in gastric emptying (>35% retention at 4 h) was present in 28% of patients. Severe delay in gastric emptying was associated with more severe symptoms of nausea and vomiting and loss of appetite compared with patients with mild or moderate delay. Eighty-six percent of these patients with idiopathic gastroparesis met criteria for functional dyspepsia, predominately postprandial distress syndrome. Thus, idiopathic gastroparesis appears to be a heterogeneous syndrome that primarily affects young women. A minority of patients with idiopathic gastroparesis (19%) in the NIH Gastroparesis Clinical Research Consortium Registry study report an initial infectious prodrome such as gastroenteritis or respiratory infection [20]. Herpes family viruses including cytomegalovirus (CMV), Epstein-Barr virus (EBV), and varicella-zoster virus (VZV) as well Norwalk and rotavirus have been associated with gastroparesis. It has been suggested that idiopathic gastroparesis of acute onset with infectious prodrome could constitute postviral or viral injury to the neural innervation of the stomach or the interstitial cells of Cajal in the stomach. In some series, patients with postviral gastroparesis improve over time, generally several years.

Pathophysiology

Gastric emptying is mediated by the vagus nerve, which helps regulate fundic accommodation, antral contractions, and pyloric relaxation [10]. These regional gastric motility changes with food ingestion are then mediated through smooth muscle cells, which control stomach contractions; interstitial cells of Cajal, which

regulate gastric pacemaker activity; and enteric neurons, which initiate smooth muscle cell activity [10].

The pathophysiology of gastroparesis has not been fully elucidated but appears to involve abnormalities in functioning of several elements including the autonomic nervous system, smooth muscle cells, enteric neurons, and interstitial cells of Cajal. Histologic studies demonstrate defects in the morphology of enteric neurons, smooth muscle cells, and interstitial cells of Cajal and increased concentrations of inflammatory cells in gastric tissue [10, 20, 29]. Nitric oxide synthase is reduced in diabetic mice's myenteric plexi with delayed gastric emptying [33]. Animal models of diabetic gastroparesis also show reduced expression of heme oxygenase-1 (HO-1) and CD206+ M2 macrophages and activated M1 macrophages secreting TNF-alpha which damages ICC cells [34].

Diagnosis

Differential diagnosis of gastroparesis entails excluding other causes of symptoms and/or delay in gastric emptying including peptic ulcer disease, gastric outlet obstruction, neoplasm, and small bowel obstruction [29]. For evaluation of these, an upper endoscopy is generally performed. Other conditions which can mimic gastroparesis symptoms include functional dyspepsia, rumination syndrome, and cyclic vomiting syndrome.

For evaluating gastric emptying, the standard test is gastric emptying scintigraphy, which uses a labeled isotope bound to solid food to image gastric emptying [29, 35]. There is variable methodology used at different centers. Standardization of gastric emptying among different centers has been suggested using a 4-h imaging protocol with scans taken 0, 1, 2, and 4 h after ingestion of a radioactive Tc-99m-labeled low-fat egg white with jam and two pieces of toast [2]. Medications that slow gastric emptying such as narcotic and anticholinergic agents and glucagon-like peptide-1 (GLP-1) and amylin analogs should be stopped at least 48 h before the test [10]. In patients with diabetes, blood glucose level measured before starting the gastric emptying test is recommended to be <275 mg/dL. Normal values for gastric emptying are 37–90% at 1 h, 30–60% at 2 h, and 0–10% at 4 h [36]. More than 10% retention at 4 h is considered abnormal which may need to be increased in women given their slower gastric emptying at baseline.

Use of the wireless motility capsule to quantify luminal pH and pressure is an alternative to gastric emptying scintigraphy [29]. Gastric emptying is manifested by a sharp increase in pH representing the capsule passing from the acidic stomach to the alkaline small intestine [37]. Using a 5 h cutoff for gastric emptying, the capsule discriminated between normal or delayed gastric emptying with a sensitivity of 0.87 and a specificity of 0.92. This test also measures whole-gut transit—that is, gastric emptying, small bowel transit, and colonic transit. Colonic transit abnormalities have been reported in 18% of patients with gastroparesis, possibly suggesting a more diffuse GI motility disorder, and it could be contributing to symptom presentation [38].

Breath tests for gastric emptying, another alternative to gastric emptying scintigraphy, measure labeled nonradioactive 13-CO_2 in exhaled breath samples after ingestion of a 13-CO_2-labeled meal. Breath samples are obtained periodically over several hours. The exhaled 13-CO_2 represents a combination of gastric emptying, duodenal absorption, hepatic metabolism, and pulmonary excretion; overall, gastric emptying is the rate limiting step [35]. Findings generally correlate well with results of gastric emptying scintigraphy. This test has been used clinically in Europe for years, whereas in the United States, breath tests for gastric emptying have been generally used for research studies but are now available for clinical evaluation [39].

Gastric emptying testing is useful in diagnosing gastroparesis. There are several caveats that bring into question the value of the assessment of gastric emptying. First, gastric emptying rates generally correlate poorly with symptoms and quality-of-life measures for gastroparesis [40, 41]. Patients can have severe nausea and vomiting with normal gastric emptying [41]. These patients also represent a significant medical problem and are, for the most part, indistinguishable from those with gastroparesis. These findings suggest that factors in addition to slow gastric emptying contribute to symptoms. Relatively high interindividual and intraindividual variability in gastric emptying rates measured with gastric motor testing constitutes another limitation of gastric motor testing [29]. The relative contributions to these variabilities of gastric motor testing methodology and biologic inconsistency in gastric emptying are not currently known.

Gender Aspects of Gastric Motility

In healthy patients, gastric emptying is affected by age, gender, menopausal status, and even phase of the menstrual cycle. Gastric emptying in premenopausal females is delayed compared to that in males [42–45]. Some investigators [46], but not all [47, 48], have reported that gastric emptying is slower during the luteal phase (days 18–20) of the menstrual cycle when there are elevated estrogen and progesterone than in the follicular phase (days 8–10) when levels of these sex hormones are low. Postmenopausal women on sex hormone replacement therapy have slower gastric emptying of solids than men [47]. These observations suggest that the female reproductive hormones, estrogen and progesterone, have inhibitory effects on gastric motility [45]. The slower gastric emptying is thought to be due to reduced gastric smooth muscle contractility caused by the female reproductive hormones, particularly progesterone [49, 50]. Interestingly, nausea of pregnancy, which occurs predominantly during the first trimester, when estradiol and progesterone are elevated, is associated with gastric dysrhythmias [51–53]. However, delayed gastric emptying has also been reported during the follicular phase (first 10 days of the menstrual cycle) [43, 54], suggesting that gender differences exist that may not be related to levels of estrogen and progesterone. Studies by Knight et al. have shown that gastric emptying of solid food in normal young women is slower than in aged matched men, even in the first 10 days of the menstrual cycle when estrogen and

progesterone levels are low [54]. The slower gastric emptying as reflected by the higher gastric retention seen in women seen in this study was associated with normal proximal gastric emptying but a decreased rate of distal gastric emptying. Females had decreased antral contractility as recorded by dynamic antral scintigraphy and antroduodenal manometry. Thus, the delay in gastric emptying of solids in women appears to be primarily due to altered distal gastric motor function. One explanation may be that less vigorous antral contractions may contribute to slower breakdown of food particles and delay the rate of gastric emptying.

Gender-related differences have also been reported to be present in the proximal stomach affecting motility and perception [55]. In women, postprandial proximal gastric relaxation was prolonged as assessed using a gastric barostat. This was associated with an increase in symptom of nausea in the postprandial state.

The mechanism of the female gender effect on gastrointestinal motility is unknown [56]. As discussed above, most presume this is a hormonal effect. The mechanism through which these sex hormones exert their effects on GI motility is unclear. In baboons, sex steroid receptors have been found throughout the GI tract [57]. Studies in animals have shown that female sex hormones have an inhibitory effect on GI motility.

Progesterone may also exert its inhibitory effect on GI motility by reducing plasma motilin levels [58]. Progesterone also has effects on calcium channels, G proteins, and nuclear transcription [59]. Progesterone may act via genomic and nongenomic mechanisms to influence contractile elements of the gut. Xiao et al. showed that acute administration of progesterone produced a transient blocking of calcium release from storage sites [59].

Estrogen has also been shown to have effects on gastrointestinal motility, although not as prominent as progesterone's effects. Estrogen has been suggested to prime and enhance the inhibitory effects of progesterone. Previous studies have demonstrated that estradiol-17beta administration delays gastric emptying for liquids in both male and female rats.

Studies by Pasricha et al. have shown that diabetes induces sex-dependent changes in neuronal nitric oxide synthase dimerization and function in the rat gastric antrum [60]. nNOS expression, dimerization, and function are sex dependent and furthermore that diabetes affects these processes differently in males and females. Female animals had more delayed gastric emptying than male—both in normal animals and those with diabetes.

The effect of gender on upper GI symptoms in the community was studied by Camilleri et al. [61] In this study, a telephone survey of 21,128 adults was conducted including questions about the presence of upper GI symptoms during the past 3 months. Interestingly, symptoms of early satiety and nausea are more common in females than in males, by a 2:1 ratio. The symptom on nausea was present in 1.4% of males and 3.0% of females. The symptom of early satiety was present in 3.7% of males and 5.7% of females [61].

The practical clinical practice corollary of these studies is that this suggests the need to compare females with symptoms of gastric dysfunction using gastric emptying parameters derived in normal women rather than to those derived in normal men. However, this is not done in most centers. Stanghellini et al. evaluated indica-

tors of delayed gastric emptying of solids in patients with functional dyspepsia. Sex-specific normal ranges were used where the normal ranges in females were slower than males [62]. Interestingly female sex, postprandial fullness, and vomiting were the only factors independently associated with gastric emptying in patients with functional dyspepsia.

In gastroparesis, there are gender effects on the presentation and treatment of gastroparesis. Studies from the NIH Gastroparesis Consortium show that females were more likely to have idiopathic gastroparesis with higher symptom severity of total GCSI total score, bloating and postprandial fullness subscore. Postmenopausal women had less severe nausea, retching, and vomiting compared to premenopausal women. Postmenopausal women taking hormone replacement therapy had greater upper abdominal pain and discomfort than those not taking hormone replacement therapy. In a recent study, the response to treatment with metoclopramide for diabetic gastroparesis was better in females than in males [48]. In a multicenter, double-blind randomized controlled trial of metoclopramide in diabetic gastroparesis, of 285 patients, 71% were female patients. Metoclopramide given by a nasal spray reduced overall symptom scores in females but not in men [63].

Management

Management of gastroparesis is guided by the goals of correcting fluid, electrolyte, and nutritional deficiencies, identifying and treating the cause of delayed gastric emptying (e.g., diabetes), and suppressing or eliminating symptoms [10]. Care of patients generally relies on dietary modification, medications that stimulate gastric motor activity, and antiemetic drug therapy. Commonly used medications are summarized in Table 5.2 and treatment algorithm is depicted in Fig. 5.1.

Gastroparesis can be a difficult disorder to treat, reflecting the paucity of medications that are available for this condition. The outcomes of gastroparesis patients were assessed in the NIH Gastroparesis Consortium in patients with either diabetic or idiopathic gastroparesis [4]. Surprisingly, only 28% of 262 patients symptomatically improved at 48 weeks as determined by a decrease in GCSI $\geq$1. This illustrates the chronic nature of gastroparesis and that the disease burden remains high. Predictors for improvement included more severe gastroparesis symptoms, more severe delay in gastric emptying, and an initial infectious prodrome. Predictors for a poor improvement included moderate/severe abdominal pain and being overweight.

Dietary Treatment

Dietary measures entail adjustment to meal composition and frequency [10, 29]. Eating small meals is recommended as patients often have early satiety, that is, feeling full after eating a normal size meal; in addition, larger meals may alter gastric

Table 5.2 Medications commonly used in gastroparesis

Prokinetics	Metoclopramide Macrolides: Erythromycin Azithromycin Domperidone
Antiemetics	Phenothiazines: Promethazine Prochlorperazine Anticholinergics: Scopolamine 5-HT-3 antagonists: Ondansetron Granisetron NK-1 antagonists: Aprepitant Fosaprepitant Miscellaneous: TCAs Cannabinoids Benzodiazepines Haloperidol
Analgesics and neuromodulators	TCAs: Amitriptyline Nortriptyline Imipramine Desipramine

emptying times. Consuming mainly nutritious liquids such as soups can be useful as gastric emptying of liquids is often preserved in patients with gastroparesis [10]. Avoidance of fats and indigestible fibers is recommended because they delay gastric emptying [10, 29]. When small meals are used in the gastroparesis diet, more frequent meals, three meals per day plus two snack-type meals, are often needed to maintain caloric intake. These dietary recommendations have often been made empirically given the effects on gastric emptying [64, 65]. Recently, these have been looked at in respect to symptom generation. A high-fat solid meal significantly increased overall symptoms among individuals with gastroparesis, whereas a low-fat liquid meal had the least effect [66]. With respect to nausea, low-fat meals were better tolerated than high-fat meals, and liquid meals were better tolerated than solid meals. These data provide support for recommendations that low-fat and increased liquid content meals are best tolerated in patients with symptomatic gastroparesis. Another study assessed patient tolerances to foods [67]. Foods provoking symptoms were generally fatty, acidic, spicy, and roughage-based. Foods worsening symptoms included orange juice, fried chicken, cabbage, oranges, sausage, pizza, peppers, onions, tomato juice, lettuce, coffee, salsa, broccoli, bacon, and roast beef. The foods that were generally tolerable were generally bland, sweet, salty, and starchy. Saltine crackers, jello, and graham crackers moderately improved symptoms. Twelve additional foods were tolerated by patients (not provoking symptoms): ginger ale, gluten-free foods, tea, sweet potatoes, pretzels, white fish, clear soup, salmon, potatoes, white rice, popsicles, and applesauce.

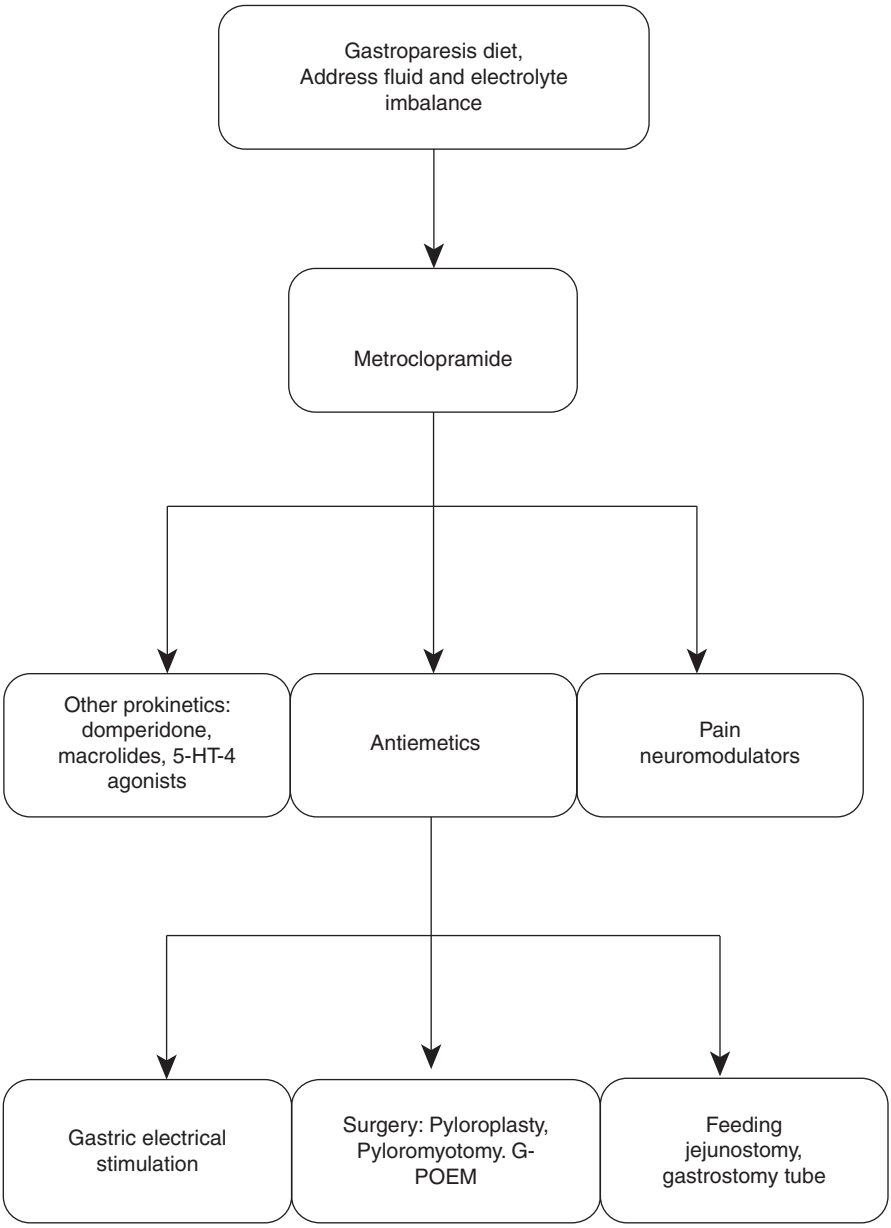

Fig. 5.1 Treatment approach to gastroparesis

Many patients with gastroparesis have diets deficient in calories, vitamins, and minerals. Unfortunately, nutritional consultation is obtained infrequently, but this is suggested for dietary therapy and to address nutritional deficiencies [7].

Prokinetic Agents

Medications with gastric prokinetic properties, which are the mainstay of treatment for gastroparesis, include metoclopramide, erythromycin, and domperidone [68]. Intravenous agents currently available to treat hospitalized patients include metoclopramide and erythromycin. Several prokinetic agents are being studied for patients with gastroparesis; these include (1) newer 5-HT4 receptor agonists that improve gastric motility but minimal cardiac side effects, (2) newer motilin receptor agonists without tachyphylaxis phenomenon and without antibiotic properties, and (3) newer ghrelin receptor agonists.

Metoclopramide

Metoclopramide, a substituted benzamide structurally related to procainamide, exhibits both prokinetic and antiemetic actions. The drug is a dopamine type 2 receptor antagonist both in the CNS and in the stomach. Metoclopramide also has 5HT-3 receptor antagonist activity that might also provide an antiemetic effect. In addition, it has some 5HT-4 agonist activity releasing acetylcholine from intrinsic myenteric cholinergic neurons that might help enhance gastric emptying. The prokinetic properties of metoclopramide are limited primarily to the stomach. Metoclopramide can cause both acute and chronic CNS side effects in some patients including acute dystonia and tardive dyskinesia which are more commonly seen in female patients [10]. These side effects should be discussed with the patient prior to treatment. Another side effect is QT interval prolongation, which is mostly observed in patients who are taking other QT prolonging medications. In the United States, metoclopramide is approved for diabetic gastroparesis for up to 12 weeks duration. Patients with gastroparesis have chronic nausea and often need longer periods of treatment. Recently, in Europe, it has been suggested that metoclopramide be used for only several days duration for acute treatment of chemotherapy-induced vomiting. Metoclopramide is contraindicated in patients with pheochromocytoma and seizure disorders.

Erythromycin

The macrolide antibiotic erythromycin exerts prokinetic effects via action on gastroduodenal receptors for motilin, an endogenous peptide responsible for initiation of the migrating motor complex (MMC) in the upper gut. When administered

exogenously, motilin stimulates antral contractility and elicits premature antroduodenal phase III activity. Erythromycin produces effects on gastroduodenal motility similar to motilin. It is not recommended to be used more than 4 weeks as patients develop tachyphylaxis due to motilin receptor downregulation.

Clinically, erythromycin has been shown to stimulate gastric emptying in diabetic gastroparesis, idiopathic gastroparesis, and postvagotomy gastroparesis. Erythromycin may be most potent when used intravenously; it is often used to clear blood from the stomach prior to an upper endoscopy for a patient with upper gastrointestinal bleeding. Limited data exist concerning the clinical efficacy of erythromycin in reducing symptoms of gastroparesis. In a systematic review of studies on oral erythromycin with symptom assessment as a clinical end point, improvement was noted in 43% of patients. One study comparing erythromycin and metoclopramide in an open-label, crossover fashion in diabetic gastroparesis found similar efficacy.

Oral administration of erythromycin should be initiated at low doses (e.g., 100–125 mg three times daily before meals). Liquid suspension erythromycin may be preferred because it is rapidly and more reliably absorbed. Intravenous erythromycin (100 mg every 8 h) is used for inpatients hospitalized for severe refractory gastroparesis. Side effects of erythromycin at higher doses (500 mg) include nausea, vomiting, and abdominal pain. Because these symptoms may mimic those of gastroparesis, erythromycin may have a narrow therapeutic window in some patients. There is report that erythromycin chronically may be associated with higher mortality from cardiac disease, especially when combined with agents that inhibit cytochrome p-450 (CYP3A4 isoform), such as calcium channel blockers. Azithromycin has shown to be as effective as erythromycin with less cardiac risk and drug interaction [69].

Domperidone

The effects of domperidone on the upper gut are similar to those of metoclopramide, including stimulation of antral contractions and promotion of antroduodenal coordination. In addition to prokinetic actions in the stomach, domperidone exhibits antiemetic properties via action on the area postrema, a brainstem region with a porous blood-brain barrier. Domperidone does not readily cross the blood-brain barrier; therefore, it is much less likely to cause extrapyramidal side effects than metoclopramide. Side effects to domperidone include breast lactation, headaches, and palpitations. Domperidone has been associated with prolongation of the cardiac QTc interval.

The FDA has developed a program for physicians who would like to prescribe domperidone for their patients with severe upper GI motility disorders that are refractory to standard therapy to open an Investigational New Drug (IND) application. An IND is a request for FDA authorization to administer an investigational drug to humans. Such authorization would allow the importation, interstate shipment, and administration of the drug even though it is not approved for sale in the United States. Use of this IND mechanism for use of domperidone also will require IRB approval. An EKG and blood work to check potassium and magnesium are

obtained prior to starting domperidone; these are repeated after 4–8 weeks of treatment. The patient will need to pay for their domperidone medication since insurance companies do not for this nonapproved treatment.

The benefits and side effects of domperidone to treat symptoms of gastroparesis were recently reported from a large single-center cohort [70]. In this large single-center study of 125 patients treated with domperidone, side effects necessitating discontinuing treatment occurred in 12%. The most common side effects were headache, tachycardia/palpitations, and diarrhea. The majority of patients (60%) experienced an improvement in symptoms of gastroparesis, particularly postprandial fullness, nausea, vomiting, and stomach fullness.

Antiemetic Medications

Antiemetic agents are given acutely for symptomatic nausea and vomiting. The principal classes of drugs that have been used for symptomatic treatment of nausea and vomiting are phenothiazines, antihistamines, anticholinergics, dopamine receptor antagonists, and more recently serotonin receptor antagonists. The antiemetic action of phenothiazine compounds appears to be mediated primarily through a central antidopaminergic mechanism in the area postrema of the brain. Commonly used agents include prochlorperazine (Compazine), trimethobenzamide (Tigan), and promethazine (Phenergan).

Serotonin (5-HT-3) receptor antagonists, such as ondansetron (Zofran) and granisetron (Kytril), have been shown to be helpful in treating or preventing chemotherapy-induced nausea and vomiting. The primary site of action of these compounds is probably the chemoreceptor trigger zone, since there is a high density of 5-HT-3 receptors in the area postrema. Zofran is now frequently used for nausea and vomiting of a variety of other etiologies. It is best given on a prn basis due to their expense. Granisetron transdermal system (GTS) is an appealing delivery system for patients with gastroparesis. In an open label study, GTS was moderately effective in reducing nausea and/or vomiting in 76% of gastroparesis patients [71]. Side effects can occur such as constipation, skin rash from the patch, and headaches.

Neurokinin receptor antagonists are being used for chemotherapy induced nausea and vomiting. Aprepitant (Emend) is a recently approved substance P/neurokinin 1 receptor antagonist for chemotherapy-induced nausea and vomiting. The effects of the neurokinin-1 receptor antagonist aprepitant, on symptoms in patients with gastroparesis (Gp) and related syndromes, are associated with chronic nausea and vomiting patients. Aprepitant resulted in a greater decline in mean 4-week daily hours of nausea and mean 4-week GCSI score. These data suggest that aprepitant has potential for safe improvement of a variety of symptoms in gastroparesis and related disorders. A recent double-blind RCT by the NIDDK Gastroparesis Clinical Research Consortium (GpCRC) of 126 patients with at least moderate symptoms of chronic nausea and vomiting of presumed gastric origin showed reduction of the severity of nausea and showed varying improvement of other symptoms such as fullness, bloating, and abdominal pain [72].

Combination Medical Therapy

In moderately to severely symptomatic patients, often therapy with both a prokinetic agent and antiemetic agent is needed. One needs to be careful about added side effects with combination therapy. Prokinetic agents can act via different mechanisms to enhance gastric emptying. Theoretically, addition of a second prokinetic agent may augment the response of the first drug if the two agents act on different receptor subtypes. Dual prokinetic therapy with domperidone and cisapride had been reported to accelerate emptying and reduce symptoms in some patients with refractory gastroparesis. Combinations of available prokinetic agents in the United States, such as metoclopramide and erythromycin or domperidone and erythromycin, have not been specifically studied. Usually, these are not combined due to the possibility if increasing cardiac side effects. Since metoclopramide and domperidone are both D2 receptor antagonists, these should not be used together.

Pyloric Botulinum Toxin Injection

Gastric emptying is a highly regulated process reflecting the integration of the propulsive forces of proximal fundic tone and distal antral contractions with the functional resistance provided by the pylorus. Manometric studies of patients with diabetic gastroparesis have shown in some patients prolonged periods of increased pyloric tone and phasic contractions, a phenomenon termed pylorospasm. Botulinum toxin is a potent inhibitor of acetylcholine neuromuscular transmission and has been used to treat spastic somatic muscle disorders as well as achalasia. Several studies have tested the effects of endoscopic injection of the pyloric sphincter with botulinum toxin in patients with diabetic and idiopathic gastroparesis [10]. Initial studies were “open label” in small numbers of patients from single centers and have observed mild improvements in gastric emptying and modest reductions in symptoms for several months. Two double-blind studies have been reported; these show an improvement in gastric emptying, but no effect on symptoms compared to placebo. Thus, botulinum toxin injections do not result in sustained improvement in symptoms of gastroparesis.

Psychotropic Medications as Symptom Modulators

Tricyclic antidepressants may have significant benefits in suppressing symptoms in some patients with nausea and vomiting as well as patients with abdominal pain. Doses of tricyclic antidepressants used are lower than used to treat depression. A reasonable starting dose for a tricyclic drug is 10–25 mg at bedtime. If benefit is not observed in several weeks, doses are increased by 10- to 25-mg increments up to 50–100 mg. Side effects are common with use of tricyclic antidepressants and can interfere with management and lead to a change in medication in 25% of patients.

The secondary amines, nortriptyline and desipramine, may have fewer side effects. The recent NIH gastroparesis consortium study with nortriptyline in idiopathic gastroparesis did not show an effect on overall symptoms of gastroparesis [73]. However, there was a suggestion that low nortriptyline doses (10–25 mg) might decrease nausea, whereas higher doses (50–75 mg) might decrease fullness. There are limited data on the use of selective serotonin reuptake inhibitors in gastroparesis or functional dyspepsia.

Refractory Patients with Gastroparesis

Patients with refractory gastroparesis need treatment at a variety of levels directed at nutritional care, prokinetic medications, antiemetic therapies, pain control, glycemic control, and, often, psychological measures. Surgical and endoscopic approaches are considered in patients in whom drug therapy is ineffective and who cannot meet their nutritional requirements [10]. Surgical treatments include placement of jejunostomy tubes, gastric electrical stimulation, and pyloromyotomy [10]. These options are typically considered only in patients with severe, refractory gastroparesis.

Feeding Jejunostomy and Venting Gastrostomy Tubes

Other treatments include feeding jejunostomy for nutritional support with a jejunostomy tube that bypasses the affected stomach for feedings. Venting gastrostomy tubes have been tried with success in some patients.

Gastric Electric Stimulation

Gastric electric stimulation is a treatment for refractory gastroparesis. It involves an implantable neurostimulator that delivers a high-frequency (12 cpm), low-energy signal with short pulses. With this device, stimulating wires are sutured into the gastric muscle along the greater curvature during laparoscopy or laparotomy. These leads are attached to the electric stimulator, which is positioned in a subcutaneous abdominal pouch. Based on the initial studies that have shown symptom benefit especially in patients with diabetic gastroparesis, the gastric electric neurostimulator was granted humanitarian approval from the FDA for the treatment of chronic, refractory nausea and vomiting secondary to idiopathic or diabetic gastroparesis. The main complication of the implantable neurostimulator has been infection, which has necessitated device removal in approximately 5% of cases. More recently, a small minority of patients can at times have a shocking sensation. Symptoms of

nausea and vomiting can improve with stimulation; however abdominal pain often does not. The symptomatic benefit occurs more often in diabetic gastroparesis than in idiopathic gastroparesis. Further investigation would be helpful to definitively show the effectiveness of gastric stimulation in long-term blinded fashion, which patients are likely to respond, the optimal electrode position, and the optimal stimulation parameters, none of which have been rigorously evaluated to date. Future improvements may include devices that sequentially stimulate the stomach in a peristaltic sequence to promote gastric emptying as well as endoscopically placed gastric electric stimulators.

In a recently reported cohort of 151 patients with refractory gastroparesis treated at a single center, GES improved symptoms in 75% of patients with 43% being at least moderately improved [74]. A meta-analysis showed significant improvement of total symptom severity score and gastric emptying in patients with diabetic gastroparesis, while gastric retention did not change significantly in idiopathic or postsurgical subgroups [75]. Response in diabetics was better than in nondiabetic patients. Nausea, loss of appetite, and early satiety responded the best.

Pyloroplasty/Pyloromyotomy

Recently, pyloromyotomy has reemerged as a treatment for patients with gastroparesis. This can be performed surgically or more recently endoscopically. Open-label studies report good responses.

Surgical pyloroplasty, often performed laparoscopically, has shown to help reduce symptoms. One series that included 28 patients, pyloroplasty resulted in symptom improvement, gastric emptying, and decrease in prokinetic medication use at 3 months after surgery [76]. Endoscopic gastric peroral endoscopic myotomy (G-POEM) is a novel minimally invasive procedure which is based on the principles of submucosal tunneling and dissection and is very similar to peroral endoscopic myotomy for achalasia. Several series and studies have shown improvement in post-procedure emptying study and improvement in GCSI score [77].

Other Surgical Approaches

Partial gastrectomy should be used rarely and only in carefully selected patients. In postsurgical gastroparesis, occasionally completion gastrectomy is performed for persistent gastroparetic symptoms. Completion of subtotal gastrectomy after a peptic ulcer disease, which was more common in the past, has not shown very promising results. Gastrojejunostomy has been performed in the past with limited success. Gastric bypass with gastrojejunostomy has been used by several centers to treat gastroparesis.

Conclusions

Gastroparesis is identified through the recognition of the clinical symptoms and documentation of delayed gastric emptying. Management of gastroparesis includes assessment and correction of nutritional state, relief of symptoms, improvement of gastric emptying, and, in diabetics, glycemic control. Patient nutritional state should be managed by oral dietary modifications. Medical treatment entails use of prokinetic and antiemetic therapies. Unfortunately, current approved treatment options do not adequately address clinical need.

Progress being made for new effective therapies for symptomatic control in patients with gastroparesis is being studied. The FDA issued a guidance document in 2015 for treatment trials in gastroparesis [78]. This has enhanced interest in treatments with gastroparesis. Studies are ongoing with ghrelin receptor agonists, motilin receptor agonists, 5HT-4 receptor agonists, dopamine D2/D3 receptor antagonists, and novel metoclopramide delivery systems. Agents for specific symptoms, especially for nausea and vomiting, are also being tested including the use of 5HT-3 receptor antagonists and NK1 receptor antagonists. In addition, surgical procedures such as gastric bypass, endoscopic pyloromyotomy, and combining gastric electric stimulation with pyloromyotomy are being explored.

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Chapter 6
Autoimmune Hepatitis

Margarita N. German and Adnan Said

Abbreviations

6-MP	6-mercaptopurine
AAA	Anti-F actin antibodies
AIH	Autoimmune hepatitis
ALC-1	Liver cytosol 1 antibodies
ALKM-1	Liver-kidney-microsome 1 antibodies
ALT	Alanine aminotransferase
AMA	Antimitochondrial antibodies
ANA	Antinuclear antibodies
AST	Aspartate aminotransferase
HLA	Human leukocyte antigen
IgG	Immunoglobulin G
INR	International normalized ratio
MHC	Major histocompatibility complex
pANCA	Atypical perinuclear antineutrophil cytoplasmic antibodies
PBC	Primary biliary cholangitis
SLA/LP	Soluble liver antigen/liver-pancreas antigen antibodies
SMA	Smooth muscle antibodies
TPMT	Thiopurine methyltransferase

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Questions from Patients

1. *How did I get autoimmune hepatitis?*
   Autoimmune hepatitis is a chronic disease that causes inflammation in the liver. It is more common in women than men but can occur in kids or adults of any ethnicity. It is thought to arise after an environmental trigger, such as a viral infection, a medication/herb, or immunization, which causes activation of an inflammatory response directed at the liver in a genetically predisposed patient. This response can occur years after the exposure to the "trigger" which itself remains unknown in the majority of patients.
2. *How is autoimmune hepatitis diagnosed?*
   After ruling out other causes of liver disease, including viral infections and medication injury among others, the diagnosis of autoimmune hepatitis is made when a patient is noted to have elevated liver enzymes, elevated levels of certain immunoglobulins, and the presence of autoantibodies in their blood. Typically, a liver biopsy showing a characteristic pattern of inflammation is also needed to confirm the diagnosis.
3. *How do we treat this disease and will I have to stay on these medications forever?*
   Autoimmune hepatitis is typically treated with medications that suppress the immune system, such as steroids or azathioprine. Most patients require lifelong therapy. After at minimum of 2 years on therapy, a reassessment can be made regarding tapering or stopping the medications. If, however, symptoms recur or the liver enzymes begin to rise after stopping therapy, immunosuppression will need to be restarted and continued lifelong.
4. *What are the possible long-term complications of this disease?*
   Autoimmune hepatitis is a progressive, chronic liver disease. Elderly patients are more likely to present with underlying cirrhosis when they are first diagnosed. Even with treatment, some patients may progress to cirrhosis and end-stage liver disease with complications. If this occurs, certain patients may be eligible to receive a liver transplant.
5. *What about my kids?*
   While there is a genetic predisposition to developing autoimmune hepatitis, environmental triggers and the host's immune response play a major role in the development of autoimmune hepatitis. Therefore, while a patient's children may have an increased risk for developing autoimmune hepatitis, the overall risk is small.
6. *Can women have a safe and successful pregnancy?*
   Given significant improvements in the medical management of autoimmune hepatitis, pregnancies are now much more common and successful. It is important to have well-controlled disease prior to conception as this lowers any potential risks to the mother and fetus during pregnancy. While some women may flare during pregnancy, it is more common to flare after delivery; therefore, close follow-up before and after delivery is paramount. The medications used to treat autoimmune hepatitis should be continued before, during, and after pregnancy as the benefits of having well-controlled disease outweighs the possible risks to the fetus.

Epidemiology

Autoimmune hepatitis (AIH) is a chronic, inflammatory disease of the liver of unclear etiology. It can affect children and adults at any age in diverse ethnic groups globally. Two variants of autoimmune hepatitis have been described based on the presence of circulating autoantibodies: type 1 and type 2. Both type 1 disease, or classic AIH, and type 2 disease affect women predominantly, with a female to male ratio of 4:1 for type 1 and 10:1 for type 2 disease [1, 2]. Type 2 autoimmune hepatitis, more commonly seen in children and young females, is rare in North America [3, 4]. The clinical presentation, severity of disease, and response to treatment of autoimmune hepatitis vary based on region and ethnic origins [5].

Pathogenesis

While the pathogenesis of autoimmune hepatitis is not entirely understood, it is thought to be caused by an environmental trigger in a genetically predisposed patient. The trigger leads to an imbalance between the number of regulatory T cells and effector T cells, resulting in unchecked effector T cell activation [2, 6]. This causes loss of tolerance to liver self-antigens and progressive necroinflammation and fibrosis of the liver [4, 7]. Infectious agents, particularly viruses (e.g., Epstein-Barr virus, cytomegalovirus, hepatitis viruses, measles, etc.), drugs (e.g., methyldopa, nitrofurantoin, diclofenac, minocycline, statins, etc.), herbs (e.g., black cohosh, dai-saiko-to), and immunizations (e.g., hepatitis A and B), have been suggested as possible triggers [4, 7]. As the latency period may be years between infection with a virus and the overt presentation of AIH, a specific inducer is rarely identified. Drug-induced hepatocellular injury, frequently due to nitrofurantoin and minocycline, mimics the clinical and histologic pattern of injury of AIH. It is unclear whether these drugs induce AIH or cause a separate entity entirely. After response to immunosuppression, those with drug-induced autoimmune hepatitis do not typically require lifelong immunosuppressive therapy, unlike in AIH [8].

While multiple genes have been implicated in the predisposition to AIH, HLA (human leukocyte antigen) genes residing on the major histocompatibility complex (MHC) appear to play a key role [7, 9]. Variants of HLA serotypes are found in association with different ethnic groups and type 1 or type 2 disease. The presence of certain HLA serotypes may predict the timing of onset, severity, and response to therapy of the disease [10].

Diagnosis

In the appropriate clinical setting, autoimmune hepatitis is diagnosed based on a combination of factors: elevated liver enzymes in a predominantly hepatocellular pattern (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]

elevation), high immunoglobulins, and high titers of circulating autoantibodies, described below. A liver biopsy is typically required to confirm the diagnosis [4]. All other etiologies, including viral, cholestatic, metabolic, medication-induced, and hereditary causes of hepatitis (e.g., Wilson's disease, alpha-1 antitrypsin deficiency, hereditary hemochromatosis), must be ruled out.

Signs and Symptoms

Autoimmune hepatitis has a heterogeneous presentation and, occasionally, a fluctuating course of disease activity. Patients may present entirely asymptomatic in the setting of a progressive chronic liver disease, with mild nonspecific symptoms in the setting of an acute hepatitis or with debilitating symptoms in the setting of acute liver failure [11]. Asymptomatic patients may be identified by noting elevated liver enzymes on routine screening. Nonspecific symptoms include fatigue, malaise, anorexia, nausea, abdominal pain, and itching. Arthralgia, particularly of the small joints, is common. Physical findings may be entirely normal but can reveal hepatomegaly, splenomegaly, jaundice, or signs and symptoms of chronic liver disease, such as spider angiomas, caput medusae, or ascites. Of those patients presenting acutely, many already have histologic evidence of chronic liver disease, suggesting patients likely had subclinical disease for years before diagnosis [7].

Patients with autoimmune hepatitis commonly have a concurrent extrahepatic autoimmune-mediated disorder, such as autoimmune thyroiditis, rheumatoid arthritis, type 1 diabetes mellitus, ulcerative colitis, and celiac disease [11, 12].

Laboratory Features and Autoantibodies

Elevations in liver enzymes are noted in a predominantly hepatocellular pattern, with aminotransferases (AST/ALT) greater than 10–20 times the upper limit of normal. Patients presenting with acute liver failure may have aminotransferase levels in the thousands along with a prolonged prothrombin time and elevated international normalized ratio (INR) [13]. Elevation in gamma globulins, particularly immunoglobulin G (IgG), is also frequently seen. Immunoglobulin A and M are typically normal [7].

In type 1 disease, the main circulating autoantibodies, traditionally detected by immunofluorescence, are antinuclear antibodies (ANA), smooth muscle antibodies (SMA), anti-F actin antibodies (AAA) (less commonly measured in clinical practice), and atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA). Type 2 disease, first described in 1987, is defined by the presence of antibodies against liver-kidney-microsome 1 (ALKM-1) and liver cytosol 1 (ALC-1) [14]. The antibodies described above, however, are not specific to autoimmune hepatitis. Antibodies against soluble liver antigen/liver-pancreas antigen (SLA/LP) have been

Table 6.1 Autoantibody classification of autoimmune hepatitis

	Type 1 (classic)	Type 2
Characteristic autoantibodies	Antinuclear antibody (ANA) Smooth muscle antibody (SMA) Anti-F actin antibody (AAA) Anti-soluble liver/liver-pancreas antigen (SLA/LP) Atypical perinuclear antineutrophil cytoplasmic antibody (pANCA) AMA (antimitochondrial antibody)[a]	Anti-liver-kidney microsome-1 (ALKM-1) (rarely detected in North America) Anti-liver cytosol-1 (ALC-1)

[a]If present, consider overlap syndrome with PBC

described in both type 1 and type 2 disease and have a high degree of specificity for AIH, occurring in about 10–30% of patients [15, 16]. Antimitochondrial antibodies (AMAs) that are occasionally seen in type 1 disease, however, are more specific and sensitive for a diagnosis of primary biliary cholangitis (PBC) [17] (Table 6.1). Titers of greater than or equal to 1:80 are generally accepted as positive [4]. While autoantibodies are important to assist in the diagnosis, up to 20–30% of patients do not have detectable autoantibodies [2, 18]. Interestingly, despite the prevalence of circulating autoantibodies in AIH, these antibodies do not appear to have a direct role in inducing hepatocellular injury.

Histology

Liver biopsy is important for the initial diagnosis of autoimmune hepatitis and for long-term follow-up. The histologic appearance of autoimmune hepatitis is characterized by certain features of chronic hepatitis; however, they are nonspecific. Typically, a mixed inflammatory mononuclear cell infiltrate made up of plasma cells, lymphocytes, and occasional eosinophils is noted within the portal tract invading into the limiting plate: the sharply demarcated hepatocyte boundary around the portal tract. This invasion, referred to as interface hepatitis along with extension of the infiltrate into the lobule (lobular hepatitis), is characteristic of AIH [4] (Fig. 6.1). The biliary tree is usually spared. Varying degrees of fibrosis are usually present on biopsy, except in very mild cases of AIH [4, 18].

Diagnostic Criteria

Initial criteria for the diagnosis of autoimmune hepatitis were created by the International Autoimmune Hepatitis Group in 1992, updated in 1999, and subsequently simplified for clinical application in 2008. The criteria use serum autoantibodies, serum IgG levels, histologic findings, and the absence of viral hepatitis to make the diagnosis (Table 6.2). A probable diagnosis of AIH is made with a score of 6 points, while a definite diagnosis is made if the total points are ≥ 7 [19].

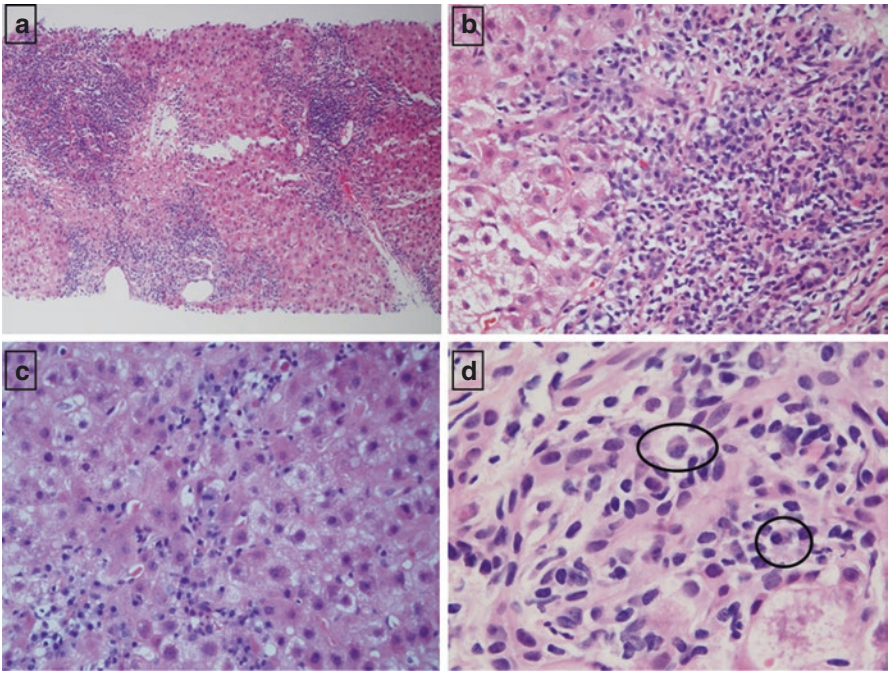

Fig. 6.1 Histology of AIH. (**a**) Evidence of autoimmune hepatitis on liver biopsy. Hematoxylin and eosin (H&E) stain at low power (20×). (**b**) Histologic features of portal and periportal inflammation. H&E, 200×. (**c**) Lobular inflammation and ballooning degeneration noted. H&E, 400×. (**d**) Evidence of portal tract inflammation with plasma cells (circled). Note the ballooned hepatocyte in the lower right corner. H&E, 400×. (Courtesy of Agni RM, Department of Pathology and Laboratory Medicine, University of Wisconsin School of Medicine and Public Health)

Table 6.2 Simplified criteria for the diagnosis of autoimmune hepatitis

Variable	Cutoff	Points[a]
ANA or SMA	≥1:40	1
ANA or SMA	≥1:80	2[b]
or ALKM-1	≥1:40	–
or SLA	Positive	–
IgG	>Upper limit normal	1
–	>1.1 times upper limit normal	2
Liver histology	Compatible with AIH	1
–	Typical of AIH	2
Absence of viral hepatitis	Yes	2

[a]Score ≥6 indicates probable AIH; score ≥7 indicates definite AIH
[b]Maximum of 2 points for autoantibodies

Variant Syndromes

In addition to isolated autoimmune hepatitis, there are entities in which there is overlap between AIH and cholestatic liver diseases, including primary biliary cholangitis and primary sclerosing cholangitis. These variant, or "overlap," syndromes are diagnosed when patients demonstrate clinical, biochemical, imaging, and histologic features of both entities [4].

Treatment

Patients with autoimmune hepatitis respond well to immunosuppressive agents, equally in both men and women [1]. Treatment is indicated in most patients with autoimmune hepatitis who present with elevated AST and gamma globulin levels, inflammation or evidence of fibrosis on liver histology, and symptoms. However, a subset of patients who are asymptomatic with normal or near normal aminotransferases or those with inactive cirrhosis may be at increased risk of developing medication-related side effects without benefiting from treatment [20].

Typically, patients are initially treated with corticosteroids (prednisone or prednisolone) alone or in combination with azathioprine (or 6-mercaptopurine [6-MP]) [20]. Prior to initiation of azathioprine or 6-MP, a thiopurine methyltransferase (TPMT) level is usually measured as those with homozygosity or heterozygosity for mutations in TPMT genes may accumulate toxic levels of azathioprine/6-MP metabolites. This accumulation can lead to bone marrow toxicity and possible death. Caution must be taken when initiating high doses of corticosteroids to monitor for steroid-related side effects, particularly in those with osteoporosis, brittle diabetes, emotional lability, and poorly controlled hypertension [4].

The goal of treatment is to achieve remission, identified by normalization of transaminases and gamma globulin or IgG levels along with histological improvement, which can lag behind by several months. Liver enzymes are monitored frequently to assess for response to therapy. Clinical and biochemical remission can be achieved in up to 85% of cases. Initial improvements are seen in the majority of patients within 2 weeks. Relapses are less likely when complete normalization of lab indices is achieved [21]. Treatment is typically continued for at least 2 years. Resolution of inflammation must be documented on liver biopsy prior to considering termination of immunosuppressive therapy. Therapy can then be gradually weaned over several weeks under close monitoring of symptoms and lab indices. While some patients may achieve and remain in remission when therapy is withdrawn, approximately 80% will relapse and require lifelong immunosuppression [20]. When a relapse occurs, patients are resumed on initial induction doses of drug

therapy, and medications are weaned again once clinical remission is achieved to the lowest dose of immunosuppressive agents to control symptoms and laboratory tests [4, 20].

Patients with refractory AIH who develop decompensated cirrhosis or those with acute liver failure from AIH should be considered for liver transplantation.

Autoimmune Hepatitis and Pregnancy

While amenorrhea and anovulation are common in women who have cirrhosis, pregnancies are becoming more common and successful with improved clinical management of AIH [22]. For those women with underlying AIH that become pregnant, maternal and fetal outcomes depend on the level of disease control during the preconception period. Women who are in disease remission prior to conception, without evidence of cirrhosis or portal hypertension, have favorable pregnancy outcomes [23]. The major risk to the fetus is prematurity; otherwise, outcomes in pregnancy are similar to the general population including rates of fetal loss, caesarian section, and still births [20]. AIH can also develop during or after pregnancy, typically in the first few months postpartum [24]. While approximately 20% of women with AIH will flare during pregnancy, due to either discontinuation of medications or changes in the immune state during pregnancy, AIH can actually improve during pregnancy [23, 25]. Postpartum, flares are much more common, reported as high as 52%, due to immune reconstitution after pregnancy and falling blood estrogen levels [23, 25, 26]. The presence of these flares does not appear to be associated with an increase in the number of fetal and maternal complications [26, 27].

Treatment of AIH in pregnancy with glucocorticoids and/or azathioprine appears to be safe [22]. Both medications are US FDA pregnancy category D. While certain guidelines recommend prednisone monotherapy [20] due to the minimal potential fetal risks associated with azathioprine, other societies recommend continuation of prior treatment with prednisone and/or azathioprine during pregnancy as adequate control of the underlying AIH outweighs the risks associated with the medications [22, 23]. Given the high rates of flares postpartum, it is recommended to increase immunosuppressive therapy approximately 2 weeks prior to anticipated delivery and monitor the patient closely postpartum [20, 22, 23, 25].

Mycophenolic acid (MPA), which is occasionally used in autoimmune hepatitis is, however, associated with an increased risk of first trimester pregnancy loss and congenital malformations and should be avoided in pregnancy (category D). Females of childbearing potential must be counseled about pregnancy planning and prevention while on MPA and have two negative pregnancy tests documented prior to initiating therapy and periodically while on therapy. Furthermore, in sexually active females of childbearing potential, a reliable form of contraception should be used before beginning MPA, during therapy, and for 6 weeks after stopping [28].

Long-Term Prognosis and Complications

In some patients, chronic autoimmune hepatitis progresses to cirrhosis and end-stage liver disease with or without the presence of complications of portal hypertension (e.g., ascites, esophageal or gastric varices, and hepatic encephalopathy). Hepatocellular carcinoma, while rare, can also arise in the setting of cirrhosis secondary to AIH at an incidence rate of about 0.3–1.1% per year [29, 30]. In those patients who progress to end-stage liver disease or have acute liver failure due to AIH, liver transplantation has excellent outcomes, with a 70–90% 5-year patient survival rate [2, 20, 31, 32]. Recurrent AIH post-liver transplantation can occur in about 30% of adults, usually occurring within 5 years after transplantation [20].

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Chapter 7
Diseases of the Liver: Primary Biliary Cholangitis

Paulina K. Phillips and Adnan Said

Abbreviations

AIH Autoimmune hepatitis
ALP Alkaline phosphatase
ALT Alanine aminotransferase
AMA Antimitochondrial antibody
ANA Antinuclear antibody
AST Aspartate aminotransferase
BEC Biliary epithelial cell
BMD Bone mineral density
ESLD End-stage liver disease
FDA Food and Drug Administration
FXR Farnesoid X receptor
GGT Gamma-glutamyl transferase
HLA Human leukocyte antigen
IL Interleukin
LT Liver transplantation
MELD Model for End-Stage Liver Disease
OCA Obeticholic acid
PBC Primary biliary cholangitis
PDC Pyruvate dehydrogenase complex
PPAR Peroxisome proliferator-activated receptor
SMAB Smooth muscle antibody
UDCA Ursodeoxycholic acid

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Patient Questions

1. *What is primary biliary cholangitis?*
   Primary biliary cholangitis (PBC), previously called primary biliary cirrhosis, is a disease in which the body's immune system attacks the liver—specifically, the parts of the liver that make bile (a substance that helps us absorb nutrients). Over many years, the damage causes the liver to scar (called "cirrhosis"), which can lead to many complications, including death.
2. *Why was the name changed from "cirrhosis" to "cholangitis"?*
   As described above, cirrhosis occurs when damage to the liver causes formation of scar tissue, which eventually replaces the organ. "Cholangitis" refers to inflammation (injury) of the bile ducts, which can lead to cirrhosis but also occurs in livers that do not have any scar tissue. In fact, many people with PBC *don't* have cirrhosis, so the name was changed to more accurately reflect the underlying disease process.
3. *Who gets PBC? Why do people get PBC?*
   PBC can affect both men and women but is mostly diagnosed in women over 35–40 years old. It is rarely diagnosed in children. We do not completely understand why certain people get PBC, but we do know it has a genetic component (it can run in families) and may also be affected by certain things in the environment, like smoking.
4. *What are the symptoms of PBC?*
   Many people with PBC don't have any symptoms at all! When symptoms do appear, they can include profound tiredness, itchiness, dry eyes, dry mouth, yellowing of the eyes and skin (called "jaundice"), abdominal pain, fluid retention, memory difficulties or confusion, weight loss, problems with night vision, easy bruising or bleeding, bone fractures, and liver cancer.
5. *How does someone find out she/he has PBC?*
   If PBC is suspected (based on symptoms like those listed above and/or if blood tests show abnormal liver tests), there are specific blood tests that can diagnose PBC. Sometimes, a liver biopsy may be needed to help make the diagnosis, but not always. A liver biopsy and certain types of imaging tests (including ultrasound and MRI) can also help assess how much scar tissue is in the liver.
6. *How does pregnancy affect PBC?*
   In general, women with PBC who become pregnant are able to experience good outcomes, although the data about fertility and infant outcomes in PBC is still somewhat limited. Certain symptoms—itching in particular—may worsen during pregnancy, particularly early on. Additionally, it is important to regularly monitor liver tests during pregnancy because "flares" (worsening of liver function) may occur. Close follow-up with an obstetrician and hepatologist is of utmost importance, especially if a pregnancy takes place in the setting of advanced liver disease (which is rare but does occur and carries additional risks for the mother and fetus).
7. *Are there any treatments for PBC?*
   Fortunately, we have several good medications to help treat PBC. One of these medicines helps to slow down the damage to the liver. Others help to control

itching. Because some PBC patients can have low vitamin levels, they may need to take supplements. If patients develop cirrhosis, they may need to be on certain medicines to help with the complications (e.g., water pills to treat fluid retention). Finally, some patients with severe PBC may need a liver transplant.

Introduction

Primary biliary cholangitis (PBC)—previously called primary biliary cirrhosis—is a chronic, immune-mediated disease of the liver whose incidence and prevalence are higher than previously estimated, with annual incidence rates ranging from 0.3 to 5.8 per 100,000 and prevalence rates ranging from 1.9 to 40.2 per 10,000 [1]. PBC is a chronic, cholestatic liver disease in which destruction of the intrahepatic bile ducts over time can ultimately result in cirrhosis and its sequela. The disease is usually diagnosed in middle-aged females, with a female-to-male ratio of 9–10:1 [2, 3]. Fatigue and pruritus are the most common symptoms. The hallmark serologic marker is the antimitochondrial antibody (AMA), which is present in nearly all patients with PBC. Ursodeoxycholic acid (UDCA) remains the mainstay of medical treatment. Patients with PBC who develop complications of end-stage liver disease (ESLD) should be referred for liver transplant (LT) evaluation.

Epidemiology and Pathogenesis

While all the mechanisms involved in the pathogenesis of PBC are not yet completely elucidated, it is believed that the disease is a result of the interplay between genetic predisposition and environmental factors. Studies have shown that, in patients with PBC, 1.3–5.9% of cases had a family member with PBC [4–6]. Other autoimmune diseases have also been reported to be more prevalent in PBC patients compared to non-PBC control groups [6]. The concordance rate for PBC in monozygotic twins is as high as 63%, which is as high or higher than rates observed in other autoimmune disorders and is not seen in dizygotic twins [7]. Genome-wide association studies in North America and Europe have found an association between PBC and human leukocyte antigen (HLA) genes. In a large, multicenter Italian study, the *DRB1∗08* allele was associated with susceptibility to PBC, whereas alleles *DRB1∗11* and *DRB1∗13* were found to confer protection [8]. In another large study of US and Canadian subjects, significant associations were found between PBC and 13 loci across HLA class II (*DQB1* having the strongest association) as well as genes in the interleukin (IL) 12 inflammatory pathway (specifically, *IL12A* and *IL12RB2*) [9]. To date, large-scale studies have identified over 25 non-HLA loci associated with PBC, with the genes involved encoding mediators in both the innate and adaptive immune response. Nonetheless, at this time, it is estimated that only 15% of PBC heritability can be accounted for by genetic studies. Additional

possible environmental triggers include toxic waste disposal sites, tobacco smoke, hormone replacement therapy, frequent use of nail polish, and certain illnesses, including urinary tract infections [5, 6, 10, 11]. Never having been pregnant was shown to be protective against developing PBC in a large, multicenter study [6]. Nevertheless, while the abovementioned factors have been postulated to explain why the prevalence of PBC is higher in women than in men, this is an area of research that continues to evolve. Of particular interest is collecting more data on males with PBC, as the bulk of the known literature focuses on females.

The underlying mechanism in PBC entails the loss of self-tolerance to mitochondrial and nuclear antigens. Autoantibodies target the 2-oxo-acid dehydrogenase family of enzymes, including the E2 component of the pyruvate dehydrogenase complex (PDC-E2), branched chain 2-oxo-acid dehydrogenase, and 2-oxo-glutaric acid dehydrogenase [12]. These all share the essential cofactor lipoic acid, which plays a key role in antigen recognition for both T and B cells. Biliary epithelial cells (BEC) express T-cell ligands that are thought to play an essential role in inducing apoptosis of these cells. The ensuing inflammatory cascade results in a progressive nonsuppurative cholangitis with development of fibrosis and eventually cirrhosis.

Diagnosis

To diagnose PBC, two of the three following criteria should be met after excluding other etiologies of cholestasis: (1) chronic elevation of alkaline phosphatase (ALP) ≥2 times normal, (2) a positive AMA titer of ≥1:40, and (3) liver biopsy demonstrating granulomatous or lymphocytic nonsuppurative destructive cholangitis of small- and medium-sized interlobular bile ducts [13]. Some type of abdominal imaging should also be performed as part of the investigation to exclude biliary obstruction as a cause of cholestasis. Furthermore, imaging is helpful in assessing for signs of advanced fibrosis and/or portal hypertension, which carry prognostic significance as detailed in the next section.

Liver Chemistries

Most patients with PBC will develop abnormal liver chemistries. ALP (and often gamma-glutamyl transferase [GGT]) elevation is the classic manifestation of cholestasis. Higher ALP levels have been associated with more severe inflammation and ductopenia. Additionally, mild elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may also be present. Hyperbilirubinemia—a marker of synthetic dysfunction—is seen in advanced stages of PBC as a result of progressive bile duct loss and biliary necrosis. Hyper-γ-globulinemia (especially IgM) and hypercholesterolemia are also frequently found [14, 15].

Autoantibodies

AMA is present in 90–95% of patients with PBC and appears early on in the disease course, often before symptoms appear or liver tests become elevated [16, 17]. Conversely, 5–10% of PBC patients are AMA-negative; in these patients, testing for PBC-specific autoantibodies may be helpful. One recent Scandinavian retrospective study suggested worse long-term outcomes in the AMA-negative cohort, including significantly reduced survival free of liver-related complications (including LT and death), compared to AMA-positive patients [18]. However, these differences in prognosis in AMA-positive and AMA-negative patients were not been observed in other studies [19]. Finally, it is worth noting that first-degree relatives of PBC patients are more likely to be AMA-positive compared with matched controls (13% vs. 1%, respectively), particularly if they are female [20].

While AMA titers of at least 1:40 are considered significant, higher titers do not necessarily correlate with more severe disease. Additionally, it has been estimated that <1% of the general population without clinically apparent liver disease or abnormal liver biochemistries is AMA-positive, although the true prevalence in specific populations is not well-defined [13]. In a large, prospective, observational study by Dahlqvist et al., 16% of patients with a positive AMA, normal ALP, and no cirrhosis went on to develop PBC after 5 years [17]. While this was a minority, it raised the possibility of AMA serving as markers of preclinical disease.

In addition to AMA, antinuclear antibodies (ANA) may be present in 10–40% of patients with PBC. Some of these, notably anti-gp210, have been associated with poorer outcomes in this patient population [21, 22]. Other characteristic immune mediators include OGDC-E2, PDC-E1α, Sp100, and p62 [12].

Liver Biopsy

If PBC is suspected but the AMA or ALP is nondiagnostic or the clinical picture is mixed, a liver biopsy should be pursued to ascertain the diagnosis. To minimize false-negative results, a satisfactory sample should contain at least ten portal tracts. While there are several histological classification systems for PBC, Ludwig's system is the most widely used and is comprised of four stages: (I) portal inflammation with nonsuppurative cholangitis and occasional epithelioid noncaseating granulomas ("florid duct lesions"); (II) bile ductular proliferation with the inflammatory infiltrate extending into the periportal areas (interface hepatitis); (III) septal and bridging fibrosis; and (IV) cirrhosis with regenerative nodules [23]. More recently, Nakanuma et al. proposed a novel grading and staging system for PBC [24]. Figure 7.1 depicts the usual histopathology of PBC.

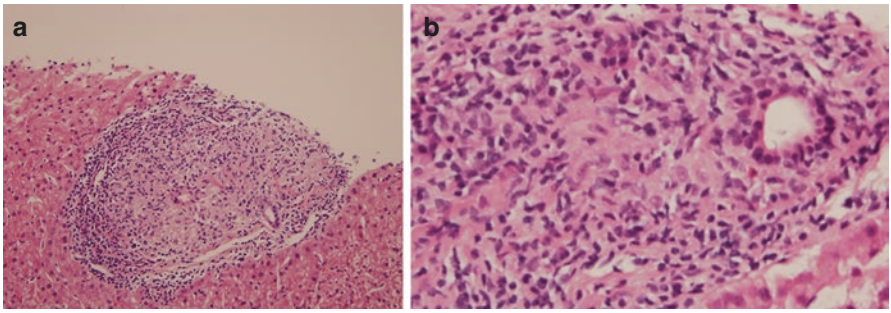

Fig. 7.1 Histologic findings in PBC. (**a**) Portal mixed chronic inflammatory infiltrates centered on a bile duct, often with a granuloma (H&E 100×). (**b**) First picture magnified to 200×. (Courtesy of Agni RM, Department of Pathology and Laboratory Medicine, University of Wisconsin School of Medicine and Public Health)

Clinical Presentation

In the current era, the majority (60%) of patients diagnosed with PBC are asymptomatic without significant physical exam findings [3]. This is related to increased disease awareness, more widespread use of screening liver chemistries—which allows for earlier detection and diagnosis—and delayed histological progression and improved survival with UDCA (described further in the "Treatment" section). When present, the most frequently reported symptoms are fatigue and pruritus. Right upper quadrant abdominal pain is seen in 17% of patients [25]. Patients with untreated and/or advanced disease may present with sequela of cirrhosis and portal hypertension, including jaundice, ascites, esophageal varices, hepatic encephalopathy, splenomegaly, or hepatocellular carcinoma. Sicca syndrome, hyperlipidemia, fat-soluble vitamin deficiencies, anemia, hypothyroidism, and osteopenia/osteoporosis are additional complications [26].

Other autoimmune disorders may be seen in one-third to one-half of all PBC patients and include Sjögren's syndrome, hyper- or hypothyroidism, rheumatoid arthritis, psoriasis, scleroderma, and inflammatory bowel disease [26]. Additionally, an overlap syndrome with autoimmune hepatitis (PBC-AIH) is diagnosed in up to 10% of PBC patients and may be related to HLA polymorphisms [27]. The diagnosis of PBC-AIH overlap is now typically established using the Paris criteria, which requires two features of both PBC and AIH to be present (Table 7.1) [27]. Patients with PBC-AIH overlap syndrome have been shown to have a worse prognosis than those with PBC alone, including more complications of cirrhosis, liver-related death, and need for LT [28, 29].

Table 7.1 Paris criteria for primary biliary cholangitis-autoimmune hepatitis (PBC-AIH) overlap syndrome

Primary biliary cholangitis (2 of 3)
ALP >2 times ULN
Positive AMA
Liver biopsy demonstrating features of PBC
Autoimmune hepatitis (2 of 3)
ALT >5 times ULN
IgG >2 times ULN and/or positive SMAB
Histopathology showing moderate or severe interface hepatitis

ALP alkaline phosphatase, *ULN* upper limit of normal, *AMA* anti-mitochondrial antibody, *PBC* primary biliary cholangitis, *ALT* alanine aminotransferase, *SMAB* smooth muscle antibody

Fatigue

Fatigue, typically characterized by excessive daytime somnolence, affects up to 80% of PBC patients and is associated with a reduced quality of life as reported by validated questionnaires; there appears to be no correlation between the severity of fatigue and degree of cholestasis, histological stage, or duration of disease [30–32]. The exact pathophysiology of fatigue is incompletely understood and is likely multifactorial. It is important to evaluate for competing or contributing causes of fatigue, including hypothyroidism, depression, anemia, restless leg syndrome, and sleep apnea or other sleep disorders. UDCA does not change the severity or frequency of fatigue. While other agents (including the selective serotonin 5-HT3 receptor antagonist ondansetron, the selective serotonin reuptake inhibitor fluoxetine, and the stimulant modafinil) have been studied in PBC patients with fatigue, none have shown consistent benefit; consequently, at this time, there is no recommended therapy for PBC-related fatigue [13].

Pruritus

Generalized, typically intermittent itching is noted in 19–70% of patients with PBC [3]. It may be more severe in the palms and soles and at night. It is frequently exacerbated by heat, pregnancy, or contact with clothing. As with fatigue, the severity of pruritus is not necessarily related to the grade or stage of PBC; in fact, pruritus may actually improve in very advanced liver disease. Several hypotheses have been proposed to explain the pathophysiology of pruritus in PBC, including bile acid accumulation (although this theory has been challenged) as well as

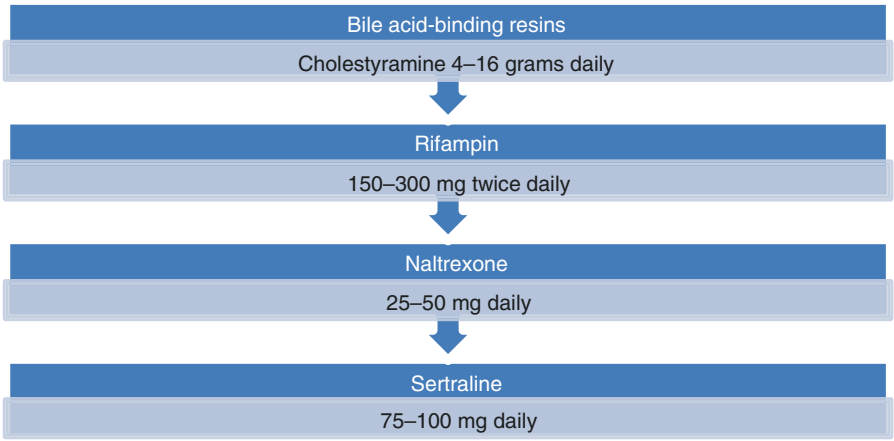

Fig. 7.2 Recommended first- and second-line therapy for pruritus in patients with PBC

increased levels of endogenous opioids and lysophosphatidic acid via autotaxin activity [33]. As with fatigue, UDCA does not relieve pruritus in PBC; however, unlike fatigue, pruritus has several treatment options that have shown to be beneficial [13]. First-line agents include bile acid-binding resins (cholestyramine, colestipol, and colesevelam), which are generally well-tolerated but may have some gastrointestinal side effects and need to be taken separately from other medications due to their sequestrant properties. If pruritus remains refractory to maximal doses of anion-exchange resins, second-line options include the antibiotic rifampin, opiate antagonists (such as naltrexone), and the selective serotonin reuptake inhibitor sertraline. Figure 7.2 summarizes the treatment algorithm for pruritus in PBC.

Osteopenia and Osteoporosis

Decreased bone formation and increased bone resorption lead to accelerated bone loss in PBC patients when compared to age- and sex-matched controls. Additional risk factors include female sex, low body mass index, older age, and history of fragility fracture. The incidence of osteoporosis in patients with PBC ranges from 20 to 44% [34]. Current guidelines recommend baseline bone mineral density (BMD) testing with follow-up based on initial results; additionally, supplementation with daily calcium (1200–1500 mg/day) and vitamin D (1000 international units/day) is advisable [13]. In PBC patients with established osteoporosis, bisphosphonate therapy has been shown to increase BMD [35].

Malabsorption

The risk of fat-soluble vitamin (A, D, E, and K) malabsorption is increased in PBC (and other cholestatic diseases) due to decreased bile acid concentrations in the intestine leading to reduced micellar solubilization [36]. In a randomized trial by Phillips et al., the proportion of PBC patients with vitamin A, D, E, or K deficiency was 33.5%, 13.2%, 1.9%, and 7.8%, respectively [37]. In PBC patients with hyperbilirubinemia, measurement—and treatment if indicated—of vitamin levels is recommended [13].

Hyperlipidemia

Cholestatic liver diseases are known to be potentially associated with a dyslipidemic state. Historically, published studies have not demonstrated hyperlipidemia in PBC to be associated with an increased risk of cardiovascular events [14, 38]. However, a more recent systematic review by Ungprasert et al. identified a pooled risk of 1.57 (95% CI, 1.21–2.06) [39]. This suggests that certain PBC patients—including those with unfavorable lipoprotein profiles, personal or family history of cardiac history, and/or presence of xanthelasma (sharply demarcated collections of cholesterol found beneath the skin surface, typically on or around the eyelids)—may be candidates for cholesterol-lowering therapy [13].

Natural History

Very early on in the disease course, the only positive finding may be AMA reactivity. Transaminase elevation (typically ALP and/or GGT) generally occurs during the asymptomatic phase. Clinical symptoms (i.e., fatigue, pruritus) appear during the early symptomatic phase, whereas the late symptomatic phase is characterized by sequela of cirrhosis and liver failure. This process has a variable rate of progression among individual patients but generally extends over several decades; however, in the absence of pharmacotherapy, the median time to development of extensive fibrosis (≥F3) has been noted to be as short as 2 years with histological stage progressing by one stage every 1.5 years [40]. The presence or absence of symptoms at the time of diagnosis does not predict prognosis.

The natural history of AMA-negative PBC and PBC-AIH overlap syndrome has been described earlier in the chapter. Before the widespread use of screening liver tests and effective therapy (i.e., in the pre-UDCA era), PBC was usually diagnosed during an advanced stage and was associated with increased morbidity and mortal-

ity, with an overall survival of 5–9 years from diagnosis [3, 41]. In the large observational study by Prince et al., liver failure was seen in 15% and 26% of PBC patients 5 and 10 years after diagnosis, respectively [3]. This study also demonstrated that most patients, even if asymptomatic at the time of diagnosis, go on to develop symptoms and/or complications of PBC, usually within the first 5 years after diagnosis.

While clinical manifestations of ESLD are similar to those seen in other chronic liver diseases, a key difference is that a small proportion of PBC patients may develop esophageal varices (EV) in the absence of cirrhosis due to nodular regenerative hyperplasia. Development of EV is associated with increased mortality, with one study of PBC patients showing a 3-year survival of 59% (which decreased to 46% after a first bleeding episode) [42]. Prevention and management of varices and variceal bleeding should follow current guidelines [43].

Pregnancy in PBC

While the majority of women with PBC present later in life, a substantial portion are diagnosed during reproductive age; as such, it is imperative to address childbearing plans early on, ideally before conception. While pregnancy outcomes are generally favorable, careful monitoring is crucial as there is a higher potential risk of maternal and fetal complications. These include de novo onset or worsening of cholestasis and pruritus, postpartum biochemical flares, miscarriage, and stillbirth [44, 45]. Additionally, worsening of portal hypertension may occur related to an increase in blood volume and compression of the inferior vena cava by the gravid uterus. A feared result of this is variceal hemorrhage, particularly during Valsalva maneuvers when in active labor. Management of acute bleeding is the same as in nonpregnant patients [43]. Screening endoscopy should be performed prior to conception (preferred) or during the second trimester. It is recommended that UDCA be continued throughout pregnancy. The safety profile of UDCA in pregnancy, along with other common medications used in PBC, is detailed in Table 7.2.

Treatment

Treatment of the various complications of PBC is detailed in the “Clinical Presentation” section of this chapter. Here the focus will be on the mainstay of medical therapy, which is UDCA. Newer agents, including obeticholic acid (OCA) and fibric acid derivatives (fibrates), will also be described, as will be the role of LT.

Table 7.2 Pregnancy safety profiles of common medications used in the treatment of PBC

Medication	Pregnancy considerations
Ursodeoxycholic acid	"Adverse events have not been observed in animal reproduction studies"
Obeticholic acid	"Adverse events have not been observed in animal reproduction studies"
Cholestyramine	Pregnancy risk factor C "Cholestyramine is not absorbed systemically, but may interfere with maternal vitamin absorption; therefore, regular prenatal supplementation may not be adequate"
Rifampin	"Adverse events have been observed in animal reproduction studies" "Rifampin crosses the human placenta" "Postnatal hemorrhages have been reported in the infant and mother with administration during the last few weeks of pregnancy"
Naltrexone	"Information related to the use of naltrexone during pregnancy is limited"
Sertraline	"Sertraline crosses the human placenta" "Studies evaluating specific birth defects have provided inconsistent results" "Long-term effects of in utero SSRI exposure on infant development and behavior are not known"
Fenofibrate	"In women who develop very severe hypertriglyceridemia…use of fenofibrate beginning in the second trimester is one intervention that may be considered"

Source: Lexicomp Online, Pregnancy Considerations, Wolters Kluwer Clinical Drug Information, Inc., 2019

Ursodeoxycholic Acid

UDCA at a dose of 13–15 mg/kg/day is the mainstay of therapy and is the only drug approved by the US Food and Drug Administration (FDA) for the treatment of PBC. UDCA is a hydrophilic bile acid that improves bile flow and reduces hepatocyte and BEC damage from cholestasis. In addition to its choleretic effect, UDCA has also been shown to have anti-inflammatory, cytoprotective, and immunomodulatory properties [46]. It is generally a very well-tolerated medication, which is important in terms of patient adherence. Multiple studies of UDCA in PBC have demonstrated improvement in liver biochemistries, slower histological progression, delayed onset of esophageal varices, and improved transplant-free survival [47–53]. Patients with an earlier stage of PBC appear to respond more favorably to UDCA than those with more advanced disease. Clinical features, disease progression, and response to UDCA have historically been found to be similar for AMA-negative and AMA-positive PBC [19]. Normalization of liver tests, specifically ALP and total bilirubin, is the goal of therapy [54]. Adjunctive therapy should be sought if biochemical response is not achieved after 1 year of treatment.

Obeticholic Acid

In 2016, the FDA approved OCA to be used in combination with UDCA in patients with PBC who did not achieve an adequate biochemical response after ≥1 year of UDCA therapy. It is also approved as monotherapy in those patients who are intolerant of UDCA. OCA is not recommended in PBC patients with decompensated liver disease.

OCA is a potent, selective agonist of the farnesoid X receptor (FXR) and is derived from chenodeoxycholic acid (a natural ligand for FXR). Via FXR signaling, OCA protects hepatocytes against bile acid toxicity by reducing bile acid synthesis and stimulating choleresis through upregulation of bile acid transporters; furthermore, it has demonstrated antifibrotic and anti-inflammatory properties via other pathways [55]. In a large, double-blind, placebo-controlled, phase 3 trial of patients who had an inadequate response to UDCA, subjects were randomized to placebo, 10 mg/day OCA, or 5 mg/day OCA with the option to increase to 10 mg/day after 3 months if they were tolerating therapy but had not achieved the primary endpoint, defined as serum ALP <1.67 times the upper limit of normal, with a reduction of at least 15% from baseline, and a normal total bilirubin level [56]. This endpoint was achieved in 46% of patients in the 5–10 mg group, 47% of patients in the 10 mg group, and 10% in the placebo group ($p < 0.001$). Pruritus was the most common adverse event and was dose-dependent. Currently, it is recommended to start OCA at a dose of 5 mg daily with titration as per the study protocol. Long-term trials examining the efficacy of OCA on survival of PBC patients are ongoing.

Fibrates

In patients with an inadequate response to UDCA, the addition of fibrates (activators of the peroxisome proliferator-activated receptor [PPAR]) could be considered. In a small open-label study of 20 patients with ALP levels >2× upper limit of normal after UDCA treatment, the addition of fenofibrate resulted in a 50% reduction in ALP [56]. A larger, multicenter study showed that patients randomized to UDCA/bezafibrate had improved liver chemistries, markers of fibrosis, and pruritus compared to patients in the UDCA/placebo arm [57]. Because fibrates have been associated with cases of hepatotoxicity, they are not recommended in patients with decompensated liver disease.

Liver Transplantation

As with other causes of chronic liver disease, decompensated ESLD is an indication for LT evaluation in PBC. In some cases, Model for End-Stage Liver Disease (MELD) exception points may be granted for intractable pruritus, although this

depends on the decision of the Regional Review Board. To assist with risk stratification of PBC patients, several prognostic models have been developed, including the Mayo natural history model, the GLOBE score, and the UK-PBC score [58–60].

Due to the effectiveness of medical therapy (UDCA), the number of LTs performed annually for PBC has declined over time despite the increase in incidence and prevalence of the disease [61]. Outcomes following LT are excellent, with 3-, 5-, and 10-year graft survival rates of 80%, 78.1%, and 71.9%, respectively, and 3-, 5-, and 10-year patient survival rates of 86.7%, 84.4%, and 79%, respectively [61]. Pruritus usually significantly improves or resolves after transplant; however, fatigue may persist.

Finally, while the rate of PBC recurrence after LT is quite variable (0–50%), this does not generally affect long-term graft and patient survival [62]. There is some evidence that the risk of PBC recurrence post-LT may be reduced with preventive UDCA treatment [63].

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Chapter 8
Diseases of the Liver: Liver Masses (Hemangioma, Focal Nodular Hyperplasia, Hepatic Adenoma)

Parul D. Agarwal and Adnan Said

Questions from Patients

1. *How did I get this?*
   Hepatic hemangiomas are thought to be congenital vascular malformation. They enlarge over time by ectasia (dilation or distension). Focal nodular hyperplasia (FNH) results from a hyperplastic response (increased number of cells) by reactive proliferating hepatocytes to increased local blood flow, usually related to arterial or portal vascular malformation. Hepatic adenoma (HA), by contrast, is a stimulated lesion that is strongly associated with use of oral contraceptives or androgens.
2. *What happens if I do nothing?*
   Hepatic hemangiomas and FNH often do not cause symptoms or result in significant complications. They are frequently managed conservatively without need for treatment or other intervention. They carry no risk for malignant transformation, and surveillance is often not required. HAs, by contrast, can be associated with significant complications, especially lesions greater than 5 cm in size, including both risks for bleeding and less commonly conversion to malignancy. Therefore, appropriate surveillance with radiological tests and/or treatment may be required to prevent future development of these serious complications.
3. *What if I get pregnant?*
   Pregnancy is not contraindicated in patients with hepatic hemangioma and FNH.

   Pregnancy is also not contraindicated in patients with HAs; however close follow-up with surveillance ultrasonography of the adenoma is usually recommended during the pregnancy. As the behavior of HAs under the influence

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of hormonal changes associated with pregnancy is unpredictable, treatment of the adenoma should be considered prior to attempting pregnancy, especially for lesions that are greater than 2 cm. This is to reduce risk for bleeding, which can potentially arise in the event of significant tumor growth under the influence of hormonal changes.

Hepatic Hemangiomas

Epidemiology

Hepatic hemangiomas are the most prevalent benign solid lesion of the liver, affecting 0.4–10% of the general population [1]. They are more common in women, with a ratio of 3:1, and in the right hepatic lobe [2]. Although they can occur at any age, most patients are diagnosed between the third and fifth decade of life.

Clinical Presentation

Hemangiomas are often solitary, but multiple lesions may be present in both hepatic lobes. They can range in size from a few millimeters to over 20 cm, although the vast majority of them are under 5 cm in size. Hemangiomas greater than 5 cm in size are sometimes referred to as giant hemangiomas [3]. Small hemangiomas are asymptomatic and are frequently found incidentally on imaging performed for other conditions. Rarely, hemangiomas can grow to a large size and may be associated with pain or mass effect on other structures. Pain or right upper quadrant fullness or discomfort may result from pressure or stretching of the liver capsule or displacement of other structures. Less commonly, nausea, vomiting, or early satiety may result with compression of adjacent structures. Acute abdominal pain due to bleeding or thrombosis within the hemangioma is exceedingly rare. Hemangiomas carry no risk for malignant transformation. Giant hemangiomas in children have been associated with high-output cardiac failure and hypothyroidism, as well as disseminated intravascular coagulation related to consumptive coagulopathy, which is also known as the Kasabach-Merritt syndrome [4].

Pathogenesis

Hepatic hemangiomas are thought to be congenital vascular malformations or hamartomas. They enlarge by ectasia rather than by hypertrophy or hyperplasia. Hemangiomas may occasionally enlarge during pregnancy or in women taking OCPs, although this potential effect of estrogen is variable among individuals.

Natural History

Most hepatic hemangiomas follow a benign clinical course, without causing symptoms. For the vast majority of patients, the long-term prognosis of most hepatic hemangiomas is highly favorable. In long-term follow-up of up to 20 years, most patients remained asymptomatic, without significant change to their quality of life [5]. Complications, such as spontaneous bleeding or thrombosis within the hemangioma, are exceedingly rare, and malignant transformation does not occur.

Diagnosis

Hemangiomas usually have characteristic features which confirm their diagnosis on ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). MRI is the most accurate modality for diagnosis of hemangiomas. The typical radiological appearance of hemangioma on MRI is a well-demarcated mass showing low signal intensity on T1-weighted images, hyperintensity on T2-weighted images, and early peripheral or globular enhancement on arterial phase imaging with progressive centripetal enhancement on delayed phases with complete homogenous enhancement observed within the lesion (Fig. 8.1).

Biopsy of the lesion is best avoided due to the risk for hemorrhage. Physical examination findings are usually unremarkable, although, rarely, a vascular bruit may be heard over a giant hemangioma. Liver tests are usually normal as are tumor markers, such as serum alpha-fetoprotein and CA19-9.

Management

As the vast majority of hemangiomas follow a benign clinical course, and do not result in symptoms or significant complications, patient reassurance is all that is required. Once the diagnosis is confirmed, based on radiological findings, ongoing surveillance imaging is not routinely recommended. Caveats to these recommendations include tumors where the diagnosis is uncertain, rapid growth, or large lesions, >5 cm, particularly if these are located in a subcapsular location. For patients who are symptomatic due to compression of adjacent structures or for those who are at risk for complications such as bleeding due to rupture, surgical resection should be considered. Nonsurgical treatment options include thermal ablation and arterial embolization of large hemangiomas, based on available center experience.

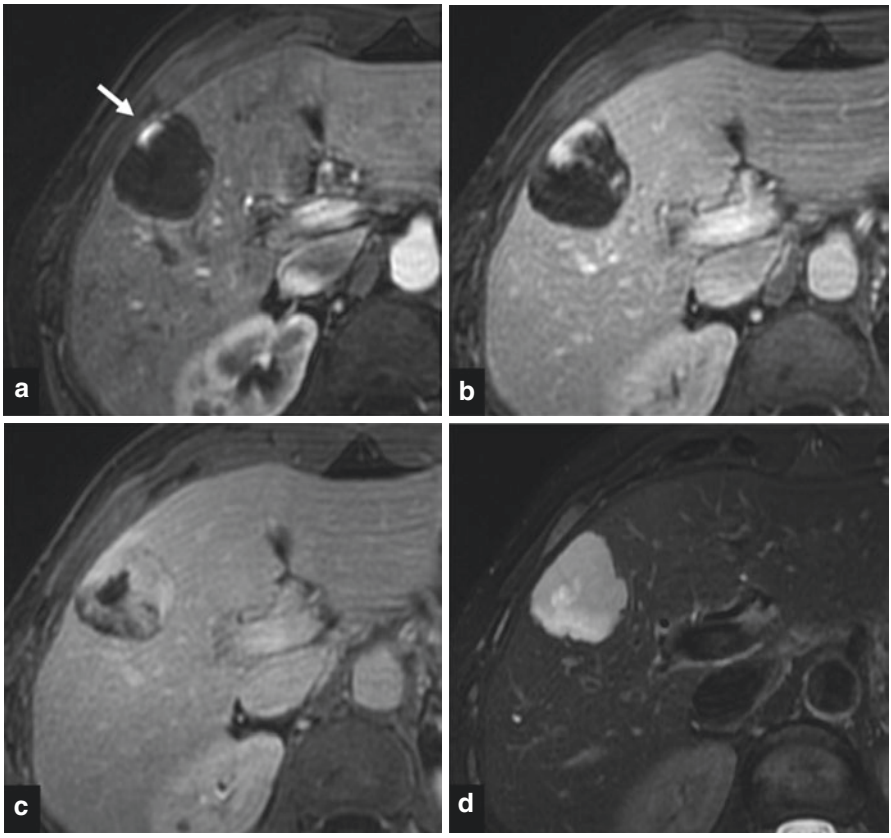

Fig. 8.1 A 41-year-old female with hemangioma who underwent MRI. (**a**) Late arterial phase image shows peripheral nodular enhancement (arrow). (**b**) Portal venous phase image shows centripetal pattern of contrast filling the hemangioma. (**c**) Delayed phase shows near-complete contrast filling of the hemangioma. (**d**) T2-weighted image shows classic increased signal

Focal Nodular Hyperplasia (FNH)

Epidemiology

Focal nodular hyperplasia (FNH) is the second most common benign tumor of the liver, with an estimated prevalence of 0.3–3% based on autopsy series [6, 7]. It is found in both sexes, however, and is predominant in women with a female/male ratio of 8:1. It can be present throughout the age spectrum, with the average age at presentation between 20 and 50 years.

Clinical Presentation

FNH are often found incidentally on abdominal imaging. They are usually solitary, often less than 5 cm in size, and do not cause symptoms. Rarely, patients with large or pedunculated FNH may present with hepatomegaly or a palpable mass. Not uncommonly, there are multiple FNH (20–30%), associated with other benign liver tumors, including hepatic hemangiomas (20%) and rarely hepatic adenomas [8]. FNH do not typically cause elevations of liver biochemistries or tumor markers, such as serum alpha-fetoprotein (AFP) and CA19-9.

Pathogenesis

FNH results from a hyperplastic response of reactive proliferating hepatocytes to increased local blood flow, usually related to an arterial or portal venous malformation. Genetic studies have confirmed a polyclonal origin of FNH tumors in the vast majority of these tumors, as would be expected of a reactive lesion [9, 10]. The role of oral contraceptives on FNH has been queried. Although debated, oral contraceptives may play a small role in growth and vascularity of FNH; however the magnitude of such risk remains uncertain.

Natural History

FNH is a stable benign entity, with little or no growth on surveillance imaging. It is not associated with significant complications, such as bleeding, and malignant transformation does not occur. Most patients with FNH are asymptomatic. As discussed above, some FNH may be responsive to estrogens, although pregnancy and use of oral contraceptives are not contraindicated in patients with FNH. It is generally recommended however that patients with FNH who continue to use oral contraceptives receive monitoring with follow-up abdominal imaging in 6–12-month intervals to assess interval change in size of FNH.

Diagnosis

FNH are usually incidentally found. A diagnosis can be confirmed solely by demonstration of characteristic radiological findings with contrast-enhanced MRI, which is the most accurate radiological modality to diagnose FNH (Fig. 8.2). They

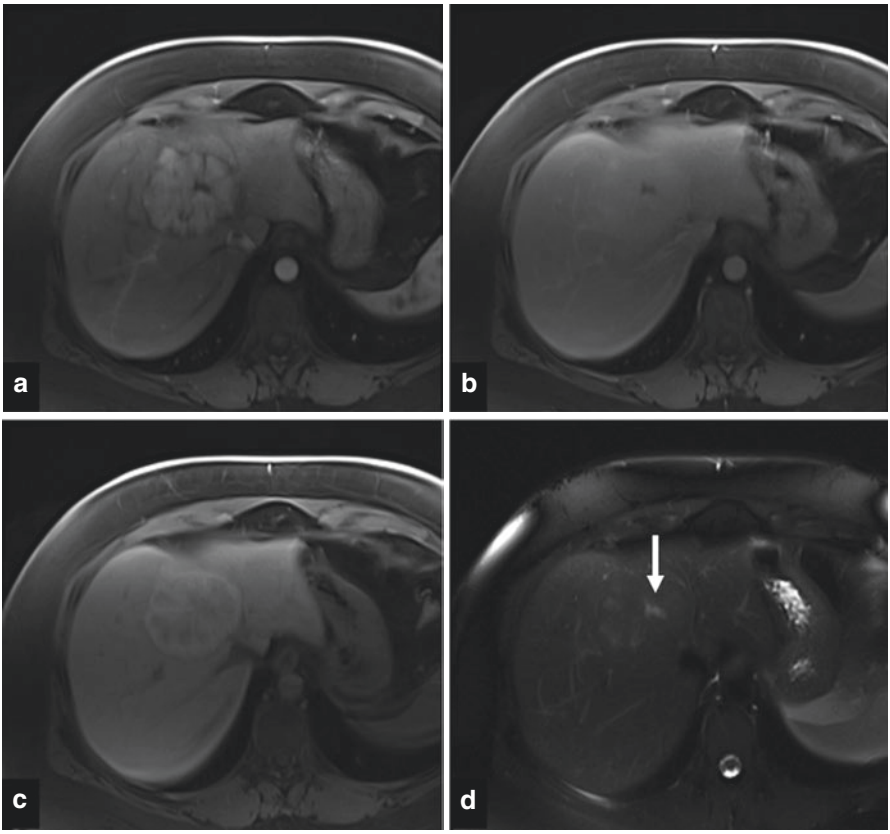

Fig. 8.2 A 34-year-old female with focal nodular hyperplasia on MRI. (**a**) Classic intense enhancement on late arterial phase imaging due to the hypervascular nature of FNH. (**b**) FNH is isointense to liver parenchyma on portal venous phase imaging and can frequently be missed on standard CT examination consisting of only a portal venous phase. (**c**) Twenty-minute delayed image performed with liver-specific contrast agent shows classic hyperintensity of the tumor relative to the normal hepatic parenchyma. (**d**) T2-weighted image demonstrates the T2-hyperintense central scar (arrow) and isointensity of the remainder of the FNH to the normal parenchyma

usually lack a capsule, demonstrate faint hypointensity, or are isointense to the normal liver parenchyma on T1-weighted images and slightly hyperintense or isointense on T2-weighted images; they diffusely enhance in the arterial phase and are isointense in the portal venous and delayed phases. The radiological hallmark of FNH is the presence of a central, or stellate, scar, which is hyperintense on T2-weighted images, and enhances on delayed phases compared to the background liver parenchyma for FNH >3 cm.

A percutaneous biopsy may be performed for enlarging lesions (Fig. 8.3) or those that do not demonstrate characteristic radiological features. Histologically,

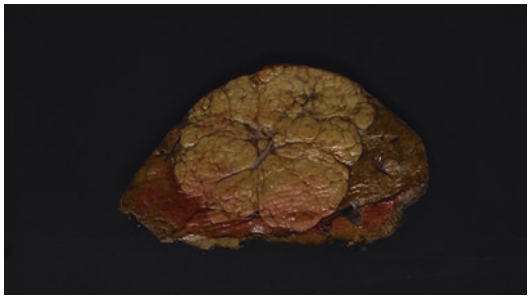

Fig. 8.3 Gross specimen of focal nodular hyperplasia resected from a 47-year-old female showing a well-circumscribed mass with nodular appearance, "central scar," and fibrous septa

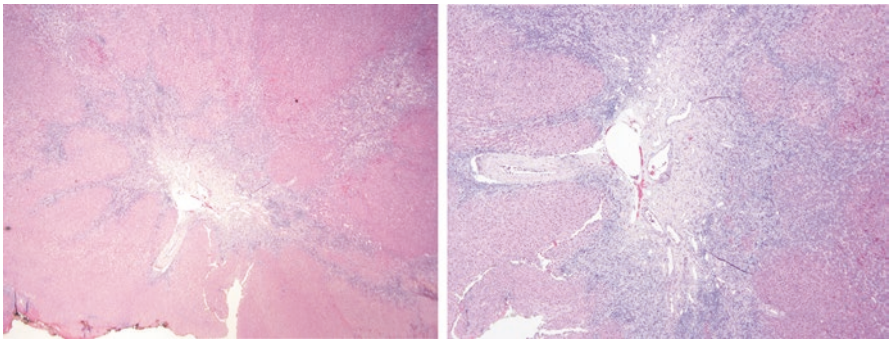

Fig. 8.4 Focal nodular hyperplasia showing central scar and fibrous septa with arteriolar vessels and proliferating bile ductules, without intact bile ducts. Benign-appearing hepatocytes in the nodules

FNH are characterized by nodular hyperplastic parenchyma, with nodules surrounded by fibrous septa. Bile ductular proliferation, from hepatocyte metaplasia, is usually featured prominently along the fibrous septa along with malformed vascular structures. Sinusoids and Kupffer cells are typically present. There may be a mild degree of macrovascular steatosis present (Fig. 8.4).

Management

Treatment of FNH is rarely required, as these tumors often do not cause symptoms and are not associated with significant complications. Surgical resection should only be reserved for patients with growing lesions or those who are symptomatic from very large or pedunculated tumors. Less invasive modalities, such as chemoembolization and ablation, which are associated with lower risk of morbidity than hepatic resection, have also been utilized in certain patients according to center expertise and experience.

Hepatic Adenoma

Epidemiology

Hepatic adenomas (HA) are uncommon benign neoplasms, composed of hepatocytes. They predominantly occur in women, with female/male ratio of 8:1, usually within their childbearing years. In the vast majority of patients (70%), adenomas are solitary; however multiple adenomas have also been described. Hepatic adenomatosis is a specific clinical entity characterized by the presence of ten or more adenomas and can be associated with presence of germline mutations and glycogen storage diseases.

HAs are strongly associated with use of sex hormones, especially oral contraceptives (or anabolic steroids), in approximately 90% of patients. The association between oral contraceptives (OCPs) and development of HAs was first described in 1973 [11] and has since been confirmed by multiple subsequent studies [12–16], which have also demonstrated a correlation between development of HAs and dose and duration of OCP use. The highest risk for development of HAs occurred in women over 30 years of age, with prolonged OCP use (greater than 25 months), and those taking OCPs with a high estrogen component [13].

Other risk factors for development of HAs include glycogen storage diseases (types 1a and III) and, less commonly, pregnancy, metabolic syndrome, obesity, and diabetes. The association between pregnancy and hepatic adenomas is thought to be due to increased presence of endogenous sex hormones [17].

Clinical Presentation

HAs are highly variable in size. They may present with symptoms, such as abdominal mass or pain. In approximately half the cases, they are found incidentally on abdominal imaging. Rarely, they may present with complications such as rupture, intraperitoneal hemorrhage, or development of hepatocellular carcinoma.

Pathogenesis

HAs result from the monoclonal proliferation of well-differentiated hepatocytes and can now be classified based on the type of mutations they harbor as shown by molecular analysis [18].

One group of HAs is defined by the presence of hepatocyte nuclear factor-1α (HNF1α) mutations in tumor cells. These account for 30–40% of all HAs. Patients with germline mutations of HNF1α are predisposed for development of hepatic adenomatosis. This gene is involved in hepatocyte differentiation, as well as lipid

and glucose metabolism. Therefore, HAs with HNF1α mutations frequently demonstrate lipogenesis, which can aid in their classification on radiological tests. A second group of HAs are inflammatory adenomas which account for approximately 40–50% of all adenomas. The hallmark of inflammatory adenomas is activation of the JAK/STAT pathway. Obesity and high alcohol consumption are for additional risk factors for development of inflammatory adenomas, but not the other subtypes. A third group includes β-catenin-mutated adenomas, which comprise approximately 10% of all HAs. Presence of β-catenin mutations and HNF1α is mutually exclusive; however half of β-catenin-activated adenomas are also inflammatory. HA with β-catenin mutations are associated with a high risk for malignant transformation [19]. Lastly, up to 10% of all HAs remain unclassified, lacking previously described mutations or inflammatory features [18].

Natural History

The natural history of HAs is not well defined. They can however be associated with significant complications, including bleeding and malignant transformation. The risk of these complications is correlated with the size of the tumor, with lesions >5 cm in size conferring the greatest risk. The risk of malignant transformation is difficult to ascertain, but is estimated to be between 4% and 8%, based on the largest published series [18–21]. The main risk factors for development of malignant transformation include β-catenin mutation and male sex. The natural history of HAs may also be influenced by continued use of OCPs or androgens which increase the risk for growth in size and number of HAs and bleeding risk. Conversely, regression of adenomas has been observed following discontinuation of OCPs [22].

Diagnosis

HA are most often found on diagnostic imaging studies, either incidentally or directed by the patient's symptoms or presentation. Although multiple imaging modalities are available for detection of HAs, including ultrasonography and computed topography (CT), which can also identify complications such as intratumoral hemorrhage or necrosis, MRI is the most thorough noninvasive radiological modality available for both diagnosis and characterization of HAs, as well as allowing differentiation from other neoplasms, including FNH (Fig. 8.5).

Specific features on MRI (Fig. 8.6) can also allow distinction between the two most common types of HA, HNF1α-inactivated and inflammatory HAs, with a high degree of sensitivity and specificity [23]. Contrast-enhanced ultrasonography can also be useful for both characterization and surveillance of HAs.

Serum biochemical tests are usually normal, often including serum AFP. A rise in the serum AFP level should raise suspicion for malignant transformation. Elevated

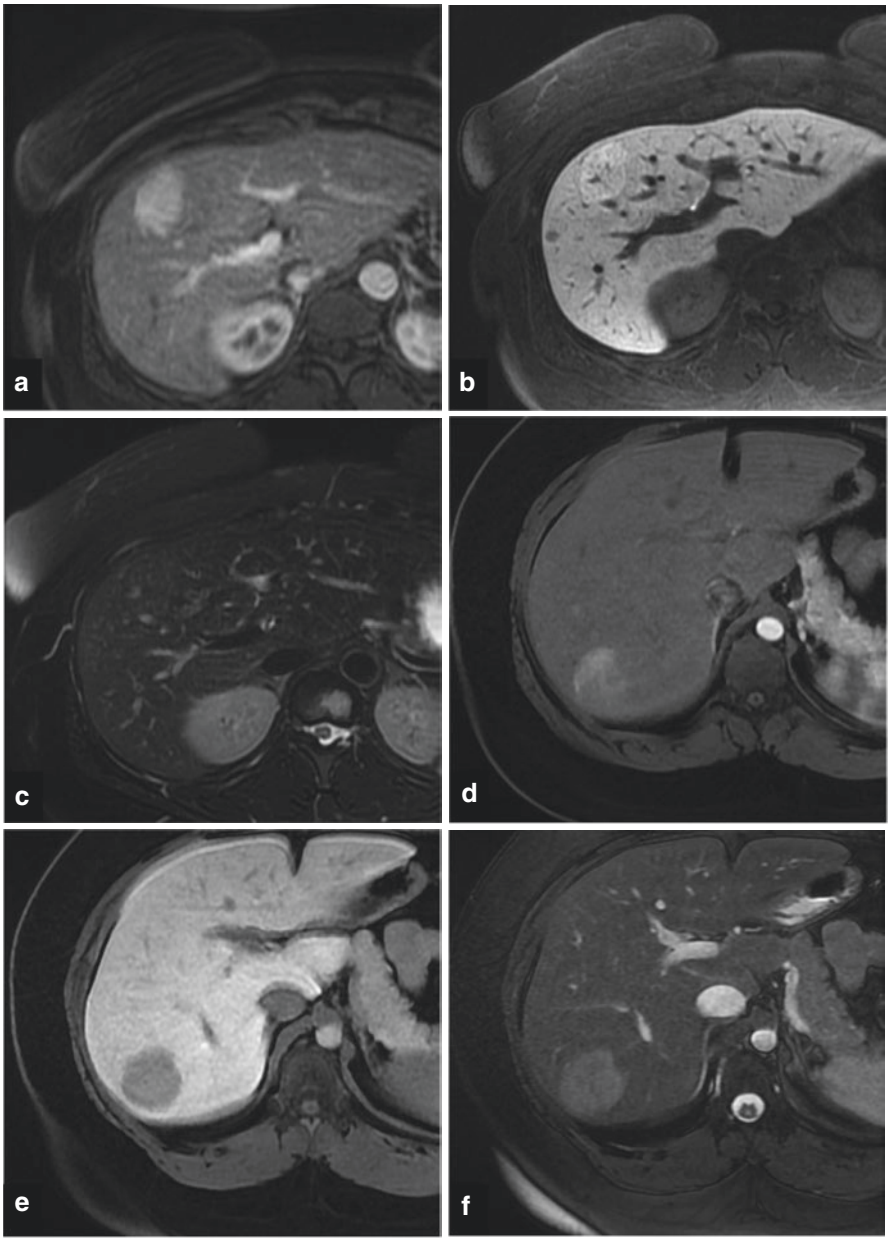

Fig. 8.5 A 40-year-old female with FNH on MRI (**a**–**c**) and 31-year-old female with adenoma on MRI (**d**–**f**). (**a**, **d**) Late arterial phase images demonstrate intense enhancement of FNH (**a**) and lesser degree of enhancement of adenoma (**d**). (**b**, **e**) 20-minute delayed images with liver-specific contrast agent show classic hyperintensity of FNH to normal hepatic parenchyma (**b**), while adenoma is typically hypointense to normal hepatic parenchyma in this phase (**e**). (**c**, **f**) T2-weighted images show isointensity of FNH to hepatic parenchyma (**c**) while adenoma can be hyperintense (**f**)

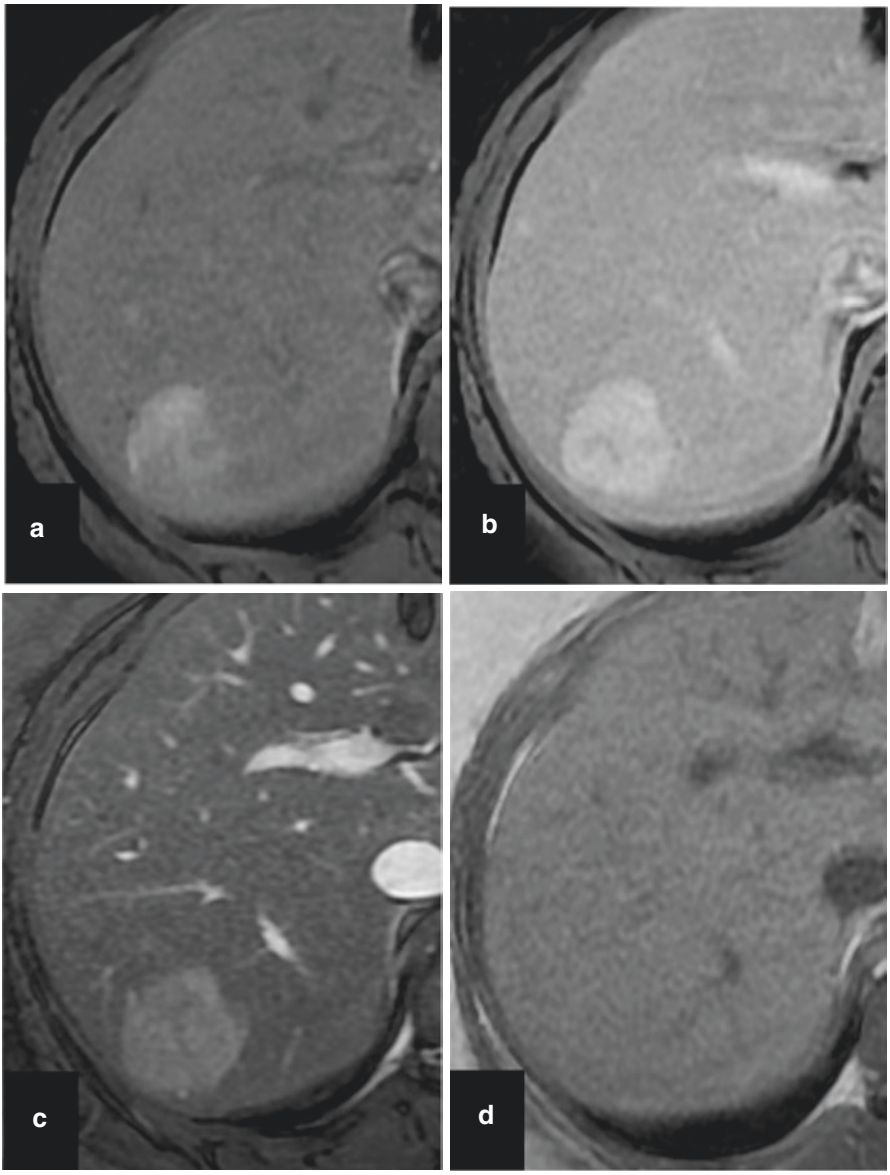

Fig. 8.6 A 31-year-old female with inflammatory adenoma (**a**–**e**) and 29-year-old female with HNF-1$^{\alpha}$ adenoma (**f**–**j**). Each of these patients underwent surgical resection, and these pre-resection MRI images demonstrate distinguishing features between these subtypes of adenomas. (**a**, **f**) Late arterial phase imaging shows hyperenhancement of inflammatory adenoma (**a**), while the HNF-1$^{\alpha}$ adenoma enhances similar to the hepatic parenchyma (**f**). (**b**, **g**) Portal venous phase imaging demonstrates maintained enhancement of the inflammatory adenoma (**b**), while the HNF-1$^{\alpha}$ adenoma washes out relative to parenchyma (**g**). (**c**, **h**) T2-weighted imaging shows hyperintensity of the inflammatory adenoma (**c**), while the HNF-1$^{\alpha}$ adenoma is isointense to mildly hyperintense (**h**). (**d**, **i**) In-phase and (**e**, **j**) out-of-phase imaging demonstrates isointensity of each subtype of adenoma to parenchyma on in-phase images (**d**, **i**), while on out-of-phase images, the inflammatory adenoma maintains signal due to lack of intralesional lipid (**e**, note liver parenchyma loses signal due to steatosis), while the HNF-1$^{\alpha}$ adenoma loses signal due to the presence of intralesional lipid (**j**)

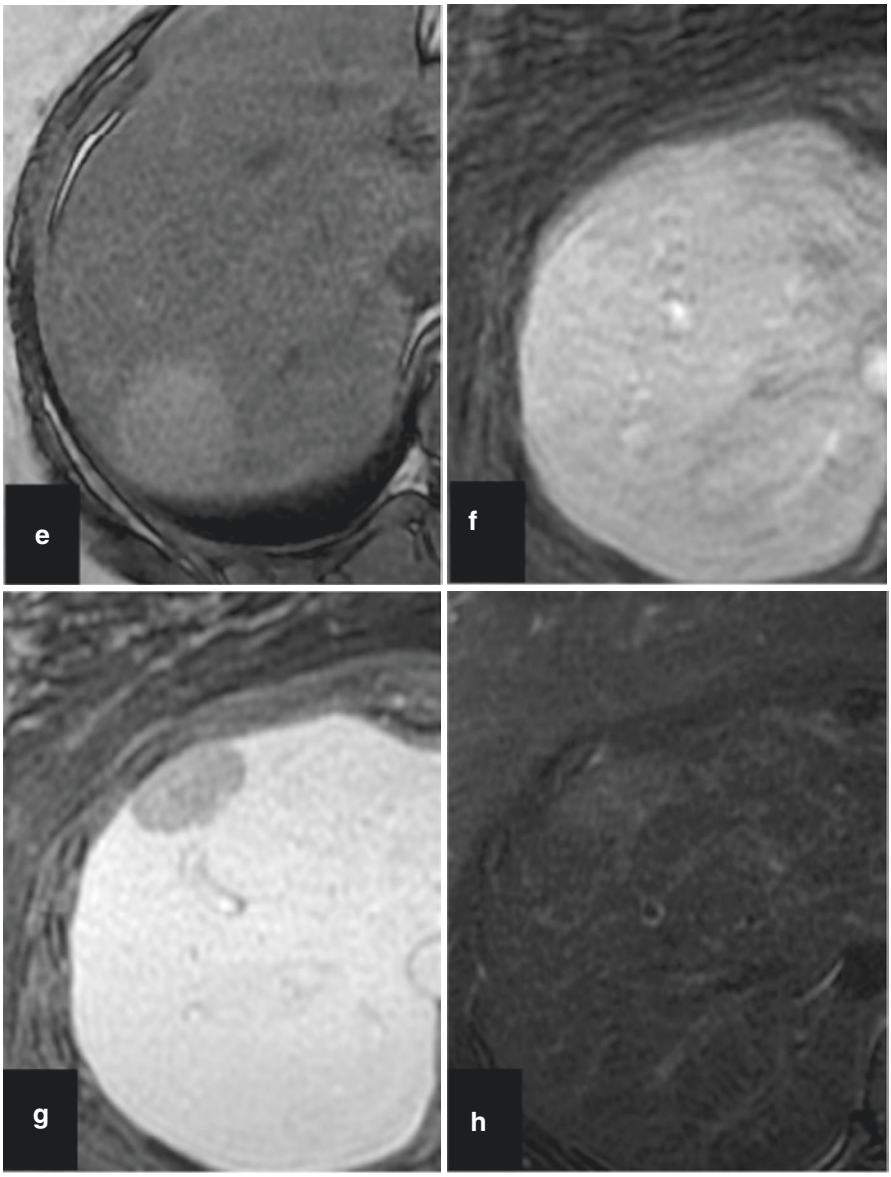

Fig. 8.6 (continued)

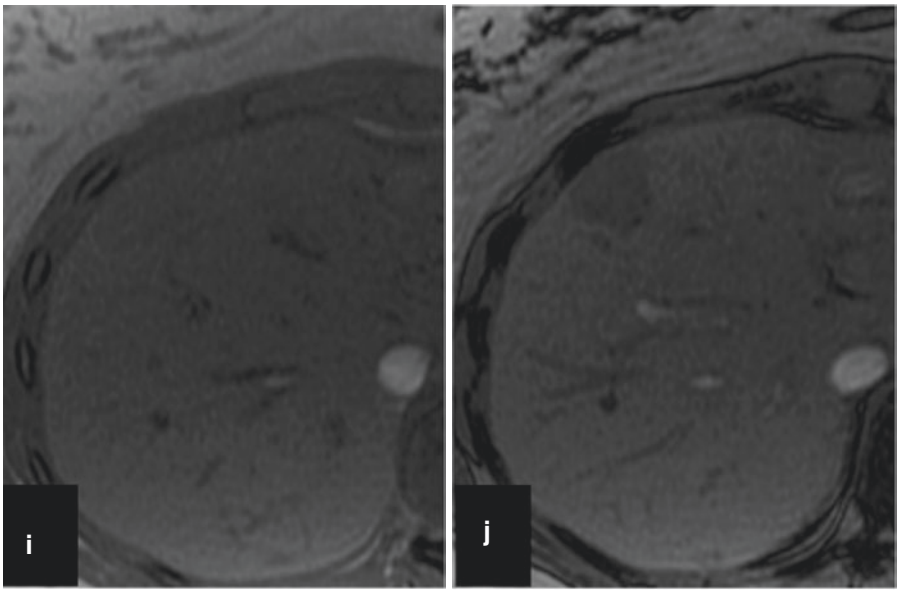

Fig. 8.6 (continued)

alkaline phosphatase and GGT may be observed in patients with hepatic adenomatosis.

A histological diagnosis of HA can be made following surgical resection of the lesion or with percutaneous biopsy of lesion. Historically, percutaneous biopsy of adenomas has been avoided given the risk of bleeding associated with needle biopsy and the scarcity of tissue which may be insufficient to be of diagnostic value. More recently, however, molecular classification of HAs, using immunohistochemical stains, performed routinely by pathologists, can provide valuable information which can guide future prognostication and management. Microscopically, HAs have a well-organized structure with hepatocytes arranged in sheets and cords, one to two cells in width, with prominent arteries, but lacking portal tracts and bile ductules (Fig. 8.7). This feature helps distinguish adenomas from FNH. Fibrosis is usually absent, although the background liver may demonstrate steatosis, steatohepatitis, or glycogen storage disease. Histologically, distinguishing hepatic adenoma from well-differentiated hepatocellular carcinoma can be challenging and requires an experienced hepatopathologist.

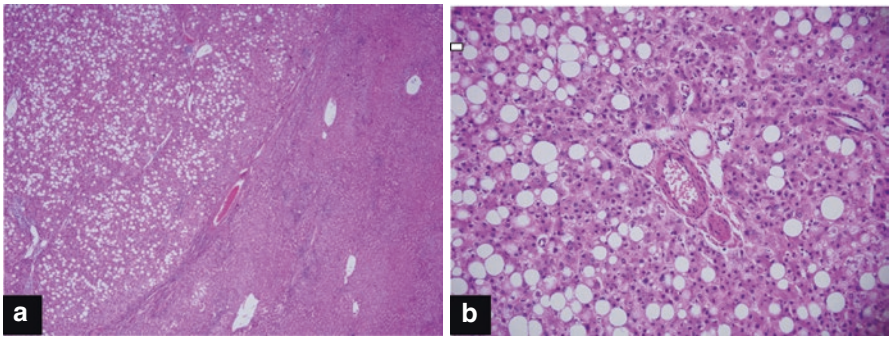

Fig. 8.7 (**a**) Hepatic adenoma characterized by well-circumscribed demarcated mass without a capsule. Hepatocytes within the lesion appear normal, some containing fat vacuoles (steatosis) in contrast to the non-tumoral hepatocytes seen on the right. (**b**) Within the lesion, numerous thin-walled unpaired arterioles without accompanying bile ducts. Portal tracts are absent

Management

There are no established guidelines for management of HAs, given the heterogeneity of this condition. Treatment decisions depend on the patient's sex, symptoms, family planning preferences, as well as tumor size, number, and location. Discontinuation of OCPs or androgens is recommended in all patients following diagnosis of HA which may allow regression of tumor(s) and may avoid need for intervention in some patients. Surgical resection is recommended for patients with large HAs, exceeding 5 cm, given the increased risk for bleeding. For male patients, HAs should be excised, regardless of size, due to increased risk for malignant transformation. For asymptomatic women with small HAs, <5 cm, surveillance imaging study should be sought in 6–12 months following discontinuation of OCPs to assess for regression. Follow-up on imaging should be continued, at least yearly, for patients who do not have complete regression of their adenomas. Indication for treatment, either by resection or ablation, will be influenced by the presence of β-catenin mutation affecting tumor cells as well as any evidence of pathological atypia on biopsy. Treatment should also be considered for patients with adenomas that grow despite withdrawal of hormonal therapy or tumors that have radiological features concerning for hepatocellular carcinoma.

Pregnancy is not contraindicated in patients with HAs; however close follow-up with surveillance ultrasonography is recommended. As the behavior of HAs, under the influence of hormonal changes associated with pregnancy, is unpredictable, resection or ablation of the adenoma, particularly for lesions >2 cm in size, should be considered prior to attempting pregnancy.

Patients with ruptured adenomas can present acutely with shock related to intraperitoneal bleeding and abdominal pain. Immediate management includes resuscitation and arterial embolization to control bleeding, followed by surgical resection.

Liver transplantation is rarely indicated, but may be appropriate for select patients with hepatic adenomatosis, development of complications such as hepatocellular carcinoma, or when complete excision is not feasible.

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Chapter 9
Pancreatic Cystic Neoplasms in Women: Mucinous Cystic Neoplasms, Serous Cystadenomas, and Solid Pseudopapillary Neoplasms

Harkirat Singh and Asif Khalid

Abbreviations

CEA	Carcinoembryonic antigen
CT	Computed tomography
EUS	Endoscopic ultrasound
HGD	High-grade dysplasia
IPMN	Intraductal papillary mucinous neoplasms
MCN	Mucinous cystic neoplasm
MRI	Magnetic resonance imaging
PC	Pancreatic cyst
PNET	Pancreatic neuroendocrine tumor
SCA	Serous cystadenoma
SPN	Solid pseudopapillary neoplasm

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Question 1: Doctor, do I have pancreatic cancer?

Answer 1: Pancreatic cysts are very common in the general population. Some pancreatic cysts can be precancerous, but a very small percentage of cysts develop cancer. We need to figure out the exact kind of cyst you have and then determine if there is any risk of cancer or not.

The reported prevalence of incidentally detected pancreatic cysts in the American population is 12.6%, with a pooled prevalence of 25% when considering MRI-based studies. Mucinous cysts are the most common pancreatic cysts. Based on a systematic review of 22 studies, the estimated incidence of invasive cancer in mucinous cysts on follow-up, based on imaging studies, was found to be 0.24% per year.

Tests used to evaluate a pancreatic cyst include cross-sectional imaging, e.g., CT and MRI, and endoscopic ultrasound. Endoscopic ultrasound can be used to obtain fluid from a pancreatic cyst through needle aspiration which can be evaluated for abnormal cells (cytology), tumor marker levels (CEA), and DNA mutations.

Question 2: Do I need surgery for a mucinous cystic neoplasm?

Answer 2: Mucinous cystic neoplasms have malignant potential, and it is usually recommended to have these surgically removed. Surgical resection is generally curative. While some small low-risk mucinous cystic neoplasms can be surveyed, we can discuss that further, but first we need to make sure that you have the correct diagnosis.

Question 3: Do I need surgery for a serous cystadenoma?

Answer 3: Serous cystadenomas are benign lesions. No surgery or follow-up is required unless it becomes symptomatic. There is essentially zero chance of it becoming a cancer. But we need to make sure that you have the correct diagnosis.

Question 4: Do I need surgery for a solid pseudopapillary neoplasm?

Answer 4: Yes, solid pseudopapillary neoplasms are low-grade tumors, and it is recommended that they are removed surgically. But we need to make sure that you have the correct diagnosis.

Introduction

With the widespread use of abdominal cross-sectional imaging, accompanied by advancements in radiological technologies, there has been an increase in the detection of incidental pancreatic cysts [PCs]. The reported prevalence of incidentally detected PCs in asymptomatic American population is 12.6% [1]. Magnetic resonance imaging [MRI] is better at identifying and detailing characteristics of PCs, compared to computed tomography [CT] scans. Reported pooled prevalence on MRI-based studies is 24.8%, compared to 2.7% on CT scans [1]. The different types of PCs have different biological behavior. Correct identification is extremely important as the management strategies vary significantly and include no follow-up,

surveillance by imaging, or surgical resection. Making an accurate diagnosis of the type of PC is often challenging, and this topic has received an enormous amount of attention over the last decade. In this review, we will discuss the epidemiology, presentation, diagnostic approach, risk of malignant potential, and management of pancreatic mucinous cystic neoplasms [MCNs], serous cystadenomas [SCAs], and solid pseudopapillary neoplasms [SPNs]. These three types of pancreatic cystic lesions are more prevalent in women, compared to men.

Types of Pancreatic Cysts (PCs)

To get a good perspective, it is important to understand the different types of PCs. PCs are categorized as neoplastic and nonneoplastic (Table 9.1). Neoplastic cysts are further classified as "neoplastic other" and "neoplastic benign" cysts. The "neoplastic other" category includes neoplastic mucinous cysts (mucinous cystic neoplasms [MCNs] and intraductal papillary mucinous neoplasms [IPMNs]), pancreatic neuroendocrine tumors [PNETs], and solid pseudopapillary neoplasms [SPNs]. The "neoplastic benign" category includes serous cystadenomas [SCAs] [2]. The nonneoplastic cysts include inflammatory cysts related to pancreatitis (pseudocysts and walled-off necrosis), lymphoepithelial cysts, squamoid cysts, true cysts, and retention cysts. Neoplastic mucinous cysts (IPMNs and MCNs) constitute the majority of the PCs [3].

Important Clinical Questions

Among the different types of PCs, IPMNs are the most common, followed by MCNs. In contrast, SCAs are less common and SPNs are rare. Of these, mucinous cysts (IPMNs and MCNs) and SPNs have malignant potential, while SCAs are considered benign. The natural history of malignant degeneration of these cysts is not well characterized, but only a small percentage of these develop malignancy. As such, in the absence of features concerning for malignancy, the majority of patients

Table 9.1 Nomenclature of pancreatic cysts

Neoplastic benign	*Serous cystadenomas*
Neoplastic other	Neoplastic mucinous (intraductal papillary mucinous neoplasms and *mucinous cystic neoplasms*), pancreatic neuroendocrine tumors, and *solid pseudopapillary neoplasms*
Nonneoplastic cysts	Inflammatory cysts related to pancreatitis (pseudocysts and walled-off necrosis), lymphoepithelial cysts, squamoid cysts, true cysts, and retention cysts

Neoplastic cyst nomenclature based on the Papanicolaou Society of Cytopathology guidelines [2]

with PCs will not be referred for surgery. On the other hand, pancreatic malignancy has poor prognosis, and due to the small risk of cancer in PCs, most patients will need some form of surveillance. This can be anxiety provoking to both patients and physicians. Therefore, the main clinical dilemmas include how to accurately identify neoplastic cysts from nonneoplastic cysts and, secondly, how to reliably determine which neoplastic cysts harbor cancer or high-grade dysplasia (HGD). Pancreatic cancer and HGD constitute "advanced neoplasia."

Epidemiology and Symptoms

MCN

MCNs occur in females and are usually incidentally discovered on imaging between ages of 40 and 60. A minority of the patients are symptomatic. Symptoms can include vague abdominal pain, heaviness or fullness, abdominal mass, nausea, vomiting, recurrent pancreatitis, or jaundice [4]. These symptoms are mainly associated with larger MCNs (>4 cm).

SCA

Around three-fourth of the SCAs occur in females, mostly in elderly women. These are also usually found incidentally. In a large study of over 2600 SCA patients, median age of diagnosis was 58 years, with 61% patients being asymptomatic, and 27% had non-specific abdominal pain [5]. SCAs are less common than neoplastic mucinous PCs (MCNs and IPMNs). In a large surgical series, SCAs comprised 16% of 851 PC resections, whereas MCNs and IPMNs were 23% and 38%, respectively [6]. Based on a prospective study of 225 patients who underwent an EUS exam with PC sampling for ancillary studies and genomic analysis, including 41/225 patients with confirmed surgical pathology, 30/225 (13.3%) patients were thought to have an SCA, and 159/225 (70.6%) had mucinous cysts (IPMNs and MCNs) [7]. SCAs are found with increased frequency in patients with von Hippel-Lindau disease [8, 9].

SPN

SPNs are rare pancreatic cystic tumors, which are predominantly found in young women (female to male ratio ~10:1), with the mean age of diagnosis at 22 years [10]. Designated by the World Health Organization as SPN [11], these lesions have previously been known as solid and papillary tumor, Frantz tumor, solid-cystic tumor, papillary cystic tumor, and solid and papillary epithelial neoplasm. The most

frequent presenting symptom is abdominal pain [12]. Since the lesion can grow significantly, other symptoms may include a palpable abdominal mass, jaundice, pancreatitis, early satiety, nausea, vomiting, and back pain [13].

Diagnosis

Currently, the diagnosis of PCs is made based on cross-sectional imaging results (MRI and CT), endoscopic ultrasound [EUS] imaging, and ancillary testing including cyst fluid cytopathology and carcinoembryonic antigen [CEA] levels. As mentioned previously, MRI is better at identifying and detailing characteristics of PCs, compared to CT scans. Since an MRI is noninvasive and does not require radiation, it is the first step in the evaluation of a PC. For patients who have a contraindication to MRI testing, a pancreatic protocol CT scan can be utilized. The accuracy of MRI in making an accurate diagnosis ranges from 50 to 86%, and its accuracy in differentiating benign from malignant lesions is 55.6–87% [14]. Thus, cross-sectional imaging is often not sufficient to make the correct diagnosis.

EUS provides high-resolution imaging of PCs, with details of cyst morphology. Though better than MRI, there is interobserver variability, and morphological appearance does not accurately distinguish between type of PCs and presence of advanced neoplasia [15, 16]. In addition to enhanced imaging, EUS allows an endoscopist to insert a needle into the PC under ultrasound guidance and obtain PC fluid and cyst wall samples (fine needle aspiration [FNA]), for cytopathological exam and determination of cyst fluid CEA levels. A recent meta-analysis showed a pooled sensitivity of 54% for detection of neoplastic mucinous cysts based on FNA cytology [17]. Though the specificity of cytology for malignancy approaches 100%, the sensitivity ranges from 25 to 88%, due to poor cellularity of the cyst fluid [15, 18–20]. In a landmark study by Brugge et al., a cyst fluid CEA level of greater than 192 ng/mL showed an accuracy of 79% in differentiating mucinous (IPMNs and MCNs) from non-mucinous cysts (SCAs and nonneoplastic cysts). This accuracy was more than that of EUS morphology, or cytology, or a combination of EUS morphology, cytology, and CEA together. Thus, fluid cyst CEA became the most accurate test available in diagnosis of mucinous vs non-mucinous cysts [21]. PC fluid CEA level, however, does not differentiate an MCN from an IPMN and does not provide information regarding the presence or absence of advanced neoplasia (HGD and cancer).

In view of the diagnostic limitations of currently used modalities to evaluate PCs, there has been considerable research focusing on biomarkers that can accurately identify pancreatic cysts and predict presence of advanced neoplasia. Even though the PC fluid is poor in cellularity which compromises utility of cytopathology, new molecular techniques have enabled investigators to isolate DNA, RNA, proteins, and metabolites from the exfoliated and lysed cells within the PC fluid. Whole exome sequencing of resected PCs led to discovery of mutation profiles associated with specific cyst types and in cysts with cancers. For example, *KRAS* and *GNAS* mutations are related to IPMNs, whereas MCNs have *KRAS* but are devoid of *GNAS*

mutations. Similarly, VHL mutations were found exclusive to SCAs. *TP53*, *PIK3CA*, *PTEN*, and *AKT1* mutations are related to IPMNs with advanced neoplasia (HGD or pancreatic cancer) [22–24]. Our group showed the utility of DNA testing in PC fluid to identify mucinous cysts and PC with advanced neoplasia [25, 26]. Since then, newer technologies like next-generation sequencing (NGS) have been shown to identify genetic alterations in DNA isolated from PC fluid, in a reproducible and cost-effective manner. In a recent large prospective study where NGS for a panel of mutations was performed on preoperative PC fluid samples, with final surgical pathology available, presence of *KRAS/GNAS* mutations in the preoperative samples had 89% sensitivity and 100% specificity for diagnosis of mucinous cysts. In addition, *KRAS/GNAS* combined with mutations in cancer-related genes (*TP53/PIK3CA/PTEN*) had a sensitivity and specificity of 89% and 100%, respectively, for detection of advanced neoplasia. Multiple studies have shown poor sensitivity and specificity of current guidelines to detect advanced neoplasia. The lower accuracy is due to the guidelines being formulated based on results of cross-sectional imaging, EUS, and ancillary studies limited to CEA levels and cytopathology, which all have limitations in their accuracies [7, 27]. Currently, PC fluid DNA analysis has not been incorporated in the clinical practice of most centers. Table 9.2 compares characteristics of different pancreatic cystic lesions.

Table 9.2 Summary of differences in the characteristics of mucinous cystic neoplasms, serous cystadenomas, and solid pseudopapillary neoplasms

	Mucinous cystic neoplasm	Serous cystadenoma	Solid pseudopapillary neoplasm
Epidemiology	Females, between ages 40 and 60	~75% in females, usually elderly	>90% in females, in the third decade
Typical imaging	Unilocular cyst in the pancreatic body or tail, can have septations and calcifications in the cyst wall	Spongelike or honeycomb appearance, central calcific scar is pathognomonic	Encapsulated with solid-cystic appearance with areas of hemorrhage
Cyst fluid CEA levels	Usually elevated (>192 ng/mL)	Usually very low (<5 ng/mL)	No correlation
Cyst fluid viscosity and appearance	Viscous, string-sign positive, appears like mucin	Thin and bloody, string sign negative	Thin and bloody
Cytopathology	Columnar mucin-producing cells surrounded by ovarian stroma	Single layer of glycogen-rich cuboidal cells	"Pseudopapillary" appearance in myxoid stroma Necrosis, hemorrhage, and irregular calcifications
DNA biomarkers	Positive *KRAS*, *RNF 43* Absent *GNAS* *TP53*, *PIK3CA*, *PTEN*, *CDKN2A*, and *SMAD4* indicate advanced neoplasia	Positive *VHL* Absent *KRAS*, *GNAS*, *TP53*, *PIK3CA*, *PTEN*, *CDKN2A*, and *SMAD4*	Positive *CTNNB1*

CEA carcinoembryonic antigen

MCN

(a) Cross-sectional imaging and EUS
Most MCNs are single, thin-walled, unilocular cysts, with over 90% located in the body and the tail of the pancreas. Occasionally, they can be septated and can have calcifications in the cyst wall. They do not communicate with the main pancreatic duct. EUS-FNA cyst fluid is usually viscous, but a thin fluid doesn't rule out an MCN. EUS can better evaluate presence of a solid mass, mural nodule, and thickened/irregular wall, which can point toward presence of malignancy or high-grade dysplasia [8]. Figure 9.1 shows representative CT scan, EUS, and gross pathology images of an MCN.

(b) Cyst fluid CEA level
CEA levels in the cyst fluid of MCNs are usually elevated [28].

(c) Cytopathology
MCNs are lined by inner layer of columnar, mucin-producing cells, surrounded by an outer layer, which is densely cellular and has ovarian-type stroma [9]. In our practice, it is rare to observe typical cytopathological features on EUS-guided FNA samples.

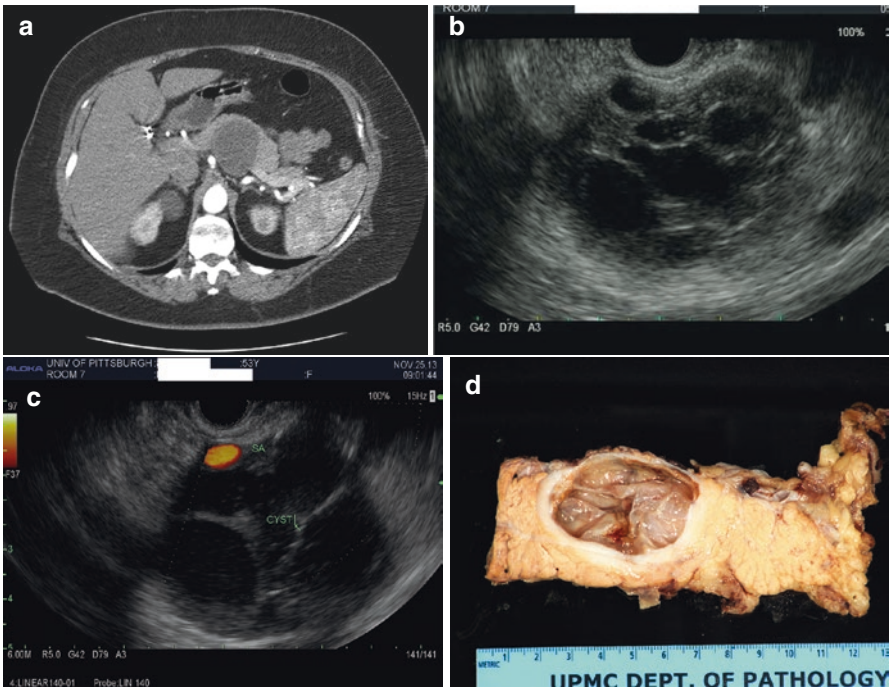

Fig. 9.1 (**a**) CT scan from a 58-year-old female with a 5 cm cyst in the pancreatic body. (**b**) EUS image of the same cyst showing a typical septated MCN. (**c**) Doppler showing splenic artery (SA) running at the cyst margin. (**d**) Gross surgical specimen after a distal pancreatectomy. Pathology showed a 5.5 cm MCN with low- to intermediate-grade dysplasia

(d) DNA-based biomarkers
The most common mutation seen in MCNs is an activating *KRAS* mutation, which is similar to IPMNs. *RNF43* gene mutations are seen in 8–26% of MCNs. In contrast to IPMNs, MCNs do not carry *GNAS* mutations. Presence of mutations in *TP53*, *PIK3CA*, *PTEN*, *CDKN2A*, and *SMAD4* points toward advanced neoplasia being present (pancreatic cancer or HGD) [22, 27].

(e) Differential diagnoses
The main differential diagnosis of an MCN is an IPMN. Other less likely possibilities include cystic PNET, SCA, or a nonneoplastic cyst. IPMNs can be differentiated by presence of communication with the main pancreatic duct or a side branch, best visualized on MRCP. They are also often seen in the head of the pancreas and can be present as multiple cysts, whereas MCN is typically a single lesion. IPMNs are also present in males and females, whereas MCNs are exclusive to females. *GNAS* mutations are absent in MCNs and can be present in IPMNs. *VHL* mutations are absent in MCNs and IPMNs and are only associated with SCAs.
Summary: A single, asymptomatic, unilocular PC in a female between 40 and 60 years of age, located in the body or the tail of the pancreas, without communication with the pancreatic duct, with elevated fluid cyst CEA levels, and with presence of *KRAS* and absence of *GNAS* mutations, will comprise a typical scenario of an MCN. Of note, in many instances, it is impossible to differentiate an MCN from an IPMN without definitive surgical pathology.

SCA

(a) Cross-sectional imaging and EUS
SCAs can be present anywhere in the pancreas and classically appear like a collection of multiple tiny cysts separated by thin septa giving it a "spongelike" or "honeycomb" appearance. Thus, these are also called microcystic adenomas. A scar-like area can be present at the center of the lesion, which, when calcified, is considered pathognomonic. SCAs do not communicate with the pancreatic ducts. Macrocystic, mixed macrocystic and microcystic (oligocystic), and rarely solid variations are also observed [5]. Small-sized lesions can appear similar to a solid mass on cross-sectional imaging, but the cystic nature can be discerned on an EUS exam. EUS-guided aspirate usually shows thin, nonviscous fluid, which can be bloody [8]. Figure 9.2 shows representative EUS and MRCP images of SCAs.

(b) Cyst fluid CEA level
SCAs typically have very low cyst fluid CEA level (<5 ng/mL) [28].

(c) Cytopathology
SCAs are defined by cysts lined by a single layer of cuboidal or flattened epithelial cells. These cells are rich in glycogen and stain positive for periodic acid-Schiff, without diastase digestion [9].

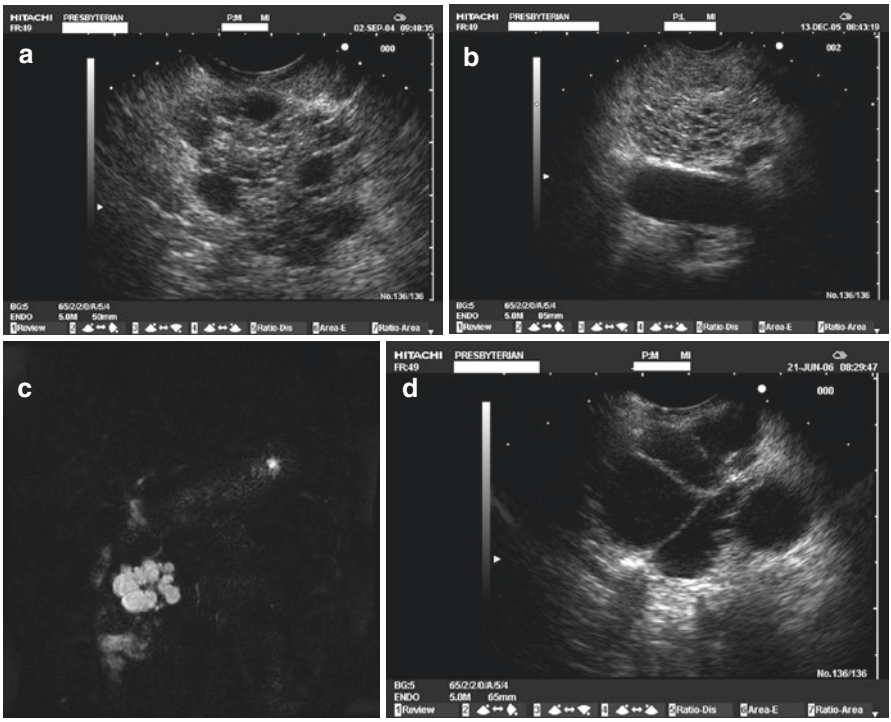

Fig. 9.2 (**a**) A typical EUS image of a microcystic SCA in a 43-year-old female. (**b**) Another typical EUS image of a microcystic SCA. (**c**) A 60-year-old female with MRCP showing a pancreatic head multicystic lesion that could represent branched-duct IPMN or an oligocystic SCA. (**d**) Follow-up EUS of (**c**) shows an oligocystic SCA

(d) DNA-based biomarkers
SCAs can frequently have mutations and/or deletions in the *VHL* tumor suppressor gene. SCAs do not harbor mutations in *KRAS*, *GNAS*, or *RNF43* genes or mutations related to advanced neoplasia (*TP53*, *PIK3CA*, *PTEN*, *CDKN2A*, and *SMAD4*) [27].

(e) Differential diagnoses
The differential diagnosis of an SCA mainly incudes IPMNs and MCNs. A typical image of a microcystic adenoma can differentiate an SCA from an IPMN or an MCN. However, oligocystic and macrocystic SCAs can be more challenging to diagnose with certainty. SCAs do not communicate with the pancreatic duct, in contrast to an IPMN. EUS-guided FNA yields a thin or bloody fluid with extremely low CEA levels. In contrast IPMNs and MCNs usually have viscous fluid and high CEA levels. Also, SCAs are characterized by *VHL* gene alterations, which are absent in both MCNs and IPMNs. Mutations in *KRAS*, *GNAS*, and *RNF43* genes are absent in SCAs, which further helps differentiating them from IPMNs and MCNs.

Summary

A single, asymptomatic cystic lesion, in an elderly female, with honeycomb or spongelike appearance, almost clinches the diagnosis of an SCA. An extremely low cyst fluid CEA level and presence of *VHL* gene alteration confirm the diagnosis.

SPN

(a) Cross-sectional imaging and EUS

On cross-sectional imaging, SPNs are usually seen as encapsulated lesions with both solid and cystic component, including hemorrhage, and without any septations. EUS exam usually shows a well-demarcated, hypoechoic, and heterogenous solid lesion with cystic areas. About 20% of the lesions can have irregular calcifications [8, 13, 29]. The solid and mixed solid-cystic varieties are more common than purely cystic lesions. Occasionally the hemorrhagic component can comprise the entire lesion and can give appearance of a purely cystic lesion [9]. SPNs are mostly located in the body or tail of the pancreas. EUS-guided sampling usually shows a bloody aspirate. Figure 9.3 shows representative CT and EUS images of SPNs.

(b) Cyst fluid CEA level

There is insufficient data to correlate CEA levels with an SPN diagnosis.

(c) Cytopathology

SPNs are characterized by presence of extensive necrosis with preserved tissue architecture in the periphery of the lesion, under the fibrous capsule. Uniform polyhedral cells are loosely arranged around fibrovascular stalks with small vessels, giving it a pseudopapillary appearance. The stroma shows variable hyalinization with degeneration, e.g., hemorrhage, foamy macrophages, cholesterol clefts, and calcifications. Glycogen and mucin are absent. It is important to obtain EUS-guided sampling from the solid component. Unlike other pancreatic cysts, samples from EUS are sufficient to make an accurate diagnosis in 75–100% of the cases, based on histological appearance and immunohistochemistry [13, 29, 30]. Immunohistochemistry is usually performed to distinguish SPNs from PNETs and acinar cell cancer. SPNs are positive for beta-catenin, vimentin, CD10, and CD56 [13].

(d) DNA-based biomarkers

SPNs appear to be devoid of significant DNA alterations with the exception of mutations in the oncogene *CTNNB1*. Rarely, *TP53* and *PIK3CA* alterations are present. Mutations in *KRAS*, *GNAS*, *RNF43*, and *VHL* genes, which are related to IPMNs, MCNs, and SCAs, are absent in SPNs [23, 27].

(e) Differential diagnoses

Major differentials of an SPN are PNETs and walled-off pancreatic necrosis [WOPN]. Usually, an SPN has more of a solid and solid-cystic nature compared to PNETs and WOPN. These are usually not preceded by an attack of necrotizing pancreatitis, as is a WOPN. SPNs are also larger in size (>4 cm) at time of diagnosis compared to a PNET. EUS-guided sampling shows a typical pseudo-

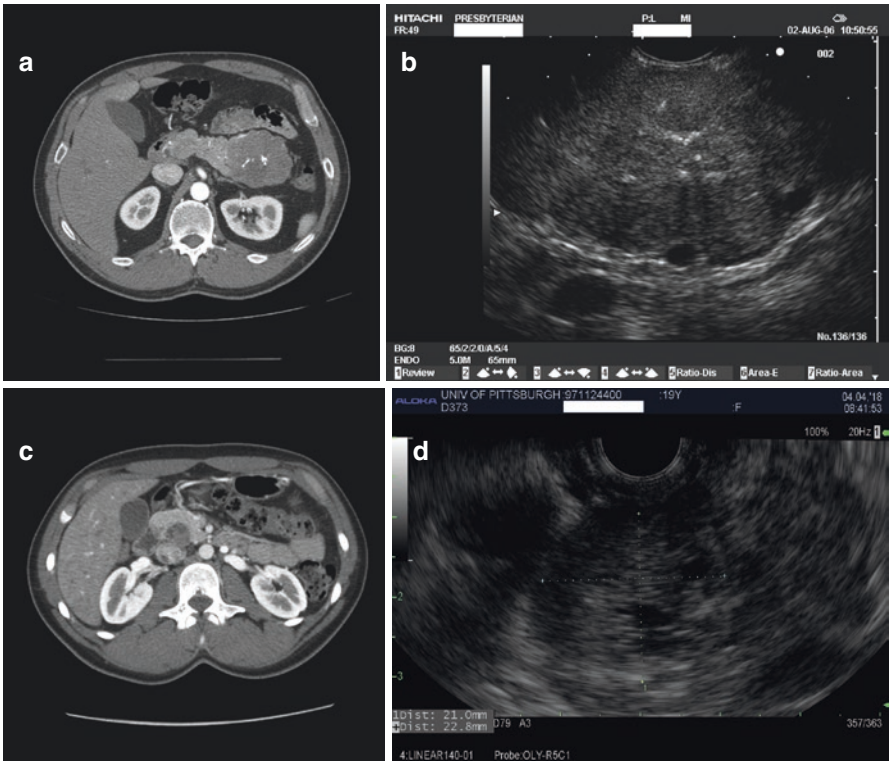

Fig. 9.3 (**a**) CT with a large solid lesion with irregular calcifications in the pancreatic tail. (**b**) EUS image of the lesion in (**a**), FNA consistent with an SPN. (**c**) Solid-cystic lesion in the pancreatic head on CT of a 19-year-old female with abdominal pain. (**d**) EUS of the lesion in (**c**) showing a 2.2 cm solid-cystic mass. EUS-FNA showed an SPN with CTNNB1 mutation

papillary histopathology, and immunostaining is the most important test that differentiates them from PNETs.

Summary

A single, mixed solid-cystic lesion, without septations and with irregular calcifications, in the pancreatic body or tail, in a female, in her 20s, is highly suggestive of an SPN. A bloody aspirate on EUS-guided sampling, and cytopathology showing pseudopapillary pattern of cells in a background of myxoid stroma, with immunohistochemistry positive for beta-catenin and vimentin, confirms the diagnosis for a SPN.

Risk of Malignant Potential

MCNs and SPNs can become malignant. Unfortunately, there is little clarity regarding natural history of malignant transformation in MCNs. Most studies are surgical resection series, and the follow-up studies combine MCNs with IPMNs, since it is

frequently difficult to differentiate between them. SPNs are rare which makes prospective studies difficult. Moreover, they are usually large in size when diagnosed; thus data comes from surgically resected series.

MCN

MCNs have malignant potential. In a systematic review of 12 retrospective studies with a total of 603 patients, with surgically resected MCNs, the overall rate of invasive malignancy was 15% [15]. There was significant heterogeneity between these studies, and this review did not include studies which reported incidence of HGD or carcinoma in situ. We also believe that patient selection bias has led to the high 15% malignancy rate reported here, as lesions which are thought to harbor a malignancy are more likely to undergo surgical resection. In another review of 22 studies of imaging follow-up of mainly or exclusively mucinous cysts (IPMNs or MCNs), including 6240 patients, with 18,079 patient-years of follow-up, 42 invasive cancers were observed. This suggests an estimated incidence of invasive cancer on imaging follow-up to be 0.24% per year [15]. Certain features on imaging correlate with the presence of malignancy within a cystic lesion and are termed as high-risk features. These include a cyst size >3 cm, a dilated main pancreatic duct, and the presence of a solid component or intramural nodule associated with a cyst. In a recent systematic review, if surgically resected MCNs were <4 cm in size and were not associated with high-risk features, invasive cancer was seen in only 0.03% of the cases [4].

In summary, MCNs have malignant potential, but the rate of malignancy is much lower than thought earlier.

SCA

For practical purposes, SCAs are considered as benign lesions. Risk of malignant transformation of an SCA into a serous cystadenocarcinoma is extremely low. In a large study of SCAs, spanning over 25 years, with 2622 patients, only 3 (0.1%) cystadenocarcinomas were recorded [5]. Some other cases of SCAs reported as malignant in the literature do not fulfil the WHO diagnostic criteria [31]. There have been no deaths attributed to malignant behavior of an SCA [5, 32].

SPN

SPNs are considered low-grade tumors that have malignant potential. A small percentage of SPNs can have local invasion or metastasis at the time of diagnosis. A large systematic review of 2744 patients reported 1.6% patients with lymph node involvement, 4.6% with vascular involvement, and 7.7% with metastasis [33]. In surgical resection series, 15–16% of SPNs have been found to be malignant on pathology [34, 35].

Management

Management of PCs may consist of no follow-up, surveillance by imaging, or surgical resection. The primary goal is to first accurately identify the type of pancreatic cyst which dictates the appropriate management algorithm. As discussed above, this is often challenging. Once a diagnosis is confirmed, there is little controversy in the management of SCAs and SPNs. These are also relatively easier to diagnose based on currently available imaging modalities, EUS, and ancillary studies. On the other hand, the various guidelines have suggested a different approach to the management of MCNs by default, primarily due to the difficulty in differentiating a single small MCN (<3 cm) from a branched-duct IPMN [BD-IPMN]. In other words, a small mucinous PC can be a BD-IPMN or an MCN, and in many cases, the differentiation can only be possible at pathology, after a surgical resection. Hence, guidelines recommend applying IPMN surveillance protocols to mucinous lesions which cannot be definitively classified as a BD-IPMN or an MCN.

Since making an accurate diagnosis is challenging, and various guidelines provide different recommendations, any patient with a cyst with a questionable diagnosis or having high-risk features should be referred to a high-volume center with a multidisciplinary team approach in managing patients with PCs [36]. Review by a multidisciplinary group has shown to alter management in 30% of the patients [37]. Also, high-volume centers have lower mortality rates for pancreatoduodenectomies, compared to low-volume centers [38].

MCN

Surgical Management

The International Consensus Guidelines (2012, aka Fukuoka guidelines) recommend surgical resection of all MCNs irrespective of size, presence/absence of high-risk features, or symptoms [39]. This is based on the fact that MCNs have malignant potential, patients are younger at diagnosis, and non-operative surveillance includes years of imaging studies which are costly, inconvenient, and a source of anxiety for the patient [4, 39]. This approach is followed at most centers in the USA. A recent systematic review reported exceptionally low rate (0.03%) of invasive adenocarcinoma in resected MCNs that were <4 cm in size and devoid of high-risk features. Based on this new data, European Guidelines (2018) recommend surgical resection in symptomatic MCNs, any MCN >4 cm in size, and any MCN with a mural nodule irrespective of size. Surveillance is recommended for asymptomatic MCNs <4 cm in size and without a mural nodule. The American Gastroenterological Association (AGA) Guidelines (2015) recommend resection in mucinous cysts (IPMNs and MCNs), if they are associated with both a solid component and main pancreatic duct dilation (confirmed both on MRI and EUS) and/or with positive cytology (high-grade dysplasia or cancer) on EUS-guided FNA [40].

As MCNs are usually located in the body and tail of the pancreas, a distal pancreatectomy is usually performed. If there is high risk of presence of malignancy, an oncological resection is performed which includes lymph node dissection and splenectomy. For low-risk lesions, distal pancreatectomy with splenic preservation can be performed. Lesions in the body can require extended distal pancreatectomy. In some small-sized and low-risk cases, parenchyma-sparing surgeries like central pancreatectomy or enucleation can be performed, but these are associated with higher postoperative pancreatic fistula rates. Lesions in the head of the pancreas require pancreatoduodenectomy [4, 32, 39].

Surveillance

Surveillance should only be performed in patients that are fit for surgery, and surveillance should be discontinued if a patient no longer remains a surgical candidate [40]. The European Guidelines recommend surveillance of asymptomatic MCNs that are <4 cm in size and have no associated mural nodule. Surveillance intervals recommended are every 6 months for the first year and then annually, provided no changes are observed. For cyst size between 3 and 4 cm, factors like patient age, comorbidities, surgical candidacy, and patient preference can be analyzed to determine management. Due to some reports of faster growth of MCNs during pregnancy, and potential tumor rupture, these guidelines recommend close surveillance during pregnancy. For lesions <3 cm in size, where it is difficult to make a definitive diagnosis of an MCN, surveillance similar to an IPMN is recommended [32].

The American Gastroenterological Association (AGA) Guidelines recommend imaging surveillance in asymptomatic neoplastic cysts (IPMNs and MCNs) that do not have any of the three high-risk features (size >3 cm, associated solid component, and main pancreatic duct dilation). Surveillance includes an MRI at 1 year and, if stable, every 2 years thereafter for a total of 5 years. They recommend stopping surveillance at 5 years if there is no change in the cyst characteristics, a recommendation viewed as controversial in the gastroenterology community. EUS exam is recommended if a cyst has any two of the three high-risk features. If no concerning findings are evident on EUS, patients are placed back on MRI surveillance. EUS is also recommended if any high-risk feature develops during ongoing surveillance. All of these are conditional recommendations, with low quality of evidence.

The American College of Gastroenterology (ACG) Guidelines recommend surveillance of presumed mucinous cysts (IPMNs and MCNs) based on cyst size (Table 9.4). This surveillance is applicable to cysts without high-risk features. For cysts with high-risk features (obstructive jaundice, acute pancreatitis secondary to cyst, cyst-associated solid mass or solid mass in pancreatic parenchyma, main duct dilation >5 mm, cyst size >3 cm, change in main duct caliber with upstream atrophy, elevated serum Ca 19-9, increase in cyst size of >3 mm/year during surveillance, new-onset diabetes during surveillance, and cytology with high-grade dysplasia or cancer), EUS with FNA and/or referral to a multidisciplinary group is recommended. These recommendations are also based on low quality of evidence. Table 9.3 summarizes the criteria for surveillance, indications for EUS, and surgery in MCNs, from the major international guidelines. Table 9.4 summarizes recommended surveillance intervals of MCNs without any high-risk features.

Table 9.3 Summary of criteria for surveillance, indications for endoscopic ultrasound [EUS], and surgery in mucinous cystic neoplasm [MCN] from major international guidelines

Guidelines	Surveillance	Indications for EUS ± FNA	Indications for surgery
European 2018 [32]	Surgically fit candidates with size <40 mm and without any high-risk features like mural nodule Close surveillance during pregnancy since MCNs can grow in size faster and there is potential risk of tumor rupture Management of cysts 30–40 mm can be individualized based on patient age, comorbidities, surgical risk, and patient preference	For any clinical or radiological feature of concern To differentiate a mucinous cyst from a non-mucinous cyst by evaluating cyst fluid CEA, cytology, and *KRAS/GNAS* mutation analysis, if cyst type is unclear on standard imaging Contrast enhanced EUS can be performed to evaluate mural nodules as it is superior to conventional EUS	Any of the following: symptomatic cyst (pain, jaundice, pancreatitis, etc.) Size >40 mm Mural nodule irrespective of size High-grade dysplasia or cancer on cytology
American College of Gastroenterology 2018 [36]	Surgically fit candidates with cyst size <2 cm when cyst is presumed mucinous (IPMN or MCN) Surgically fit candidates with cyst size between 2 and 3 cm, if cyst is clearly mucinous (IPMN or MCN) Individualized approach in patients aged 76–85, including informed discussion regarding surgical candidacy	Cyst causing obstructive jaundice Cyst causing acute pancreatitis Associated solid mass Main duct dilation >5 mm Size >3 cm Change in main duct caliber with upstream atrophy Size between 2 and 3 cm, if cyst is not clearly a mucinous cyst (IPMN or MCN) Elevated serum Ca 19-9 Any of the above features that develop during surveillance Increase in cyst size of >3 mm/year during surveillance New-onset diabetes during surveillance Any cyst where diagnosis is unclear and EUS FNA will alter management	–

(continued)

Table 9.3 (continued)

Guidelines	Surveillance	Indications for EUS ± FNA	Indications for surgery
American Gastroenterological Association 2015 [40]	Cyst <3 cm in size without a solid component or dilated pancreatic duct Before any surveillance program, patients should have a clear understanding of risks and benefits (applies to both branched-duct IPMNs and MCNs)	Presence of any two of the following three high-risk features Size >3 cm Dilated main pancreatic duct Presence of solid component	Presence of both a solid component and main pancreatic duct dilation and/or positive EUS FNA cytology for cancer or high-grade dysplasia
International Consensus Guidelines 2012 [39]	–	–	All surgically fit patients with an MCN

IPMN intraductal papillary mucinous neoplasm, *CEA* carcinoembryonic antigen, *FNA* fine needle aspiration

Table 9.4 Surveillance of mucinous cystic neoplasm [MCN] without high-risk features

Guidelines	Cyst type	Surveillance intervals
European 2018 [32]	Definitive MCN <4 cm in size Mucinous lesion <3 cm in size (IPMN vs MCN)	MRI every 6 months × 1 year. If stable, then MRI every year till patient is a surgical candidate, provided stable lesion
American College of Gastroenterology 2018 [36]	Presumed MCN or IPMN <1 cm 1–2 cm 2–3 cm	MRI every 2 years × 4 years. If stable, then can lengthen interval MRI every year × 3 years. If stable, then MRI every 2 years × 4 years; if stable, then can lengthen interval MRI or EUS every 6–12 months × 3 years. If stable, then MRI every year × 4 years. If stable, then can lengthen interval For increase is size of >3 mm/year or change in cyst characteristics, EUS ± FNA or short interval MRI imaging is recommended
American Gastroenterological Association 2015 [40]	Presumed branched-duct IPMN or MCN <3 cm in size	MRI at 1 year, if stable then MRI every 2 years for a total of 5 years. Stop surveillance if no change in cyst character over 5 years Proceed with EUS ± FNA if development of any high-risk feature (size >3 cm, solid component or main PD dilation)

IPMN intraductal papillary mucinous neoplasm, *MRI* magnetic resonance imaging, *EUS* endoscopic ultrasound, *FNA* fine needle aspiration

Prognosis and Postsurgical Follow-Up

Surgery for MCNs without invasive cancer is curative, and prognosis is excellent. No postoperative surveillance is required. For patients with cancer, surveillance recommendations are similar to those for pancreatic cancer [4, 36, 39].

In summary, confirmed MCNs are generally resected, but there is emerging data to suggest that small MCNs (<4 cm) without high-risk features can be surveyed. For presumed mucinous cysts without high-risk features, where a definitive diagnosis is unclear (IPMN vs MCN), surveillance is recommended following IPMN guidelines. We suggest following the ACG or European Guidelines for surveillance criteria and intervals.

SCA

Surveillance

Since SCAs are considered benign, no surveillance or further evaluation is recommended for asymptomatic cysts by ACG guidelines [36]. This is the usual practice in the USA. Further evaluation is only performed if an SCA does not have a typical appearance on imaging, and there is concern for a mucinous cyst. European Guidelines recommend follow-up at 1 year and then symptom-based follow-up [32].

Surgical Management

Surgery is only performed for symptomatic SCAs. Symptoms may include abdominal pain, duodenal or biliary obstruction, pancreatitis, etc. attributable to an SCA.

Prognosis and Postsurgical Follow-Up

Most SCAs do not increase in size. Even if they increase in size, the rate of growth is very slow and new-onset symptoms are rare. Prognosis is excellent. No surveillance is required following resection [5, 32, 36].

SPN

Surgical Management

Complete surgical resection at a high-volume center is recommended for an SPN [13, 36, 41]. Pylorus-sparing pancreatoduodenectomy is performed for SPNs in the pancreatic head. For an SPN in the tail of the pancreas, with local or vascular

invasion, oncological surgery is performed with distal pancreatectomy, splenectomy, and lymph node dissection. Otherwise, parenchyma preservation is preferred. Lymph node involvement is rare and dissection is not pursued in most cases. Metastasis to the liver is also resected during the primary surgery or at recurrence. Debulking is recommended for other extensions [13].

Prognosis and Postsurgical Follow-Up

The post-resection prognosis of SPN is good. Five-year survival is over 95% including metastatic cases. Ten-year survival is over 90%. Risk of recurrence is about 6.6% at 1–10 years of follow-up, with most common sites being liver and lymph nodes [10, 41]. Postoperative surveillance is recommended, and the ACG guidelines suggest yearly follow-up for at least 5 years [10, 36].

Conclusion

Pancreatic cysts are common. It is challenging but important to make an accurate diagnosis of the type of pancreatic cyst, which determines management. MCNs and SPNs have malignant potential and require surgical resection even if asymptomatic. SCAs are benign. Physicians should have low threshold to refer patients with complicated pancreatic cysts to large-volume multidisciplinary centers.

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Chapter 10
Obesity and Bariatric Surgery

Semeret Munie and Tammy Kindel

Introduction

The disease of obesity is an escalating global epidemic that affects both adults and children and men and women worldwide. The World Health Organization (WHO) defines obesity as the excessive fat accumulation in the body, which adversely affects and impairs health. For adults, the WHO classifies being overweight as having body mass index (BMI) ≥25 kg/m^2 and obesity to be a BMI ≥30 kg/m^2 (Table 10.1). In 2016, more than 1.9 billion adults were overweight, and of these, over 650 million were obese [1].

Although men have been reported to have higher prevalence of being overweight, women actually have higher rates of obesity which puts them at significant risk for obesity-related diseases such as hypertension, type 2 diabetes, cardiovascular diseases, and obstructive sleep apnea (Table 10.2). Obesity also increases the risk of certain cancers such as uterine and breast cancer with an overall increased rate of mortality [2].

There is also a significant impact of obesity on psychological health and well-being, with increased rates of obesity, depression, and low self-esteem among individuals with obesity. Female patients are particularly at risk due to outgoing societal and social pressures to maintain a specific body weight and suffering stigmatization and isolation due to their disease. Unfortunately, dieting is almost universally unsuccessful in cases of severe and morbid obesity. There is a complex interplay of hormonal, psychological, and environmental influences that keep individuals in a persistent state of obesity or lead to weight regain after a successful initial dieting attempt. Unlike dieting, bariatric surgery is successful in producing sustained and meaningful weight loss for the majority of patients. In this chapter, we will discuss how obesity specifically can affect women and the role of bariatric surgery.

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Table 10.1 Weight classification basssed on body mass index (BMI)

Weight classification	BMI (kg/m^2)
Underweight	<18.5
Normal	18.5–24.9
Overweight	25.0–29.9
Class I obesity	30.0–34.9
Class II obesity	35.0–39.9
Class III (morbid) obesity	≥40

Table 10.2 Obesity-associated comorbidities

Organ system	Obesity-associated comorbidity
Neurological	Migraine Depression Pseudotumor cerebri Stroke
Respiratory	Asthma Obstructive sleep apnea Hypoventilation syndrome
Cardiovascular	Coronary artery disease Heart failure
Hepatic	Nonalcoholic fatty liver disease Cirrhosis
Gastrointestinal	Gastrointestinal reflux disease
Genitourinary	Stress urinary incontinence
Musculoskeletal	Degenerative joint disease Gout Venous stasis disease
Reproductive	Menstrual irregularity Polycystic ovarian syndrome Infertility
Endocrine	Type 2 diabetes mellitus Metabolic syndrome Dyslipidemia Hypercholesterolemia
Cancer	Breast, esophagus, pancreas, kidney, colon, uterus, cervix, prostate

Question 1: Will I gain weight after menopause and is it more difficult to lose weight?

Physician answer: Weight loss is noticeably more challenging with age and can be magnified after menopause. Muscle mass declines with aging and decreased physical activity. Muscle mass increases metabolism. The less muscle mass, the lower your metabolism. Menopause is caused due to decreased estrogen in the body. Estrogen affects where your body deposits fat. Postmenopausal women are more likely to deposit fat around the abdomen rather than the soft tissue of the arms and legs. Central abdominal fat increases the risk of obesity-related diseases, like type 2 diabetes, which can also affect body weight and metabolism. When the metabolism decreases, your body needs less calories each day to maintain your weight, and weight loss requires a reduction in calories beyond your daily requirements.

Literature review: The National Institute on Aging states that on average, women enter menopause at the age 51, although it can start earlier or later in different individuals. A woman is believed to be in menopause after her menstrual periods have ceased for a consecutive 12 months without other possible causes. This natural transition to menopause occurs gradually over a period of months, where the function of the ovaries gradually declines. This transition period is called perimenopause. During perimenopause, women experience irregular periods, hot flashes, abdominal cramps, sleep disorders, as well as gradual weight gain. The decline in estrogen during this period of life is believed to play a role in the weight gain.

Aging, unrelated to hormonal changes in women, has been associated with weight gain in both sexes [3]. Men of the same age gain adipose tissue similar to women [3]. Most of the literature supports the notion that the major contributor of weight gain in middle-aged women is primarily the result of aging and lifestyle changes, rather than hormonal changes related to menopause. Aging results in loss of lean body mass, primarily skeletal muscle. This will inherently lead to a lower metabolic rate. This change in basal metabolism is accentuated by the fact that activity levels tend to decline with age, leading to a more sedentary lifestyle and decreased active metabolism. These lifestyle changes are usually gradual and may not be noticed by the patient. Studies have shown that in women between the ages of 50 and 64, only 50% of them perform regular physical exercise, and only 25% incorporated high-intensity exercise [4]. There is evidence that loss of the luteal phase during menopause reduces energy expenditure compared to premenopausal women [5]. Therefore, the combination of unchanged daily caloric intake in the setting of a lower resting and active metabolic rate due to aging and lack of regular exercise can result in noticeable weight gain and make weight loss attempts more difficult.

Aside from the changes in lean body mass and decrease in level of physical activity that is noted in middle-aged women, the decline in the level of estrogen predisposes postmenopausal women to accumulate adipose tissue in and around the abdominal organs, resulting in visceral as opposed to subcutaneous obesity. Unlike subcutaneous adiposity which increases with age, visceral adipose tissue deposition is especially prominent in postmenopausal women who, on average, have about twice the amount of visceral fat as premenopausal women [6]. This effect remains significant even after studies controlled for confounding factors such as aging, total body fat, and physical activity level [7–9]. The increase in visceral adipose tissue after menopause is correlated with decreased estrogen levels and increased FSH [10]. Central and visceral obesity is a risk factor for the development of metabolic syndrome [11].

The initial treatment of weight gain after menopause includes dietary and lifestyle intervention to increase physical activity and build skeletal muscle mass. While hormonal therapy may decrease visceral adiposity, postmenopausal hormone replacement therapy is not indicated for weight loss. Odabasi et al. randomized 90 postmenopausal overweight women with or without visceral adiposity to 17 beta-estradiol plus norethisterone at low and standard doses. While hormone replacement therapy reduced waist girth, there was no impact on BMI [12]. For severely obese patients, bariatric surgery should be considered not only for weight

loss but for best treatment of obesity-related comorbidities which increase in prevalence after menopause, such as hyperlipidemia, type 2 diabetes mellitus, and insulin resistance.

Question 2: Am I a candidate and what are the options for weight loss surgery?

Physician answer: Weight loss surgery, or bariatric surgery, is considered for patients with severe obesity (class 2 or 3 obesity). For patients with class 2 obesity (BMI 35–39 kg/m^2), there should be an obesity-related medical problem, like type 2 diabetes mellitus, in addition to the disease of obesity. Bariatric surgery candidates should be committed to a lifelong change in their health, including the nutritional requirements for bariatric surgery, and not have unstable or untreated severe medical or mental health disease. There are two commonly performed bariatric procedures in the United States, the laparoscopic sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB). These procedures work through both shared and unique mechanisms to result in successful and sustained weight loss. Multiple obesity-associated medical problems improve after weight loss surgery and should be one of the strongest reasons to consider weight loss surgery in patients with severe obesity.

Literature review: Candidacy for weight loss surgery begins with BMI classification and obesity-associated comorbidities. In 1991, the NIH established guidelines for eligibility for adult patients considering bariatric surgery:

- BMI greater than 40 kg/m^2 (class 3 obesity) with or without any comorbidities
- BMI between 35 and 39.9 kg/m^2 (class 2 obesity) with obesity-related comorbidities such as type 2 diabetes or obstructive sleep apnea (full list Table 10.2)

Bariatric surgery should also be considered for adolescent patients using age- and sex-matched growth charts to define obesity. Adolescents with class 2 obesity (120% of the 95th percentile) and obesity-associated comorbidities or class 3 obesity (140% of the 95th percentile) with or without comorbidities are considered potential surgical candidates. The American Society of Metabolic and Bariatric Surgery recommends early intervention for adolescents with severe obesity to reduce the risk of persistent adult obesity and decrease the risk of long-term end-organ damage from inadequately treated comorbidities [13].

In addition to weight loss, bariatric surgery results in the remission or improvement in multiple obesity-associated comorbidities for the majority of patients including obstructive sleep apnea, hypertension, hyperlipidemia, polycystic ovarian syndrome, nonalcoholic fatty liver disease, and most notably type 2 diabetes mellitus. There are multiple recent randomized trials comparing bariatric surgery to best medical therapy for treatment of type 2 diabetes. Although multiple studies have shown an improvement in type 2 diabetes mellitus after bariatric surgery, there is importantly a 92% reduction in diabetes-related mortality for patients undergoing surgery [14]. These studies among others led to a 53 international society and organization consensus conference called the Diabetes Surgery Summit-II (DSS-II) where guidelines were developed for the inclusion of bariatric surgery as a metabolic

procedure to be included as standard of care treatment for type 2 diabetes mellitus and obesity [15]. These guidelines state that metabolic surgery, including a RYGB and SG, should be considered for patients with a BMI >30 kg/m^2 and uncontrolled type 2 diabetes. The DSS-II also performed a meta-analysis of bariatric surgery compared to best medical therapy that demonstrated superior improvement in body weight, glycemic control, lipid levels, and quality of life in the bariatric surgery group [16]. Bariatric surgery is believed to improve type 2 diabetes through multiple mechanisms which include weight loss but also weight loss-independent mechanisms. A few of these weight loss-independent mechanisms include increased glucagon-like peptide-1 secretion, increased postprandial bile acids, beneficial changes in the gut microbiome, and changes in intestinal nutrient sensing [16].

Modern bariatric surgery has evolved significantly since its inception as surgeons have modified techniques to maximize patient safety with meaningful weight loss and improvement in obesity-associated comorbidities. The SG is now the most popular bariatric surgery with RYGB maintaining steady utilization at about 30% of cases. A SG removes 75% of the greater curvature of the stomach leaving the lesser curvature intact. There is no small bowel intestinal rerouting (Fig. 10.1). Most patients lose about 60% of their extra weight, or around 27% of their total body weight. This occurs over about 12 months. Complications of a sleeve gastrectomy include staple-line leak (<1%), venothromboembolic events (<1%), and rarely bleeding or infection. Long-term complications can include cholelithiasis and de

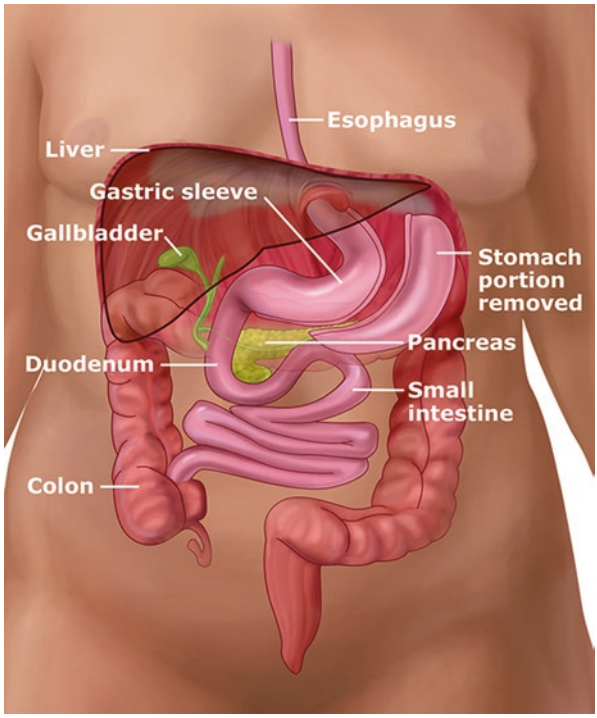

Fig. 10.1 Anatomy of a sleeve gastrectomy

novo or worsening gastroesophageal reflux disease reported in the literature at a rate of 10–30% [17].

A RYGB involves dividing the stomach into a small gastric pouch (about 30–50 cc) made of upper cardia. The small intestine is divided about 75 cm distal to the ligament of Treitz and a jejunal Roux limb brought up to the pouch to create a gastrojejunostomy. The divided jejunum (biliopancreatic limb) is then reconnected distal on the Roux limb at a length of around 100–150 cm to create a jeju-jejunostomy. The distal small bowel from the jeju-jejunostomy is called the common channel and allows for adequate length for nutrient absorption of macronutrients without malabsorption (Fig. 10.2). Complications of a RYGB include the same as with a SG but also uniquely include dumping syndrome, internal hernia formation, marginal ulcers, and gastrojejunostomy stenosis. The weight loss after a RYGB is 75% excess weight loss and 34% total body weight loss occurring over 12–18 months after surgery [17].

The incidence of revisional surgery done per year on bariatric procedures in 2014 was 11.5% [18]. Long-term complications from historical bariatric procedures have likely contributed to the rise in revisional bariatric surgery. It is critical for providers to recognize the difference between modern and historical bariatric procedures to aid in patient counseling and to correctly describe current benefits versus actual and perceived risks of surgery based on historical concerns.

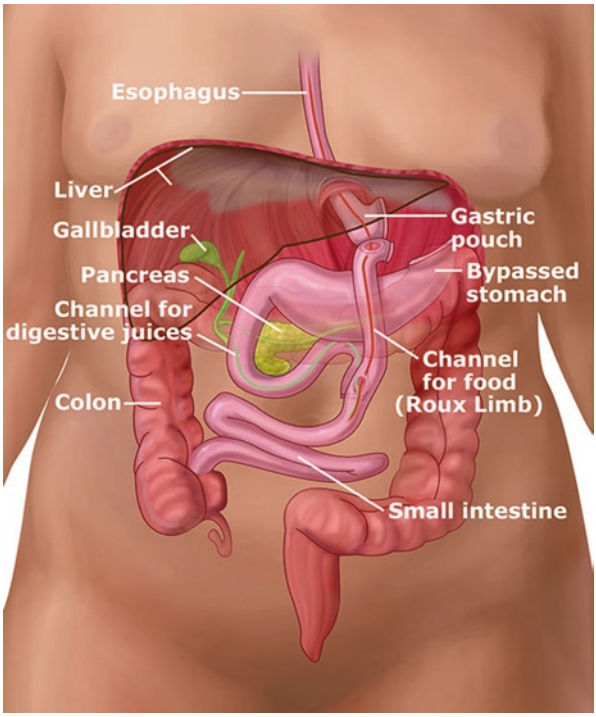

Fig. 10.2 Anatomy of a Roux-en-Y gastric bypass

In response to the initial concerns of the increasing incidence of severe obesity in the United States in the 1960–1970s, the infancy of bariatric surgery began with intestinal bypasses such as the jejunoileal (JI) bypass to replicate the weight loss seen in short bowel syndrome patients. The JI bypass consisted of dividing the proximal jejunum 35 cm distal to the ligament of Treitz with reanastomosis of the divided proximal end of jejunum to the distal terminal ileum (10 cm proximal to the ileocecal valve) or directly to the ascending colon usually in an end-to-side fashion. The surgery was designed to maintain gastric anatomy, and thus patients could still eat normal to large portions with weight loss through extreme nutrient malabsorption. Patients after a JI bypass would develop acute complications such as fulminant liver failure, renal failure, or death due to dehydration and nutrient and electrolyte disturbances. Chronic complications included troublesome and life-altering diarrhea, calcium oxalate nephrolithiasis, gallstones, steatohepatitis and cirrhosis, micronutrient and fat-soluble vitamin deficiencies, and bacterial overgrowth [19, 20].

Due to these morbid nutrient deficiencies and complications, the JI bypass was abandoned by most surgeons in the 1980s. It is estimated that approximately 25,000 JI bypasses were performed in the United States [21]. While many patients have had their JI bypasses reversed or unfortunately did not survive the sequelae of the surgery, it is unknown what percentage of these patients have subsequently died or have been reversed. Late reversal is indicated for any of the above complications and most frequently is undertaken for chronic liver and renal disease. The earlier in the disease process the bypass is reversed, the better the likelihood of organ recovery and disease resolution. Unfortunately, many patients are referred for reversal late with a perioperative mortality rate of almost 22% reported in the literature when performed on patients who had already developed cirrhosis [21].

As surgeons and medical professionals encountered significant postoperative complications from protein and nutrient malabsorption of the JI bypass, Drs. Mason and Ito introduced the original nondivided Roux-en-Y gastric bypass (RYGB) in 1965 to decrease the risk of malabsorption and associated sequelae. The most common complications of the original RYGB are related to the stapling technology available in the open era of bariatrics. The small 30–50 cc gastric pouch was created with nondivided staplers, which partitioned the pouch from the remnant stomach with rows of staples but did not divide the segments. Long-term, this led to staple-line disruptions or gastro-gastric (GG) fistulas, with access once again for food and liquids to the gastric remnant and biliopancreatic limb. This causes not only weight regain but the potential for abnormal acid exposure to the jejunal Roux limb or esophagus, resulting in marginal ulcers or gastroesophageal reflux disease (GERD). The incidence of GG fistula after a nondivided RYGB is as high as 50% [22]. When a patient presents with any of these outlined symptoms and has a history of an open RYGB, unless the operative reports can be obtained specifically stating the tissue was fully divided between staples, the assumption should be that a nondivided stapler was used and the patient is at risk for GG fistula formation. This is most easily diagnosed with an upper gastrointestinal series (Fig. 10.3) and complemented by an endoscopy to assess the location and size of the fistula, as well as the presence of a marginal ulcer.

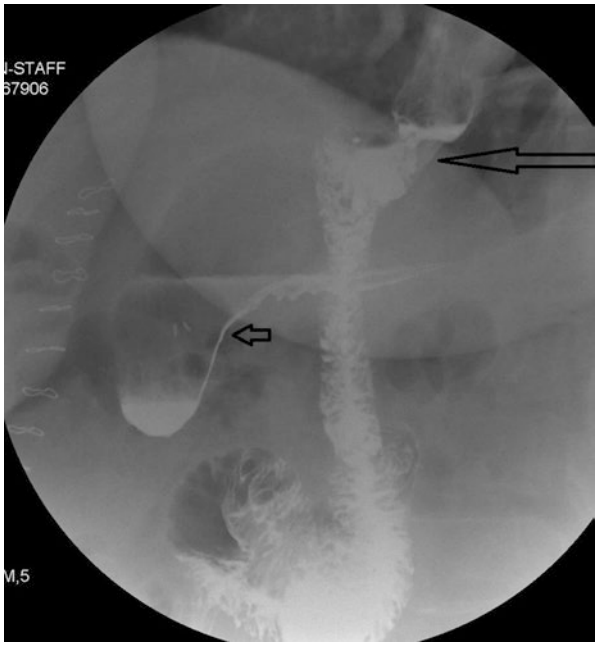

Fig. 10.3 Upper gastrointestinal series showing filling of the gastric pouch and Roux limb (long arrow) with contrast also flowing into the remnant stomach and duodenum (short arrow), suspicious for a gastro-gastric fistula after an open, nondivided RYGB

If the GG fistula is <1 cm, attempt at endoscopic closure can be made although the endoscopic closure rate is only 33%. Endoscopic closure is associated with minimal morbidity and does not further complicate the ability to perform a surgical revision if needed [23]. Fistulas >1 cm are unlikely to heal with endoscopic intervention, and revisional surgery can be attempted. Revision of a GG fistula after a nondivided RYGB involves remnant gastrectomy to include the fistula tract, often requiring a redo gastrojejunostomy allowing for complete takedown of the GG fistula [24]. The major complication rate of takedown of a GG fistula after RYGB is 16% [24].

The vertical-banded gastroplasty (VBG) was introduced in the 1970s as a procedure which carried no risk of malabsorption like the JI bypass and decreased morbidity from an open gastric bypass as there is no anastomosis. As shown in Fig. 10.4, a VBG consists of the partitioning of a small gastric pouch along the lesser curve, similar to a gastric bypass, but the distal aspect of the pouch is banded with a variety of materials (often with synthetic mesh or a Silastic band) to create a narrow outlet which then empties into the remainder of the distal stomach [17]. Despite its popularity through the 1980s, patients struggled long-term with failed weight loss, with or without a GG fistula, or symptoms related to a gastric outlet obstruction. In a 10-year study of 392 patients who underwent VBG, 58% of patients developed long-term complications [25].

Gastric outlet obstruction typically occurs chronically, due to erosion or obstruction by the Silastic band or mesh placed to create the gastric pouch [26]. Because of this chronic gastric outlet obstruction, patients can develop vomiting, dysphagia

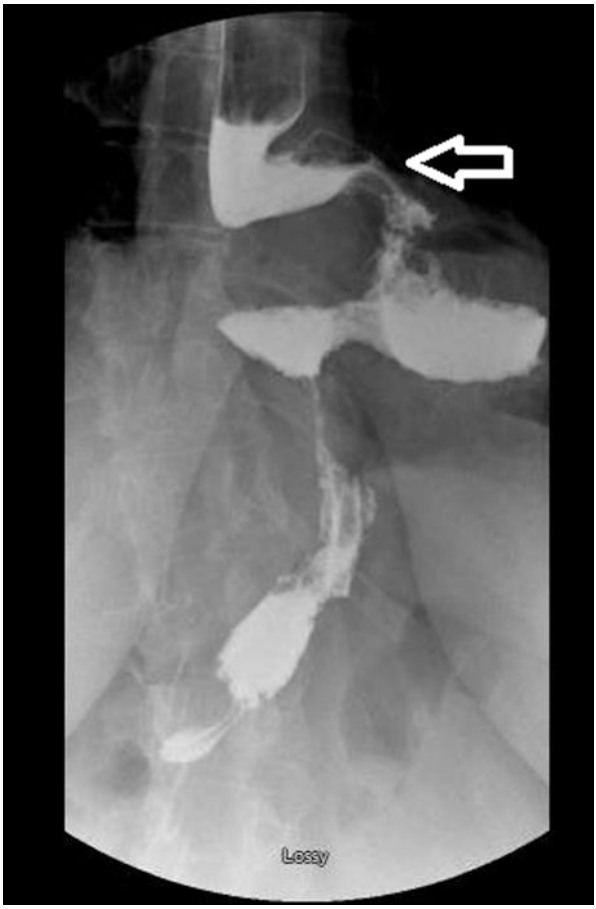

Fig. 10.4 UGI on a patient with a prior VBG. The UGI shows enlargement of the gastric pouch over time with expected narrowing and angulation of contrast at the site of the mesh band (white arrow). Contrast passes through the band into the remaining stomach. No GG fistula is present

secondary to esophageal dysmotility, and significant reflux symptoms. Reflux symptoms can be significant enough to contribute to the development of Barrett's esophagus [25]. Endoscopic removal of an eroded band is not usually possible when mesh was used due to tissue ingrowth. Endoscopic dilations for stomal obstruction almost universally fail as well. Revisional surgery to a gastric bypass is the procedure of choice for complications of a VBG and can often be performed laparoscopically by experienced bariatric surgeons [26]. Patients who undergo reoperation after a VBG have increased risk of perioperative morbidity.

GG fistula, like in nondivided RYGB patients, presents with weight regain and gastroesophageal reflux. To try to reduce the incidence of GG fistula, MacLean et al. modified this technique by dividing this staple line; however, this is still a complication that can occur given the proximity of the pouch to the divided stomach [27]. Operative treatment of weight regain or symptoms of a GG fistula is as described above with conversion to a gastric bypass.

The laparoscopic adjustable gastric band (LAGB) became a popular bariatric surgery option in the early 2000s. In this surgery, a Silastic band with an inflatable and adjustable inner balloon is placed circumferentially around the superior portion of the stomach to create a small pouch [28]. Patients return for adjustments where fluid is removed or added to the inner balloon to decrease or increase their restriction, respectively. The LAGB has become less popular over the past several years, primarily due to the long-term complications that have arisen, which have required revisional surgery. According to a study of the UHC database of over 10,000 LAGB patients, those who undergo revisional surgery have a longer hospital length of stay, high complication rates, readmissions, and overall cost [28].

One long-term complication of the LAGB is a slipped band, with an incidence of approximately 4.9% [29]. This refers to slippage of the band on the stomach, so that a portion of the stomach herniates above the band. Patients with this complication can present with failure to lose weight, heartburn, dysphagia, or gastric outlet obstruction. Patients can also have more emergent complications related to this, such as ischemia or necrosis of the stomach. The diagnosis is made with plain abdominal films or an esophagram, which demonstrate rotation of the band away from its usual orientation, which is at a 45° angle toward the left shoulder (Fig. 10.5). Patients that present with an acute band slip require emergent removal.

Another complication of the LAGB is band erosion, with an incidence of 0.2–32% [30]. Patients can present with infection of their subcutaneous port or weight regain. Patients are not typically acutely ill as the erosion occurs over time. Diagnosis is confirmed on endoscopy, and treatment requires surgical removal of the entire band and port.

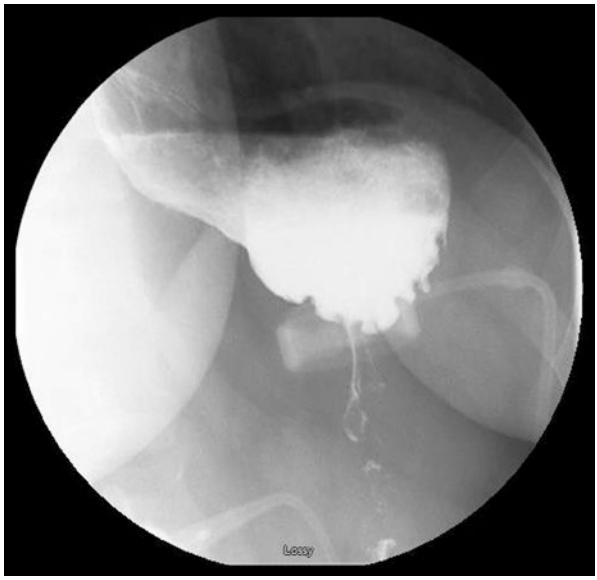

Fig. 10.5 An esophagram of a patient with slipped band resulting in a gastric outlet obstruction. The band is positioned in an abnormal horizontal orientation with excess stomach above the band and minimal contrast able to pass through the band

While revisional bariatric surgery is associated with known increased morbidity, these postoperative complications are minimized with bariatric surgeons who are experienced in the surgical care of revisional bariatric patients and in a bariatric hospital accredited by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program.

The initial introduction into many bariatric programs begins with either an online or in-person seminar that reviews basic information on obesity and bariatric surgery. This gives the patients a safe and comfortable environment to ask any questions they have and receive information from medical professionals. Most bariatric programs require preoperative laboratory testing, psychological evaluation, medical optimization, nutritional education, variable time periods of medical weight loss, as well as insurance approval before they can be scheduled for surgery. The timeframe of these processes ranges from 2 months to 1 year before surgery is scheduled. Most bariatric programs require preoperative tobacco cessation, having a stable mental health disease, treated food-related disorders (binge eating disorder), and being free of illicit drug use. Patients with significant comorbidities (advanced heart failure, organ transplant recipients, cirrhosis, revisional bariatrics) can be evaluated, considered, and managed safely at an accredited, high-volume bariatric center.

Question 3: How does significant weight loss affect fertility and pregnancy?
Physician answer: Obesity increases the risk of multiple reproductive problems, including infertility- and pregnancy-related complications like gestational diabetes, high blood pressure, and large for gestational age newborns. Weight loss with bariatric surgery significantly improves fertility. Patients after bariatric surgery should not get pregnant for 18 months to optimize nutrition and the health of the mom. During pregnancy, the expectant mom should be monitored closely by their bariatric surgery team to minimize surgery-related complications during pregnancy.

Literature review: Excess abdominal adipose tissue impacts women's reproductive health. These reproductive health issues range from general menstrual cycle-related pathophysiologic changes to specific issues such as infertility or complications related to pregnancy. Weight loss and bariatric surgery can beneficially affect reproductive health outcomes, and reproductive health status can impact the outcomes of weight loss surgeries [31, 32].

Both animal and human data exist highlighting the negative effect of obesity at all levels of hypothalamic-pituitary-ovarian (HPO) axis. Obesity is associated with anovulation that results in menstrual irregularity. This is presumed to be secondary to metabolic abnormalities induced by obesity, like insulin resistance that can promote the development of polycystic ovarian syndrome (PCOS). Higher levels of androgenic hormones and lower level of binding proteins found with obesity also disrupt normal ovulation and menstrual cycle [33]. Obese women tend to have decreased LH pulse amplitude, which is needed for secretion of progesterone from the ovaries. Although the mechanisms for improved reproductive function after bariatric surgery are not very well understood, several studies have demonstrated more regular menstrual cycle patterns and resumption of ovulation after bariatric surgery-related weight loss [34].

Obesity affects not only ovulation but also oocyte maturation, endometrial development, uterine receptivity, implantation, and miscarriage rates resulting in a higher level of infertility among obese women [35]. Weight loss with bariatric surgery improves fertility. Milone et al. found 58% of infertile, obese women became spontaneously pregnant after weight loss surgery [36]. In addition, patients having undergone assisted reproductive technology, such as artificial insemination and in vitro fertilization, before and after bariatric surgery were found to have an increased number of eggs, better egg quality, and higher rate of live births during postoperative treatment cycles [37].

Given the likelihood of improved fertility and possible decreased efficacy of oral contraceptives with malabsorptive procedures, the preferred method of postoperative birth control would be with parenteral dosage forms or non-hormonal methods such as an intrauterine device [38]. The American College of Obstetrics and Gynecology (ACOG) recommends that women not conceive for 12–18 months postoperatively so that the fetus is not affected by rapid maternal weight loss, so that all micronutrient deficiencies can be addressed and adequately supplemented, and so that the patient can achieve her weight loss goals [39, 40]. Once pregnant, ACOG recommends considering a broad evaluation for deficiencies in micronutrients at the beginning of pregnancy in women who have had bariatric surgery, and treatment should be initiated if any deficits are present (Table 10.3).

Pregnancy is associated with weight gain as a physiologic adaptation to a new state of metabolism. As part of this adaptation, metabolic syndromes such as gestational

Table 10.3 Micronutrient requirement during pregnancy in post-bariatric patients[a] [45]

Micronutrient	Changes in pregnancy and recommended supplementation
Iron	800 mg elemental iron daily recommended Most common deficiency in post-bariatric surgery pregnancy, especially following Roux-en-Y gastric bypass Supplement vitamin C if iron persistently low to aid in iron absorption Intravenous infusion may be needed if oral supplementation fails
Calcium	1500 mg per daily recommended Avoid taking iron and calcium at the same time to improve calcium absorption There is increased demand of calcium from enlarging fetus as well as for production of breast milk
Vitamin D	800 IU daily recommended Replacement may vary depending on baseline vitamin D levels
Vitamin B12	Deficiency results in anemia and irreversible neurological changes and neural tube defects in fetus Deficiency very common after bariatric surgery 1 mg of hydroxocobalamin IM injection every 2–3 months
Vitamin A	Deficiency can result in preterm birth 4000 IU/day recommended
Folate	Deficiency can lead to anemia, low white cell count, low platelet in mother, and neural tube defects in fetus 400 μg/day In some patients, an additional 5 mg daily supplementation may be given for the first 12 weeks of pregnancy

[a]Post-bariatric surgery pregnant women's micronutrient replacement may need to be individualized and should be monitored as well as supplemented by well-trained medical providers

diabetes, pregnancy-induced hypertension, and hyperuricemia tend to be unmasked during pregnancy in predisposed women. In obese pregnant women, however, these physiologic changes are accentuated by the presence of a relative abundance of adipose tissue, which is now recognized as a metabolically active endocrine organ. Of note, obesity is the most common medical condition in women of reproductive age in the United States. Studies confirm a relative increase in pro-inflammatory cytokine production by the adipose tissue and placentas of obese women, which may be responsible for exaggerated physiological adaptations in pregnancy [41]. As a result, the usual complications of pregnancy such as diabetes, hypertension, preeclampsia, and neonatal macrosomia are frequently reported in obese women [32].

Besides maternal complications, there is a higher incidence of poor fetal outcomes in obese pregnant women. Obesity has been identified as an independent risk factor for recurrent, unexplained miscarriage, with up to a 73% increased risk of another miscarriage [42]. Other poor pregnancy and neonatal outcomes associated with obesity include still birth, increased rate of congenital malformations, sudden infant death syndrome, large for gestational age (LGA) infants, birth trauma, and increased odds of admission to a neonatal intensive care unit. In the long term, children born to pregnant mothers with obesity have higher odds of developing obesity and other metabolic syndromes such as insulin resistance, hypertension, dyslipidemia, and cardiovascular disease [35].

Optimization of prepregnancy weight can improve maternal and perinatal outcomes, and bariatric surgery has become a viable option to achieve prepregnancy weight loss [43]. Post-bariatric surgery pregnant women with GI complaints need early consultation with a bariatric surgeon to determine whether certain common pregnancy symptoms might be confused with symptoms related to the bariatric procedure. Given the risk of anemia, internal hernia, altered glucose metabolism, and small for gestational age offspring, post-bariatric pregnant women need a more frequent follow-up by a multidisciplinary bariatric team [44].

Pregnant women with a history of gastric bypass should not undergo the oral glucose tolerance test (OGTT) due to the high risk of hypoglycemia. Instead, alternative screening methods, such as home glucose monitoring, should be considered in patients who have undergone bariatric surgery. There are no contraindications for vaginal delivery nor postpartum breastfeeding [45]. Current studies are examining whether malabsorptive procedures affect the composition of breast milk; however, the current available data suggest there is no change in the composition of the breast milk after bariatric surgery [46, 47].

Conclusion

Obesity is a global epidemic with no racial, age, and gender discrimination. With advanced age, the risk of obesity increases due to the decreased level of physical activity and decreased lean body mass. Hormonal changes of the postmenopausal state increase central obesity and the risk for metabolic syndrome.

Obesity detrimentally affects female fertility with improvements after weight loss surgery. Hormonal changes coupled with altered gastrointestinal absorption of

contraceptive pills can increase the chances of unplanned pregnancy after bariatric surgery, and appropriate physical barrier contraceptives should be used. In the event of pregnancy, close follow-up with replacement of any necessary nutritional deficiencies is mandatory to optimize pregnancy outcomes.

For patients with morbid obesity, bariatric surgery is the only treatment option to result in and maintain long-term weight loss with resolution of most obesity-associated comorbidities and increased lifespan with reduction in all-cause and multiple disease-specific mortalities. While a SG and RYGB are the most commonly performed procedures in the United States, revisional surgery is occurring more frequently as historical operations are surgically addressed for complications or weight recidivism. The future of bariatric surgical procedures lies in optimizing outcomes with continued reduction in perioperative complications as well as the application of bariatric surgical procedures targeted to specific metabolic diseases and disease-specific pathophysiology, like type 2 diabetes mellitus.

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Chapter 11
Celiac Disease

Marium Khan and Daniel Stein

Introduction

Celiac disease is precipitated by consumption of food products containing gluten in genetically predisposed patients. This results in a chronic immune-mediated small bowel (predominately duodenal) enteropathy that leads to a broad array of clinical presentations. Gluten is a large complex insoluble protein that is contained in wheat, barley, and rye [1]. On the mucosal level, villous atrophy develops as an immune reaction to gluten and subsequent nutrient malabsorption. With removal of gluten from the diet, patients experience improvement in clinical symptoms, nutritional deficiencies, as well as resolution of the villous atrophy. Symptoms and histologic abnormalities return following reintroduction of gluten or nonadherence to a gluten-free diet [2].

How Do I Know If I Have Celiac Disease?

In both men and women, the clinical presentation of celiac disease can vary widely. Historically, "classic or typical celiac disease" presented with signs and symptoms of malabsorption including diarrhea, abdominal pain, weight loss, nutritional deficiencies, and amenorrhea in women. Because most patients do not present with

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these signs and symptoms in the current era, this term is falling out of favor. In the modern clinic, presentations previously labeled as "atypical" are more "typical or common" (e.g., anemia, fatigue, abdominal bloating and discomfort, osteoporosis, or infertility). "Asymptomatic or silent" celiac disease is found when patients who are screened for and diagnosed with celiac disease but who lack many of the classic signs and symptoms attributed to the disease. "Potential or latent" celiac disease is described among those patients with genetic predisposition and positive serological markers of celiac disease but who lack the histologic findings of villous atrophy [1, 3].

Serologies that may indicate the diagnosis of celiac disease include immunoglobulin (Ig)A or IgG tissue transglutaminase (TTG), IgA or IgG endomysium, and IgA or IgG deamidated gliadin peptide antibodies. IgA or IgG antigliadin antibodies are excluded because they are nonspecific [2]. The mucosal lesion of celiac disease varies in severity and in extent but is characterized by the endoscopic findings of mucosal "notching" or "scalloping" [4]. Histologic findings on small intestinal biopsy show intraepithelial lymphocytes, absence of normal intestinal villi, loss of normal villus structure, and intestinal crypt elongation which all lead to a flattened intestinal surface that can no longer efficiently absorb nutrients [4].

Are There Any Genetic Associations with Celiac Disease?

Celiac disease has been associated with a genetic predisposition based on human leukocyte antigen (HLA) complexes. HLA genes are known to encode for major histocompatibility complex (MHC) proteins that are found on chromosome six within the human genome [5]. The genes found in this region are demonstrated to play a role in the immune system and susceptibility to autoimmune disorders [5]. The HLA class II molecule DQ2 is present in more than 90% of persons with celiac disease with the HLA-DQ8 heterodimer found in almost all of the remaining patients with celiac disease. Approximately 40% of the general white population carry either the DQ2 or DQ8 heterodimer, but only a small percentage (approximately 1%) go on to develop celiac disease [6].

Who Gets Celiac Disease?

Epidemiologic studies using specific celiac serology testing indicate that celiac disease has a wide geographic distribution and affects individuals from multiple and diverse ethnic and racial backgrounds. The overall prevalence of celiac disease in Europe has been estimated at 1%, with the highest reported prevalence of 2.4% in Finland [7]. Studies in the United States indicate that the prevalence is comparable with that in Europe. A large multicenter study by Fasano and others determined the prevalence of anti-endomysial antibodies in more than 13,000 at-risk and not-at-risk

American subjects to be 1 in 22 and 1 in 39 among first-degree and second-degree relatives of subjects with celiac disease, respectively [8]. There is a prevalence of 1 in 56 among patients with celiac-like gastrointestinal symptoms or with associated disorders. Of most significance, these investigators found a prevalence of anti-endomysial antibodies of 1:133 among 4126 "not-at-risk" subjects.

When examining gender predisposition for prevalence and incidence of celiac disease, there is no significant difference in gender predominance [7, 8]. When first identified, celiac disease was believed to be predominately a disease affecting pediatric populations with classic onset between 4 and 24 months [1, 9–11]. More recently, diagnosis of celiac disease is being made in adult ages with case series describing 20% prevalence among adults aged 60 years and older [12].

As described earlier, due to the HLA association in celiac disease, other disease entities associated which share the same HLA molecules may be seen among patients with celiac disease. Type 1 diabetes mellitus, IgA deficiency, and autoimmune thyroiditis are among some of the autoimmune diseases that share prevalence among those with celiac disease [1, 3]. It is estimated that about 3–8% of individuals with type 1 diabetes may also have celiac disease [1]. Microscopic colitis is an inflammatory condition of the colon that may present with chronic diarrhea [13]. While specific HLA molecules have not been identified as to be associated with microscopic colitis, prevalence of celiac disease among these patients as well as among patients with poorly responding celiac disease has been observed possibly due to similarly associated HLA molecules [13].

How Do I Know I Have Celiac Disease?

Diagnosis of celiac disease involves the proper approach integrating all aspects of the aforementioned characteristic that may be present in celiac disease patients. The understanding that approximately 40% of the white population carry the genetic predisposition for celiac disease, but only approximately 1% will develop celiac disease has led to the metaphor of the "celiac iceberg" (Fig. 11.1). All patients with a genetic predisposition to celiac disease (HLA-DQ2- or HLA-DQ8-positive) make up the "iceberg" of patients that could develop celiac disease, but like any good iceberg, only a small percentage of them will be "above water" and develop celiac disease. To be considered "above water," patient must first be evaluated with celiac serologies and found to be IgA tissue transglutaminase antibody (TTG) positive; however not all patients with positive serologies will have celiac disease. Sensitivity and specificity for IgA TTG has been noted to be 97% and 96%, respectively [14]. Serological tests for IgA anti-endomysial autoantibody through immunofluorescence have been used as a confirmatory test with about 85–98% sensitivity and 97–100% specificity [1, 15]. As mentioned previously, due to tenfold increase in prevalence IgA deficiency among those with celiac disease, this serology testing may be falsely negative and therefore must be further evaluated with other serological testing [3].

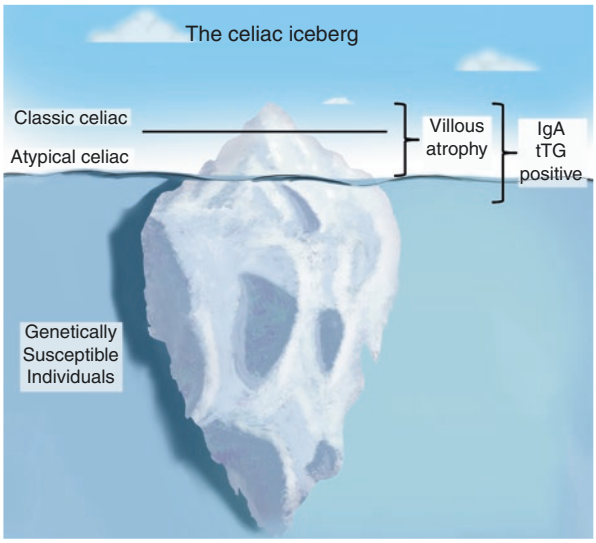

Fig. 11.1 All patients who are DQ2- and DQ8-positive represent the "celiac iceberg". Only those with positive IGA TTG serologies and small bowel villous atrophy are "above water" and are diagnosed with celiac disease. (Courtesy of Theresa Maatman MD)

It is only those that undergo upper endoscopy with duodenal biopsies, which confirm the presence of villous atrophy and intraepithelial lymphocytes, is the diagnosis of celiac disease confirmed. The small number of patients with positive serologies who are "below water" is considered potential celiac disease, the exact proportion of which will go on to develop celiac disease is unknown. To further the iceberg analogy, only the very tip of the above-water component will have "classic celiac disease" which highlights that most newly diagnosed patients will have "atypical" or "silent" celiac disease.

How Does Celiac Disease Affect Me as a Female?

Celiac disease may affect female patients in several different ways ranging from menstrual cycle irregularities, infertility, obstetric complications, and lactation [16]. Retrospective studies have allowed clinicians to observe the effects of celiac disease to improve women's specific health issues. Additionally, while not female-specific, studies have elucidated the possible effects celiac disease may have on their offspring.

Celiac Disease and Menstruation

Oftentimes, early onset of celiac disease presents with alterations in a women's menstrual cycle which then leads to the formal diagnosis [15]. Observational studies have illustrated a statistically significant delay in the onset of menarche among women untreated for celiac disease [17]. Hypogonadism among these individuals

may result in delay in puberty [18] as well as secondary amenorrhea among women which in turn can affect fertility [15]. In addition to later onset of menarche, undiagnosed celiac disease results in earlier onset age of menopause, further reducing the years of viable fertility [19]. However, maintenance of a gluten-free diet when compared to control populations resulted in no difference in the fertile life-span [19, 20]. While the specific mechanism of how celiac disease results in delayed onset of puberty is unclear, it is proposed that lack of key nutrients due to malabsorption may play a role in the production and regulation of the hypothalamic pituitary system and sex hormones [15, 20]. In particular, malabsorption of zinc and selenium affects the synthesis of follicle stimulating hormone (FSH) and luteinizing hormone (LH) which are essential hormones in maintenance of proper signaling pathways between the pituitary gland and ovaries [21].

Celiac Disease and Fertility

The earliest support for a gluten-free diet improving infertility among women with celiac disease was discussed in the 1970s [22]. In a meta-analysis evaluating infertility, it was suggested that women struggling with infertility had an increased risk (odds ratio of 3.5–6.0) of having celiac disease [16]. Furthermore, due to this increased prevalence, presentation of infertility may actually be the first manifestation of subclinical or latent celiac disease [23]. A case series described a group of celiac disease women who were off their prescribed gluten-free diet (GFD) all of whom dealt with fertility concerns over a period of 2–12 years. All of these women were able to conceive within 2–9 months after resuming a GFD [24]. Although such case series help to illustrate reduced fertility prior to the initiation of a GFD, population-based fertility rates among women with celiac disease on a GFD appear similar to those without celiac disease [25]. While overall fertility rates may be similar, it was observed that women with celiac disease are more likely to become pregnant at an older age compared to the general population [25]. Given this information, newly diagnosed women of childbearing age starting a GFD should be advised that they may become pregnant, particularly those with irregular or absent menstrual cycles at diagnosis. Family planning discussion is advised at the time of starting a gluten-free diet in these patients.

The immunological response resulting in malabsorption in celiac disease patients is thought to be the underlying factor leading to infertility. However, the presence of the antibodies to tissue transglutaminase may result in placental malfunction and therefore disrupt the implantation process resulting in infertility [26]. The presence of these antibodies attacks the dividing cells of the fetus causing abnormalities in the proper blood supply development to the endometrium further hindering implantation [21]. The presence of gluten consumed by women with celiac disease causes increase in inflammation resulting in an increase in gliden induced apoptosis of extravillous trophoblast cells of the placenta. This cell death further contributes to improper placental implantation and therefore spontaneous abortions [26].

How Does Celiac Disease Affect My Pregnancy If I Become Pregnant?

After successful implantation and maintenance of pregnancy, women with celiac disease should be aware of possible adverse effects related to obstetric outcomes. A Danish study evaluating obstetric outcomes showed that women with and without celiac disease prior to pregnancy had the same rate of pregnancies resulting in term live births and the same rates of pregnancy-related adverse events. However, women with undiagnosed celiac disease are at greater risk for development of low birth and placental weight, spontaneous abortions, and stillbirths [27, 28]. Additionally, women with undiagnosed celiac disease were more likely to have children with intrauterine growth restriction (IUGR) in addition to low and very low birth weight (LBW and VLBW) [27]. In a meta-analysis evaluating obstetric outcomes among women with both untreated and treated celiac disease, there was a statistically greater risk of complications including low birth weight, preterm birth, IUGR, and small gestational age when compared to those women without celiac disease [29].

Risk factors in the development of IUGR, LBW, and VLBW are likely due to suboptimal nutrition in women with undiagnosed celiac disease. Undiagnosed celiac disease women are reported to have lower levels of serum ferritin, vitamin B12, and folate which are important in the development of the growing fetus [27]. Dysregulation of the immune system with increased cell-mediated immune response has also been hypothesized as a contributing factor for the development of IUGR and LBW [27]. Women with celiac disease are also known to have increased circulating levels of autoantibodies not only transglutaminase but as well as antithyroid antibodies which have been demonstrated to result in adverse pregnancy outcomes including preterm birth and stillbirth [30].

Given known deficiencies associated with untreated celiac disease, studies have further investigated if there is an effect of specific nutritional deficiencies in the development of the growing fetus. Specifically, folate deficiency may be present in celiac disease and is associated with the development of neural tube defects [31]. However, research among celiac disease women on a GFD has not shown a statistical association in the development of neural tube defects among children of women with celiac disease [25]. While other obstetric complications have been noted to be increased among celiac disease women, there is limited conclusive data to support the increase frequency of neural tube defects among women with celiac disease [32].

Given there is an increased risk for adverse obstetric events among undiagnosed celiac disease women, it is important to maintain a gluten-free diet during pregnancy. The literature suggests that the circulation of autoantibodies and the effects of key vitamin and nutrient deficits in women with undiagnosed celiac disease have more unfavorable pregnancy outcomes than those with recognized and treated

celiac disease [27, 28]. When looking at women with treated celiac disease, it is encouraging to know that these women have pregnancy outcomes similar to those women without celiac disease [28].

Can I Breastfeed If I Have Celiac Disease?

Observational research studies have previously demonstrated a possible protective role of breastfeeding in children of celiac disease mothers [33]. Previously, there was a concern of when it is safe to introduce gluten to these patients, and it was thought that later gluten introduction would decrease the risk of celiac disease in these children [33]. However, a recent study analyzed the development of celiac disease among children with at least one first-degree relative with celiac disease that had a genetic predisposition to developing celiac disease. Children were exposed to gluten at 16 weeks of age versus placebo control (exclusive breastfeeding). When assessed for celiac disease at the age of 3, children with gluten exposure did not have a significant increased risk in the development of celiac disease [34]. Furthermore, exclusive breastfeeding did not offer a protective benefit in the development of celiac disease [34]. Although current research is limited, meta-analyses further support that there is no delay in or permanent protection in the development of celiac disease among exclusively breastfed children of celiac disease mothers [35, 36].

Can I Pass Celiac Disease to My Children?

As previously mentioned, celiac disease has been associated with a genetic predisposition based on HLA complexes [5]. The genes found in this region are demonstrated to play a role in the immune system and susceptibility to autoimmune disorders [5]. Celiac disease has been demonstrated to develop in individuals that encode for certain HLA molecules, specifically HLA-DQ2 and HLA-DQ8 [37]. These specific molecules are identified in approximately 40% of the population [37]. Women with celiac disease giving birth should screen their children for celiac disease if symptoms arise as they may have a predisposition to the development of celiac disease due to the HLA association. Similarly, screening should be considered among symptomatic patients with other known HLA-associated conditions such as glandular autoimmune disorders including type 1 diabetes, Hashimoto's thyroiditis, and Graves' disease [38]. Screening should be reserved among individuals who experience symptoms such as diarrhea, bloating, nausea, vomiting, or nutritional deficiencies [11]. Index of suspicion for celiac disease may also be high among individuals presenting with atypical manifestations such as iron-deficiency anemia, delay in puberty, amenorrhea, or infertility [31]. Due to the hereditary association,

patients with celiac disease and their children should make their pediatrician aware as they may need to be screened for these disorders and for celiac disease [36, 38].

Conclusion

While untreated celiac disease has been demonstrated to affect women resulting in abnormal menstrual cycles, infertility, and adverse pregnancy outcomes, maintaining a GFD appears to overcome such events. Certainly, we are relying on largely retrospective data in making this claim; however women with celiac disease should be on a GFD to avoid complications of celiac disease regardless of pregnancy status. After diagnosis of celiac disease, women should ensure to maintain a GFD for their health and outcome of their children before and during pregnancy. Also, women with celiac disease should be aware of the strong genetic component of celiac disease and their child may be at risk for celiac disease and other autoimmune disorders. Fortunately, as with most non-female-specific celiac-related complications, the female-specific complications appear to resolve with adherence to a gluten-free diet.

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Chapter 12
Inflammatory Bowel Disease: Fertility, Menses, and Contraception

Reezwana Chowdhury and Sunanda V. Kane

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disease that includes Crohn's disease (CD) and ulcerative colitis (UC). This disease affects about 800,000 women in the United States [1]. The peak incidence is between ages 15 and 40 years and can impact a woman throughout her prime childbearing years, by affecting her menstrual cycle, fertility, and menopause [1, 2]. Recently a study published by Shah et al. found that in an international pooled analysis of population-based studies, female patients had a lower risk of CD during childhood until they were 10–14 years (incidence rate ratio of 0.70), but a significantly higher risk at ages of 25–29 years and older than 35. However, the incidence of UC did not differ between men and women until after 45 years at which point men had a significantly higher risk [3]. Therefore, it is important for the gastroenterologist, who may be the patient's only physician during these formative years, to be knowledgeable about how IBD can alter the menstrual cycle, discuss contraception choices, and provide prenatal counseling to optimize timing of conception. In addition, it is important for any pregnant IBD patient to be followed closely by her gastroenterologist and maternal fetal medicine physician. The management of the pregnant patient is discussed elsewhere.

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Do Women with IBD Have a Higher Rate of Infertility Than the General Population?

As IBD is often diagnosed in men and women during their childbearing years, there is often a concern that a diagnosis of IBD can affect fertility.

Fertility is defined as the capacity to produce offspring [4]. Fecundability is the probability of becoming pregnant per month by unprotected intercourse [4]. There are differences in fertility between men and women with IBD; however, the focus of this chapter is to discuss fertility in the female patient. Medications can affect fertility differently between men and women which will be discussed below.

Studies have shown that the fertility rate between patients with IBD and the general population is similar. The rate of female infertility in population-based studies ranges from 5% to 14%, which is similar to the general population [1, 4–6]. A study by Khosla and colleagues demonstrated a similar rate of infertility (12%) in patients with Crohn's disease compared with the general population [7]. Hudson and colleagues did a retrospective study of women in North East Scotland evaluating fertility and pregnancy. They found that women with UC and CD had normal fertility compared to the general population [5]. The study also noted that the involuntary infertility rate for CD was 14% and UC was 15%, similar to the general population (14%) [5]. A systematic review by Heetun and colleagues showed that overall male and female fertility are not affected by IBD. Overall infertility rate in women with IBD varied between 7% and 12% [8]. Table 12.1 shows the effect of disease activity and treatments in females with active disease decreasing fertility. The only study that showed a lower involuntary infertility rate in IBD patients was shown by Mayberry and colleagues. In this case-control study, there was a significant reduction in the number of children in patients with CD compared to controls (0.4–0.7) [9]. There was no increase in rate of miscarriage or C-section, but prematurity was more common in patients with Crohn's disease (16% versus 7% in controls). Although CD patients used less contraception than

Table 12.1 Reasons for infertility in women with inflammatory bowel disease patients

Etiology	Rate of infertility
Involuntary infertility rate	5–14% (same as the general population)
Voluntary childlessness	14–18%[a]
Surgery – ileoanal pouch anastomosis	38–48%[b,c]
Active disease	Increases infertility
5-ASA	No change in fertility
Corticosteroids	No change in fertility
Mercaptopurine/azathioprine	No change in fertility
Biologics	No change in fertility

[a]Marri et al. [10]
[b]Nee et al. [19]
[c]Johnson et al. [23]

controls, 42% of CD failed to get pregnant vs controls at 28%, leading authors to conclude subfertility in CD patients. Infertility in this study was defined as failure to become pregnant despite lack of contraception for greater than 6 months [9], whereas others have defined infertility as failure to conceive after regular intercourse after 1 year [6]. The authors in the Mayberry study did not assess voluntary childlessness. One of the cited factors for decrease in fertility was thought to be medical advice against pregnancy; disease location was not a significant factor [9]. Other reasons that may lead to infertility in CD will be discussed later. There is no difference in infertility rates in patients with UC without surgery and the general population [1, 6].

Many factors contribute to the lower number of children in IBD patients, as stated previously. Voluntary childlessness is a large contributor to the reduced fertility rate. Rates of voluntary childlessness were evaluated by Marri et al. which surveyed 169 female patients with IBD including 110 with CD and 59 with UC [10]. IBD patients had a higher rate of voluntary childlessness (CD 18%, UC 14%) compared to 6.2% in the general population (significant at $p = 0.001$ and $p = 0.08$, respectively, for CD and UC). The rate of nonvoluntary childlessness was 5% in CD and 1.7% in UC similar to 2.5% in the general population leading the authors to conclude that these women have higher rate of voluntary childlessness as seen in Table 12.1 and tend to have fewer children, possibly due to higher educational achievement and racial background [10].

Tavernier and colleagues assessed the impact of IBD on fertility in both men and women without surgical treatment of their IBD and found a 17–44% reduction in fertility in women with CD compared to controls [4]. This reduction was linked to voluntary childlessness and was not seen in patients with UC. The reasons for voluntary childlessness included fear of worsening disease activity, inability to care for the child, IBD drug interactions during pregnancy, IBD inheritance, and fear of being infertile as seen in Table 12.1. This fear of infertility was shown in an Australian study by Mountifield and colleagues in which they attempted to determine whether IBD patients' perceptions of issues surrounding IBD, pregnancy, and childbearing influenced their reproductive behavior and describe these perceptions [11]. Both men and women were surveyed. They found that there was no difference in fertility between women with CD and UC. However, 42.7% of IBD patients reported fear of infertility (47.2% in CD versus 25.8% UC), but their rate of seeking medical advice was the same as the general population. This fear was most evident in women with CD and those having prior surgery. The main concerns were fear of passing along the disease, risk of congenital abnormalities, and medication interactions or teratogenicity [11]. Sellinger and colleagues also aimed to assess the attitudes of women with IBD regarding fertility, medication use in pregnancy and breastfeeding, delivery methods, and pregnancy outcomes [12]. They surveyed 145 women and found that 68% agreed with need for medical therapy for flares during pregnancy, but 24.3% felt it more important to tolerate the symptoms of a flare rather than taking medications, as 36.1% felt that IBD medications were "bad" for the fetus. Among the 96 nulliparous women, 90% were worried about the

effect of IBD on pregnancy, 91% were worried about the effects of pregnancy on the course of IBD, and 78.8% were worried about experiencing a flare while pregnant. About half of the patients were worried about being infertile. A large number of patients were worried about passing on their disease to their offspring at 75%. The number of women who were considering not having children at all was close to 30%. The results of the study indicate that there are poor subject knowledge and negative attitudes about IBD and infertility, pregnancy, and medications during pregnancy [12].

These studies have highlighted that there are a fear of infertility among women with IBD and fear of inheritability of the disease likely leading to higher rates of voluntary childlessness among women with IBD compared to the general population. Thus far, studies have shown that fertility in patients with UC and non-active CD is not decreased compared to the general population. The overall rate of infertility in these studies shows a rate ranging from 5% to 14%.

Regarding nonvoluntary infertility, serum anti-Mullerian hormone (AMH) is considered the most accurate hormonal marker of ovarian reserve. Ovarian reserve helps to assess the biological ability to conceive. *Studies have shown contradictory findings regarding fertility*. A retrospective study by Freour and colleagues evaluated the effect of CD on ovarian reserve in young women in remission by measuring serum AMH [13]. There were 50 women with CD in remission and 163 patients in the control group. The control group included women of reproductive age, both ovaries present, normal ovarian status, etc. There was no statistical difference in mean serum AMH levels between women less than 30 years of age with CD and the age-matched control group, but AMH levels were significantly lower in CD women >30 years old compared to the control group. Colonic location of the disease was associated with a loss of ovarian follicles. In an observational cross-sectional case-control study by Senates and colleagues, AMH levels were measured in women with CD and compared to age-matched controls [14]. AMH levels were significantly lower in CD patients 1.02 ± 0.72 compared to controls 1.89 ± 1.80. In addition, patients with active disease had lower AMH levels than patients in remission (0.33–1.53); higher CDAI score had a negative correlation with AMH levels. AMH levels reflect size of primordial follicle and decrease over time. Serum levels greater than 0.5 ng/mL are indicative of good ovarian reserve. AMH is thought to be a good indicator of ovarian reserve in women and is a member of the transforming growth factor B (*TGF-B*) family and secreted by preantral and early antral follicles. In addition, AMH levels vary slightly during menstrual cycle, so timing is not as much of a factor as trying to attain levels of FSH or estradiol which are collected on day 3 of menstrual cycle when testing for fertility as AMH levels can be measured on any day of the cycle [13, 14].

According to European Crohn's and Colitis Organization Guidelines as summarized by C.J. van der Woude and colleagues, there is no evidence that UC or inactive CD affect fertility, but active CD may reduce fertility possibly due to decreased AMH levels. High levels of voluntary childlessness contribute to the higher rate of infertility in women with IBD and indicate the need for better education. There is no evidence that medication affects fertility in females [15].

Effect of Abdominal Surgery on Fertility

Pelvic and, to a lesser extent, abdominal surgery for IBD increases risk of subfertility in females. Several meta-analyses found that IPAA is associated with a twofold to threefold increased risk of infertility compared to medical management [16]. Up to 30% of patients with UC will need total proctocolectomy despite improvements in medications due to refractory disease, dysplasia, or cancer [17, 18]. The standard surgical options include total proctocolectomy and end ileostomy, proctocolectomy with ileoanal pouch anastomosis, and abdominal colectomy with ileorectal anastomosis [17]. A review article showed that fertility is in fact reduced in women after IPAA by threefold [19]. A meta-analysis by Waljee et al. found that the rate of infertility increased from 15% to 48% post-IPAA. The reasons for the decrease may be secondary to surgical manipulation in the pelvic area or secondary to adhesions [16]. A systematic review by Cornish and colleagues that evaluated 22 studies from 1980 to 2002 including 1852 females found that the rate of infertility increased to 26% after restorative proctocolectomy from 12% prior to surgery [20]. In addition, the incidence of sexual dysfunction increased from 8% to 25% after surgery. They, however, did not show any increase in pregnancy complications after surgery [20]. Olsen KO and colleagues evaluated fecundity levels before diagnosis, from diagnosis until colectomy, and after IPAA in women compared to the reference population. There were 290 patients and 661 in the reference population who agreed to participate in the telephone interview [21]. The main finding was that the fecundability of women with UC was unaffected until they had surgery at which time, fecundability was significantly reduced. The fecundability ratio dropped to 0.20 after IPAA from 1.01 prior to IPAA [21]. They attributed the reduction primarily to the surgical procedure, i.e., the extent and location right to the pelvic floor of the IPAA surgery. Another study by Olsen KO in patients with familial adenomatous polyposis syndrome also showed that females had normal fecundity before surgery but had a drop after IPAA [22].

Johnson and colleagues studied fertility in females who have had IPAA for UC at North American tertiary care hospital and compared to patients before IPAA and UC patients managed without surgery [23]. The subjects were mailed questionnaires, and a total of 153 females had pelvic pouch surgery, and 60 females were managed nonoperatively for UC. These patients were asked if they attempted to become pregnant, when they became pregnant relative to their diagnosis or surgery, and if they were successful. They defined infertility as married or cohabiting women aged 18–44 years old and failed to become pregnant during 12 months of unprotected intercourse. The infertility rate was 38.6% in IPAA patients compared with patients managed nonoperatively (13.3%), $p < 0.001$. Among the females who reported infertility, 79.9% experienced it after surgery. Oresland and colleagues evaluated 21 patients by interview after undergoing restorative proctocolectomy to assess their relative chances of becoming pregnant [24]. These patients were evaluated by a gynecologist and hysterosalpingography. They found that two of the patients had bilateral occlusion of the fallopian tubes and nine had unilateral

occlusion and the tubes were adhering to the bottom of the pelvis in ten of the patients after proctocolectomy/IPAA. In addition, only 1 out of the 14 patients succeeded in trying to conceive during the follow-up period of 38 months [24].

Tulchinsky and colleagues investigated the effects of restorative proctocolectomy (RPC) on fertility and need for infertility treatments in a tertiary care center in Israel [25]. In addition, they investigated methods of delivery and pregnancy outcomes. The study was based on a questionnaire sent to women who underwent to RPC before age 45, and data was also obtained from a prospective database. The main results showed that RPC was associated with significant increase in infertility (0% before and 37% after RPC). This was seen in other studies as well [21, 24]. The limitations of the study include retrospective data on pregnancy and may be subject to recall bias, small number of patients, although the response rate was 87%. Pachler and colleagues did a retrospective registry-based cohort that evaluated birth rates in males and females after IPAA [26]. Birth rates were expressed as number of children born per 1000 patient-years. The results showed a 40% decrease in birth rate in females and 17% increase in males after RPC with IPAA for UC. They attributed this to the use of drugs such as mesalamine and chronic UC.

Based on the risks of infertility after IPAA, it is important for the gastroenterologist and surgeon to discuss risks of IPAA. Perhaps a discussion about laparoscopic technique, subtotal colectomy with rectal stump and ileostomy during childbearing years, and then IPAA later in life can be an alternative [6].

How Is the Menstrual Cycle Affected in Patient with Inflammatory Bowel Disease?

We know that fluctuations in hormonal levels can affect the GI system. It is important for gastroenterologists to be cognizant of a woman's menstrual cycle as the different phases of menstruation can exacerbate underlying symptoms of inflammatory bowel disease. The hypothesis is that there are sex hormone receptors in the intestinal mucosa which are affected by hormonal fluctuations during the menstrual cycle [27]. Up to one-half of asymptomatic women may experience gastrointestinal symptoms at the time of the menstrual symptoms [27]. Premenstrual syndrome was first described back in 1973 when Timonen and Procope reported symptoms of irritability, depression, diarrhea, and constipation [28, 29]. The changes in GI symptoms during the menstrual cycle are linked to hormones such as prostaglandins. Dysmenorrhea is linked to imbalance of prostaglandins and arachidonic acid metabolites such as prostaglandin subtype PGE2 [30]. PGE2 leads to increased contraction of the colonic smooth muscle. The higher frequency of bowel movements during menstrual phase may be caused by excessive prostaglandin release from the uterine cavity [31]. In addition, increased intestinal prostaglandin production (PGE2) causes an increase in colonic smooth muscle contraction, which can also

induce diarrhea due to increased intestinal secretion and altered electrolyte absorption, or changing levels of progesterone [30].

Estrogen is associated with serotonin (5-hydroxytryptamine-HT) receptors via estrogenic pathways and can lead to increased sensitivity to changing bowel symptoms and mood changes during the menstrual cycle [30]. Symptoms such as abdominal pain can appear before menstruation when there is a decline in estrogen production. Estrogen can alleviate cramps by decreasing the serotonin receptors.

The average length for a woman's menstrual cycle is 28 ± 4 days [32]. Up to 75% healthy women can experience a variation in their gastrointestinal symptoms during different phases of the menstrual cycle. In a cross-sectional cohort study of 1203 female patients with CD and UC, with 64% of the patients with CD, over half of the women with IBD reported worsening of their symptoms during menses, and the changes were similar between the CD and UC patients, except in pregnancy when symptoms were worse in UC patients [33].

Kane and colleagues retrospectively evaluated bowel symptoms and patterns in patients with IBD and IBS [34]. They evaluated premenstrual symptoms and menstrual symptoms; 93% of all patients reported experiencing premenstrual symptoms, with emotional irritability being the most common followed by depression and weight gain. In addition, they found that diarrhea occurred frequently in the premenstrual phase in IBS and IBD patients, compared to controls. CD patients were more likely to report increased symptoms during menstruation ($p < 0.01$), with diarrhea being the most common symptom. Up to Sixty-five percent of active UC patients compared to 38% of UC patients in remission reported correlation between disease activity and GI symptoms during their menstrual cycle. However, in CD, 63% of active CD and 61% CD in remission reported correlation between disease activity and GI symptoms during menstrual cycle. Diarrhea is also more common in IBS patients compared to controls ($p = 0.004$), an etiology attributed to increased prostaglandin levels.

In a prospective study by Lim and colleagues, 91 patients (47 IBD, 44 controls), IBD patients reported more frequent GI symptoms such as nausea, flatulence, and abdominal pain along with premenstrual symptoms, but not menstrual symptoms, compared with controls. PMS diagnostic criteria were characterized by cyclic recurrence of symptoms during the luteal phase of menstrual cycle. This study showed that IBD patients are more likely to report PMS and GI symptoms than healthy women without worsening of disease-specific symptoms (nocturnal diarrhea, hematochezia, fecal incontinence, and need for antidiarrheal agents) [30].

A prospective study by Parlak and colleagues evaluated frequency of defecation and GI and non-GI symptoms among women with UC and CD compared to controls [35]. The authors found that GI symptoms and frequency of defecation were higher in IBD patients for both UC and CD than in controls. The higher frequency of defecation during the menstrual phase was thought to be because progesterone is at its lowest during menstrual phase and progesterone is known to slow down GI transit

time [35]. There are conflicting results regarding progesterone and motility, as some studies have shown slower transit time by 25% in luteal phase than follicular due to progesterone, while others such as Hinds and colleagues did not find a difference in transit time [36, 37].

Women with IBD can often experience other abnormalities in their menstrual cycle including polymenorrhea, oligomenorrhea, irregular menses, and dysmenorrhea [38]. The Ocean State Crohn's and Colitis Area Registry (OSCCAR), a prospective community-based database, evaluated an incident cohort of IBD patients based in Rhode Island starting in 2008 [39]. The study included 121 patients and found menstrual abnormalities in the year preceding IBD diagnosis in 25% of patients. These patients also had alterations in cycle length and duration of flow (21%), and menstrual pain was the most common symptom [39]. In addition, steroid use was associated with increased risk for irregular cycles, and after controlling for use of thiopurines and anti-TNF alpha agents, there was no significant association with menstrual cycle outcome which leads the authors to conclude another reason to use steroid-sparing agents. These irregularities decreased with a longer duration of IBD. The authors concluded that an ovulatory cycle with menstrual irregularities could be caused by the stress of chronic disease, surgeries, or poor nutrition [39].

There is clearly a variation in GI symptoms during the menstrual cycle, and patients may confuse these symptoms with a disease flare as seen in Table 12.2. Therefore, it is important to obtain more history regarding a woman's menstrual cycle to determine if hormonal changes may be contributing to a patient's current symptoms. It might be helpful for patients to track their symptoms in relation to their menstrual cycle to differentiate if symptoms are secondary to a flare versus hormonal fluctuations.

There can be a delay in onset of the menstrual cycle in patients with inflammatory bowel disease. The delayed onset of menses has been seen more in CD over UC [1]. There can be many causes such as growth failure; lower BMI; nutritional deficiencies, vitamin D; steroid use; and flares. In a review by Ballinger and colleagues, the authors concluded from observations that in patients with IBD and in experiments with rats with colitis, inflammatory mediators adversely influence the onset and progression of puberty and can possibly augment the effects of undernutrition [40, 41]. Menarche has been shown to occur at age 16 or later in 73% of female patients in whom disease onset preceded puberty. In some patients, menarche was delayed until early 20s [42]. However, menarche occurred at 14 years old or younger in all patients with juvenile onset UC.

Gawron and colleagues evaluated the impact of hormonal contraception on disease-related cyclical symptoms in women with inflammatory bowel disease. Women on estrogen-based contraceptives had improvement in their cyclical GI symptoms in 19% of patients, and 47% of patients using levonorgestrel intrauterine devices showed improvement in cyclical GI symptoms [43]. The most common symptom improvement was diarrhea (48%), abdominal pain (44%), and cramping (41%).

Table 12.2 Various methods of birth control in inflammatory bowel disease patients

Method	Advantages	Considerations in IBD patients	Effectiveness (pregnancy rate in first year of use)	Types
Intrauterine devices and implants	Long-term reversible	Recommended first line	<1%	Copper IUD – efficacious for 10 years; no hormone exposure Levonorgestrel-releasing IUD – efficacious for 3–5 years; progestin Etonogestrel implant – efficacious for 3 years; progestin
Depot medroxyprogesterone acetate injection	Injection every 3 months	Given association with decrease in bone density, caution in patients with osteopenia or osteoporosis	6%	Progestin
Combined hormonal contraceptives	May improve cyclical GI symptoms during menstrual cycle	3× increased VTE risk in all women Avoid in IBD patients with prior h/o VTE or at high risk for VTE Active disease Steroid use Recent surgery Immobilization	9%	
Behavioral and barrier methods	Protection against sexually transmitted infections	Least effective	12–24%	

Adapted from Bonthala and Kane [1]

Does Contraception Affect Disease Activity in Inflammatory Bowel Disease?

As IBD is often diagnosed and manifests during a woman's reproductive years, it is important for the gastroenterologist to play an integrative role in preconception care as well as after a woman has conceived. This includes discussing the importance of remission prior to conception to improve maternal and fetal outcomes. The goal is

to have a woman in disease remission prior to conception in order to avoid increase in spontaneous abortion, preterm delivery, and low birth weight. It is important for the gastroenterologist to work closely with the patient's obstetrician for pregnancy planning and preconception planning. There are various contraceptive methods including behavioral methods, barrier contraceptives, oral contraceptive pills, contraceptive patch, and contraceptive ring, and the choice of the contraception depends on many things [1]. Some of the factors to consider include personal preferences such as method administration, changes to menstrual patterns, social and cultural beliefs, and consideration for protection against sexually transmitted diseases. In addition, there is concern for thromboembolic risk and bone density status which impact a patient's decision [1]. Oral contraceptives are used by women for various reasons including treatment of premenstrual symptoms in addition to pregnancy prevention. Premenstrual symptoms were discussed previously. Oral contraceptives have changed over time, and the estrogen and progesterone components have varied with the amount of estrogen decreasing over time. The various contraceptive methods will be discussed below and can be seen in Table 12.3.

Women with IBD use contraception at a lower rate than the general population [10]. Some of the factors as to why women with IBD utilize contraception at a lower rate than the general population despite the importance of pregnancy planning in IBD patients have been studied [44]. In a survey with 162 respondents, 62% had CD and 38% with UC. Twenty-three percent of women with IBD used no contraception, 17% used highly effective methods, and 41% used short-term-based hormonal methods and 19% barrier/behavioral methods [44]. Factors associated with no contraception use include prior IBD-related surgery, biologic therapy use, and low education status. Increased disease activity influences contraceptive use and method selection, and this may be due to these women altering their reproductive planning based on their disease severity [44].

Table 12.3 Symptoms and changes in menstrual cycle in patients with inflammatory bowel disease

Age at menarche	Can be delayed until early 20s (CD more than UC)
Premenstrual symptoms	Increase in symptoms of nausea, flatulence, abdominal pain, and diarrhea
Changes in cycle interval	
Increased	8.3%
Decreased	5.8%
Irregular	9.1%
Change in duration of flow	
Increased	4.1%
Decreased	9.1%
Irregular	5.8%
Change in intensity of menstrual pain	
Increased	13.2%
Decreased	2.5%

Adapted from Saha et al. [39]

The Centers for Disease Control and Prevention and US Medical Eligibility can assist women in selecting contraceptive methods for patients with a variety of medical problems based on recommendations from 2010 systematic review done by Zapata and colleagues [45, 46]. In IBD patients the preferred and unrestricted contraceptives include copper IUD (intrauterine device) and levonorgestrel-releasing IUD and implants. For medroxyprogesterone acetate (DMPA) injection and progestin-only pills (POP), the CDC states benefits outweigh the risks. For combined hormonal contraceptives, which include oral contraceptive pills (OCP), contraceptive patch, and vaginal ring, there may be thromboembolic risks that outweigh the benefits [1, 45, 46].

Bonthala and Kane summarize the different types of contraception and recommend IUDs as first-line agents with unrestricted use [1]. It appears that the most popular method of contraception by IBD patients was oral contraceptives at 41%, the patch and contraceptive ring [44]. As stated earlier, 20% of women with IBD also reported improvement in GI symptoms during their menstrual cycle while on OCPs. However, the pregnancy rate is 9 pregnancies/100 women in a year using OCPs [45]. Concerns with OCPs, however, include risk for venous thromboembolism (VTE) by threefold, according to a systematic review [47]. A meta-analysis evaluating risk of VTE in IBD patients showed that IBD is associated with a twofold increase in the risk of VTE [48]. The association between IBD and VTE was first reported by Bargen and Barker in 1936, who described 18 patients with primarily venous thromboembolic disease among 1000 patients at the Mayo Clinic [49]. Current guidelines recommend avoiding combined hormonal contraceptives in patients who might be at higher risk for developing deep venous thrombosis such as those with recent surgery, active IBD, and immobilization [46].

The progestin-only injectable contraceptive DMPA is administered every 3 months and effective at a rate of 6 pregnancies per 100 in a year. However, there has been an association with low bone density in many studies according to a systematic review [50]. Therefore, it is recommended that use of DMPA should be considered on a case-by-case basis if patients have risk factors for osteopenia or osteoporosis. Regarding implantable devices such as the copper IUD and levonorgestrel-releasing IUD, estrogenal implants are favored method of contraception by the CDC for women with IBD, and have rates of pregnancy of less than 1 per 100 women in a year [1, 45, 46]. These IUDs can be effective anywhere from 3 to 10 years depending on the type of implant. It appears, however, that only 17% of women who were surveyed used these types of implants for contraception [44]. There have been two case reports showing flares in patients who were initiated on IUDs. One of these patients had Crohn's disease [1, 51, 52].

The studies regarding use of hormonal contraceptive use and risk of IBD flares have been conflicting and small [1]. Given theoretical concerns that hormonal contraceptives may increase disease relapse and risk of other adverse events such as thrombosis, Zapata and colleagues performed a systemic review published in 2010 to evaluate the safety and effectiveness of contraception in women with IBD [45]. The authors of that study concluded that there is no increased risk of disease relapse among OCP users and no differences in absorption of higher-dose combined OCP

in patients with mild UC and small ileal resections compared to healthy women. Most absorption of oral contraceptive steroids occurs in the small bowel which comes from patients who have had jejunoileal bypass or history of small bowel inflammation as in with CD [53, 54].

There have been numerous studies which have shown an increase in IBD among users of OCPs. An earlier case-control study by Corrao and colleagues from 1998 of 819 patients in Italy showed that female patients who used OCP for 1 month prior to onset of symptoms had a higher risk of CD (OR = 3.4, 95% CI:1–11.9) whereas no significant risk for UC [55].

A study by Khalili and colleagues evaluated two large prospective cohorts of US Women-Nurses' Health Study I and II (NHS) and sought association between reproductive factors and long-term oral contraceptive use and risk of UC and CD [56]. The authors found a significant association between OCP use and risk of CD with age-adjusted HR for CD 2.88 for current OCP users and 1.50 among past users. The risk of UC and OCP use was dependent on smoking status [56].

A meta-analysis of 14 studies from 2008 by Cornish and colleagues provided evidence that there was an association between use of OCP and development of IBD, particularly CD [57]. The relative risk for CD was 1.51 and 1.46 when adjusted for CD, while that of UC was 1.53 and 1.28 when adjusted for smoking (not significant). The relative risk had increased with prolonged exposure to OCPs, and the risk was reversed to nonexposed when OCP was stopped. The increased risk of CD while taking OCPs could be to estrogen and venous hypercoagulability. In addition, estrogen may also enhance development of T helper 1-/T helper 2-mediated inflammatory diseases, and modification in gut microbiome could also be responsible. The thought is that OCP may lead to multifocal microvascular GI ischemia leading to development of colitis [57].

A study by Ortizo and colleagues performed a meta-analysis of 20 studies and found a 30% increased risk of IBD in patients that were exposed to OCP compared to patients not exposed with an odds ratio of 1.32 and specifically a higher risk of CD at 24% and 30% higher risk of developing UC [58].

Some studies have shown an increase in relapse in IBD among OCP users. A study by Timmer and colleagues prospectively followed 152 patients for 48 weeks or until relapse and found a threefold increased risk in relapse in CD patients in OCP users. Additionally, there was a twofold increased risk in smoking versus nonsmoking patients [59].

Khalili and colleagues conducted a prospective study from 2002 to 2013 in Sweden and measured first CD-related surgery and first steroid prescription in OCP users [60]. The results indicated that the hazard ratio for surgery was 1.14 (95% CI 0.80–1.63) for past users and 1.30 (95% CI, 0.89–1.92) for current users and risk of surgery increased with duration of use (>3 years) and higher prescribed daily dose. This result was noted in patients on combination type OCP versus progestin only. They estimated that for every 83 patients with CD who had received combination OCP for at least 1 year, 1 extra surgery was required. These patients were followed for median of 58 months [60].

Menopause

Given the chronicity of IBD, and bimodal presentation of UC and Crohn's disease, many women are followed from puberty to menopause. Menopause is defined as the cessation of menstrual periods. It is diagnosed after 12 months without a menstrual cycle [1]. There are conflicting data as to the effects of IBD on menopause and menopause on IBD flares. An early study published in 1989 showed that the mean age of menopause was earlier in patients with CD (47.6 years) compared to those without CD (49.6 years) [61]. However, there was no difference in age of menopause in a study by Kane and colleagues [62]. This study also evaluated the risk of IBD flares in women using hormonal replacement therapy (HRT). The authors hypothesized in this retrospective study that since estrogen has potent anti-inflammatory effects, an estrogen-deficient state should lead to increased disease activity. Estrogen receptors are expressed in the gastrointestinal tract, and down-regulation of proteins which recruit leukocytes with 17-β estradiol has shown improvement in vascular inflammation in animal models. They did not find a significant difference between disease flare in premenopausal and menopause. However, the authors did find a protective effect of HRT use and found that 80% are less likely to experience a flare in the first 2 years following menopause. The HRT used was Premarin and Prempro.

Multiple studies have shown that HRT in menopause have shown a decrease in flares in IBD. A study by Bharadwaj and colleagues also found that the use of HRT was associated with decrease in likelihood of flare during the first 2 years after menopause [32].

There is also concern among some patients regarding whether use of HRT can precipitate IBD. A study by Khalili and colleagues did show an increase in UC among HRT users [63]. This was a prospective cohort study of 108,844 postmenopausal women in the United States. The HR for UC was 1.71 among current hormone replacement patient users and 1.61 among past users, and risk was increased with longer duration of use and decreased with cessation of use when greater than 5 years [63, 64]. There was no difference in the type of HRT and whether it was estrogen or estrogen plus progestin. There was no association seen in CD. The exact mechanism, however, was unclear.

In conclusion, the hormonal differences in men and women can affect their incidence of inflammatory bowel disease, disease flares, and fertility. It is important for a gastroenterologist to work in close relation with a woman's obstetrician when she becomes pregnant, as discussions about contraception and timing of pregnancy are vital to a smooth and safe pregnancy in order to improve outcomes for the mother and fetus. In addition, the gastroenterologist must inquire about a woman's menstrual cycle, as there may be a delay in menarche due to various etiologies and dysmenorrhea. Hormonal treatment can be used as an option to control menstrual symptoms which can often be confused for IBD flares. Finally, it is equally important to assess a patient's knowledge of their disease, genetic transmission to future

offspring, and risk of infertility. Educating women about medication use during pregnancy and rates of fertility in the setting of IBD is vital. A woman with a well-controlled disease has the same fertility rate as the general population and can have favorable pregnancy outcomes.

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Chapter 13
Irritable Bowel Syndrome in Women

Shanti Eswaran and Laura O'Donohue

Patient Questions and Answers:

What is IBS and why do I have it?

Irritable bowel syndrome (IBS) is a common condition characterized by symptoms of abdominal pain, discomfort, and changes in bowel movements (diarrhea or constipation). Other common gastrointestinal symptoms include bloating, cramping, and urgency of stool. IBS impacts 7–21% of the global population and 12% of the population in North America, making it the most common GI disorder in the world [1]. There are several subtypes of IBS: IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), and IBS-M (mixed subtype). Your provider will take a thorough history of your symptoms to determine if you meet IBS diagnostic criteria (Table 13.1) [2] and may order a few tests to evaluate for other GI diseases. IBS is diagnosed by careful review of the person's symptoms, a physical examination, and selected testing or procedures that are often limited to a few basic tests. You will also be asked about so-called "alarm" or "red flag" symptoms, which can suggest other diseases besides IBS (Table 13.2). Your provider may also suggest a symptom journal to shed light on possible triggers and patterns. Unfortunately, there is no blood test or stool test for IBS, and extensive testing has not been shown to improve outcomes [3].

We don't fully understand what causes IBS, and it likely has multiple causes, differing from patient to patient. We know the gut of IBS patients is more sensitive than the gut of normal patients, but exactly why this occurs and how are still areas of intense research. A change in the intestinal microbiome and genetic factors may

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Table 13.1 Rome IV criteria for irritable bowel syndrome (IBS) with subtypes[a] [2]

Recurrent abdominal pain at least 1 day per week in the last 3 months associated with two or more of the following: 1. Related to defecation 2. Onset associated with a change in frequency of stool 3. Onset associated with a change in form (appearance) of stool
Subtyping IBS by predominant stool pattern
1. IBS with constipation—Hard or lumpy stools ≥25% and loose or watery stools <25% of bowel movements 2. IBS with diarrhea—Loose or watery stools ≥25% and hard or lumpy stools <25% of bowel movements 3. Mixed IBS—Hard or lumpy stools ≥25% and loose or watery stools ≥25% of bowel movements

[a]Criterion fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis

Table 13.2 Typical features of IBS compared to concerning "alarm" symptoms [18]

Features of irritable bowel syndrome	
Typical IBS features	Concerning features
Loose/frequent stools	Symptom onset after age 50 years
Constipation	Severe or progressively worsening symptoms
Bloating	Unexplained weight loss
Abdominal cramping/discomfort	Nocturnal diarrhea
Stool urgency	Family history of organic GI diseases including colon cancer, celiac disease, or inflammatory bowel disease
Symptom brought on by food intake/specific food sensitivities	Rectal bleeding or melena
Symptoms are dynamic over time (change in pain location, change in stool pattern from diarrhea to constipation)	Unexplained iron deficiency anemia

play a role. Factors that can give helpful clues as to the cause of your IBS include onset in relation to diet and stress, new medications including antibiotics, recent travel or infection, coexisting anxiety or depression, relation to menstrual cycle, and family history. All of these can act as triggers for IBS symptoms.

The important role that mental health plays in GI symptoms is just beginning to be understood, but it is well established as a factor in IBS. In fact, IBS was recently reclassified as a disorder of gut-brain interaction [4]. Stress, depression, and anxiety may all be a cause or contributing factor to your IBS, and addressing these issues is key to symptom management [5].

Does leaky gut cause IBS?

"Leaky gut," or increased intestinal permeability, is becoming a common term in popular vocabulary. It refers to the concept that inflammatory inputs such as foods, chemicals, chronic stress, or an infection may cause the normally tight barrier of our intestinal wall to loosen and become permeable or "leaky." This permeable

barrier may allow substances into the blood that then activate our immune system, causing inflammation and other possible downstream effects such as abdominal pain, fatigue, "brain fog," and even mood disturbance [6, 7]. It is important to understand that "leaky gut" is not a medical diagnosis and is generally a consequence of a gastrointestinal disease such as IBS, celiac disease, and inflammatory bowel disease. Some studies show that leaky gut may be associated with GI and non-GI symptoms, but we do not yet have clinical studies in humans showing such a cause and effect.

Does the microbiota play a role in IBS?

The gut microbiota is the population of microorganisms in our GI tract that includes primarily bacteria but also fungi and viruses. There are normally trillions of bacteria in your bowel that help break down the food we eat and keep us healthy. Negative changes in the type and/or number of organisms in the microbiome are termed dysbiosis.

Dysbiosis is not unique to IBS, though people with IBS often have dysbiosis as shown by stool analysis or breath testing [5]. Dysbiosis is often the inciting factor in post-infectious IBS or IBS that flares after a course of antibiotics. Most of the time though, it is unclear if dysbiosis is causing IBS symptoms [5]. While commercially available stool analyses for dysbiosis are marketed and widely available, these are not routinely recommended.

One type of dysbiosis is called small intestinal bacterial overgrowth (SIBO), a condition where increased numbers of bacteria are found in the small intestine. This can cause gas production, uncomfortable bloating, nausea, and diarrhea.

As a woman, why am I more likely to have IBS?

Women are 1.5–2 times as likely as men to have IBS in Western countries including the United States and Canada, but the split is more equal in Asia [8]. Women are also more likely to have constipation predominant IBS, whereas men are more likely to have diarrhea-predominant IBS [9]. Theories as to why women are more likely to have IBS include behavioral differences, such as likelihood of speaking with a health-care provider about symptoms and the impact of stress on the "gut-brain connection." It is observed that adverse childhood events such as abuse or trauma will increase the risk of developing IBS, and a history of these events is more common in women [10]. Finally, IBS symptoms tend to worsen around women's menstrual cycle [11, 12] and may be exacerbated by oral contraceptive use, supporting the role of sex hormones (like progesterone and estrogen) in IBS [13]. As mentioned earlier, a symptom journal can be a good strategy if you feel your symptoms worsen at the same time every month.

Can IBS change or develop in pregnancy and menopause?

Pregnancy is associated with gastrointestinal changes in most women, not just those with pre-existing IBS. Physical pressure from an enlarging uterus as well as hormonal impact on smooth muscle relaxation can commonly cause constipation, early satiety, and gastroesophageal reflux disease (GERD, or "heart burn") [14]. Nausea and vomiting are also common, and the cause is thought to be an

evolutionary tool to help mom's avoid food that were historically more likely to harbor pathogens like meat or dairy. Supplements commonly recommended in pregnancy such as iron and calcium can worsen constipation. Constipation, new or worsened, can be safely treated in pregnancy by increasing dietary fiber, fiber supplements, fluid intake, and increasing gentle exercise [15]. If you have a diagnosis of IBS going into pregnancy and are on medication for symptoms, it is important to run your medications by your doctor as some IBS drugs are not safe in pregnancy. If your symptoms are preventing you from eating enough during pregnancy, let your doctor know, so you can work together to address symptoms and find a treatment strategy that works for you.

Menopause occurs in most women at an average age of 51. Despite the fact that a decrease in estrogen should increase motility, this is not seen clinically, and many women experience constipation with menopause [16]. Estrogen plays a protective role in the tight connections of our gut lining, so decreased estrogen can lead to a temporary increase in intestinal permeability [17, 18]. Intestinal permeability is often seen in those with IBS, though is not diagnostic without symptoms (Table 13.1). People of both genders tend to eat less fiber and move less with age, which can contribute independently to constipation. Risk of colon cancer also increases with age, so if you develop new symptoms around the time of menopause, such as thin stools or blood in your stool (Table 13.2), these are not normal digestive changes in menopause, and it is important to let your doctor know.

Will I have IBS forever? Is there a cure for IBS?

IBS is a chronic disease, but symptoms can come and go over a patient's life, even switching subtypes between IBS-D (diarrhea), IBS-C (constipation), and IBS-M (mixed) [19]. Triggers can be obvious or seemingly random. The sometimes unpredictable nature of symptom onset can mean interruptions at work and social events leading to lost work productivity and decreased quality of life. Some cases of IBS may resolve with time, especially post-infection IBS or medication-associated IBS. If your IBS is exacerbated by, say, a stressful work or social situation, your symptoms may improve after that situation is resolved.

There is no cure for IBS, though there are ways to manage your symptoms. Treatment is not always straightforward, and it may take a couple different approaches to figure out what works for you. While millions of people live with this disorder, dealing with the symptoms may be tough at times. As much as possible, it's important not to put your life on hold because of your IBS. Understanding the possible long-term and varying nature of the disease can help reduce stress, and hence symptom severity [20]. Accepting the diagnosis, taking an active role in your own health care, and working with your providers long-term are all important to improve your IBS-related quality of life.

Am I at increased risk for other diseases such as colon cancer, colitis, or Crohn's disease?

People who meet the diagnostic criteria for IBS and have no "alarm symptoms" (Table 13.2) or abnormal testing on initial workup are very unlikely (1–3%) to have another disease process causing their symptoms. Patients with IBS have a normal life expectancy and are at no increased risk for diseases such as colon cancer, inflammatory bowel disease, or ulcers [21]. Extensive testing to diagnose IBS has not been shown to improve outcomes [3].

While IBS does not increase your risk of other GI diseases, it doesn't protect you from these either. If "alarm symptoms" develop along the way, let your doctor know as further workup such as an endoscopy or imaging may be required.

Should I be screened more regularly for colon cancer?

Not necessarily. While your symptoms may be disturbing, and even scary, colon cancer is not more common in patients with IBS. The rate of colon cancer is the same as that of the general healthy population. For this reason, regular colonoscopies and invasive tests are not recommended outside of normal age-appropriate screening [22].

What can I do to make my symptoms better?

I don't like taking medication, is there anything non-medication-based for IBS?

IBS can be a life-long condition whose symptoms can be managed with a combination of lifestyle modification and medicine. Understanding that IBS is not a life-threatening disease and learning to manage expectations and stress around symptoms is crucial to maintaining a high quality of life with IBS. A symptom diary can be very helpful in identifying triggers of your symptoms [23]. Establishing regular appointments with a mental health provider, or even a regular stress reduction practice, can be helpful [24]. Your provider may discuss both medication and non-medical approaches to address your symptoms (Table 13.3).

Dietary Interventions

Two thirds of patients experience IBS after meals [25]. Symptoms that occur after certain foods generally represent food intolerances and not true allergies [26], and food allergy testing is not recommended for IBS. An elimination diet can help identify food sensitivities. Gluten-free diets have gained popularity, and some people experience benefit with gluten avoidance even in the absence of celiac disease. This may be due to true non-celiac gluten sensitivity or to the multiple other elements that make up wheat products (fructans, other proteins, etc.) [5]. At this point, there is not enough evidence that a gluten-free diet will improve symptoms of IBS. It is important to rule out celiac disease, which is typically done at the initial workup for IBS.

Table 13.3 Common medications and treatments for IBS based on availability, targeted symptom(s), and common side effect(s) [18]

IBS treatment options				
Treatment	Recommendation	Quality of evidence	Treatment benefits	Most common adverse events
Over the counter				
Psyllium	Weak	Moderate	Best suited for IBS-C	Bloating, gas
PEG	Weak	Very low	Beneficial for constipation but no global symptoms or pain in IBS-C	Bloating, cramping, diarrhea
Loperamide	Strong	Very low	Beneficial for diarrhea but not global symptoms or pain in IBS-D	Constipation
Probiotics	Weak	Low	Possible benefits for global symptoms, bloating and gas as a class but unable to recommend specific probiotics	Similar to placebo
Peppermint oil	Weak	Moderate	Benefits for global symptoms and cramping	GERD, constipation
Prescription				
Antidepressants	Weak	High	TCAs and SSRIs improve global symptoms and pain. Leverage side effects to choose TCAs for IBS-D patients and SSRIs for IBS-C patients	Dry eyes/mouth, sedation, constipation, or diarrhea
Antispasmodics	Weak	Low	Some drugs offer benefits for global symptoms and pain	Dry eyes/mouth, sedation, constipation
Linaclotide	Strong	High	Improves global, abdominal, and constipation symptoms in IBS-C	Diarrhea
Plecanatide	Strong	High	Improves global, abdominal, and constipation symptoms in IBS-C	Nausea, diarrhea
Lubiprostone	Strong	Moderate	Improves global, abdominal and constipation symptoms in IBS-C	Nausea, diarrhea
Rifaximin	Weak	Moderate	Improves global symptoms, pain, and bloating in non-constipated IBS patients	Similar to placebo
Eluxadoline			Improves global symptoms in IBS-D patients	Constipation, acute pancreatitis

Table 13.3 (continued)

IBS treatment options				
Treatment	Recommendation	Quality of evidence	Treatment benefits	Most common adverse events
Alosetron	Weak	Moderate	Improves global, abdominal, and diarrhea symptoms in women with severe IBS-D	Constipation, rare ischemic colitis
Other therapies				
Psychological/ behavioral therapy	Strong	Strong	Benefits for global IBS symptoms in all subgroups	Similar to placebo
Diet	Strong	Moderate	Low FODMAP, gluten-free abdominal pain, bloating	Difficulty with adherence

FODMAP stands for "fermentable oligosaccharides, monosaccharaides, disaccharides and polyols." These are a family of carbohydrates found in many foods, even many healthy foods, all of which can lead to symptoms. In patients with IBS, FODMAPs can cause abdominal pain, bowel changes, and bloating, but they are not harmful or symptom-causing in healthy people [27]. Common FODMAP foods include lactose-containing dairy, sorbitol, legumes, many fruits, garlic, onion, and wheat. In some trials, up to 70% of people reported symptom improvement on a low FODMAP diet [28]. The help of a dietician familiar with the low FODMAP diet is important to help you navigate this tricky process of eliminating higher FODMAP foods and then reintroducing them as possible [27].

IBS-C patients are recommended to increase water and fiber intake (a fiber supplement such as psyllium works best) [29]. IBS-D patients are recommended to decrease caffeine. A trial period of eliminating lactose-containing dairy can be beneficial as well, as lactose intolerance can often overlap with IBS.

Exercise

Exercise is known to improve gut motility and overall IBS symptoms [30]. It is best to develop an exercise plan with your care provider that aligns with your preference and capabilities. Exercise does not have to be intense; even walking and yoga can have significant benefit [31].

Stress Reduction and Mood Stabilization

Even if you don't have a diagnosis of anxiety of depression, there is strong evidence that stress worsens IBS symptoms. This does not mean that your IBS is "all in your head"—your symptoms are real but may be flared by stress or anxiety. Thus, managing stress can be a cornerstone of IBS treatment and is crucial to maintaining your quality of life.

There are many modalities to reduce stress, including mediation, yoga, and formal psychological therapy. Cognitive behavioral therapy (CBT) has the most data showing improvement in IBS. Other modalities that have shown efficacy include psychotherapy, hypnotherapy, and mindfulness-based therapy. Antidepressants are also commonly used and can improve IBS symptoms even if you are not depressed [24, 32].

Probiotics and Prebiotics

Probiotics are bacteria that provide health benefits. In some people, changing the kind of gut bacteria with probiotics may make symptoms of IBS better [33]. Probiotics can be found in certain foods or supplements. There are insufficient data to recommend a specific formulation, but it is generally safe to self-experiment with over-the-counter options. If your symptoms worsen, stop taking it immediately and let your health-care provider know.

Prebiotics are fibers that are indigestible by humans, but they are ideal food for the bacteria in our gut. Foods high in prebiotics include beans, onion, garlic, artichoke, and apples. There is little evidence to support the benefit of prebiotics in IBS [33], and some people may actually find their symptoms worsen with prebiotic foods or supplements. Trying prebiotics, especially in food form, is low risk, but be on the lookout for any worsening symptoms.

Supplements

There are over-the-counter supplements that may be beneficial in IBS, but most supplements have not been adequately studied. It is important to ask your provider about adding these to your treatment plan, as there are potential interactions with other drugs. Your doctor may also give you personalized insight into which supplements may address your specific symptoms.

My doctor recommended laxatives for my IBS. What are the long-term risks associated with these? I don't want my gut to get addicted.

If dietary changes and exercise do not improve constipation, laxatives are a common additional treatment. Different laxatives work in different ways; they can increase the bulk of stool, soften the stool, or stimulate the muscles of your colon to move stool along. Some people come to rely on laxatives to have a bowel movement. Ideally, laxatives are a short-term solution, while dietary and lifestyle changes are implemented, but many people with IBS-C find long-term laxative use helpful. Long-term laxative use is not the same as addiction in the way we think about addiction to drugs or alcohol. Tolerance, which is when a higher dose is needed to achieve the same results, has not been seen with osmotic laxatives such as polyethylene glycol (MiraLax®).

Provider Questions and Answers:

IBS Pathophysiology and Gender Differences, Natural History, and Diagnosis

Pathophysiology and Gender Differences

IBS is a symptom-based disorder with multiple possible underlying causes. The Rome IV criteria reclassified IBS from a "functional GI disorder" to a "disorder of

gut-brain interaction" to reflect up-to-date understanding of mechanisms at play in IBS, as well as increase its diagnostic validity [2]. In part due to significant negative impact on quality of life and productivity, IBS has an annual burden of care in the United States of 3.1 million health-care visits and annual spending of over $20 billion [34, 35].

The pathophysiology of IBS, like the clinical presentation, is heterogeneous and driven by multiple factors. Traditionally, the pathogenesis of IBS has focused on host abnormalities in motility, visceral sensation, brain-gut interaction, and psychosocial distress, but more recently, altered gut immune activation, bile acid metabolism, intestinal permeability ("leaky gut"), and intestinal microbiome have emerged as potential causes. Multiple environmental factors have been identified as well, including the role of early adverse life events, dietary intolerances, antibiotics/medications, and prior enteric infections (post-infection IBS).

While the majority of IBS patients are women, the female predominance observed in Western countries is not seen in Asia [9]. Women with IBS are more likely to avoid socializing, avoid sexual intercourse, have a worse body image, utilize less decision-making authority, and take less advantage of opportunities at work due to IBS [9]. Some of this gender discrepancy may be attributable to biological effects of sex hormones such as estrogen and progesterone's influence on peripheral and central regulatory mechanisms contributing to alterations in visceral sensitivity, motility, permeability, and immune activation of intestinal mucosa [12, 36]. Cultural gender norms such as health-seeking behavior or gendered ideas about bowel habits may play a role as well [37].

IBS is associated with mood disorders and somatic chronic pain disorders that are more common in women, such as fibromyalgia, pelvic floor pain, and chronic fatigue syndrome [5]. Like IBS, these pain disorders may be impacted by estrogen's role as a CNS stimulant versus androgens which are CNS inhibitors [36], and past experiences of abuse or trauma can act as central pain amplifiers [38]. While an inciting event may not be readily identified on routine history, acknowledging and validating the patient's experience is an important step in establishing a trusting and effective relationship. Asking pointed questions about prior and ongoing abuse, trauma, and neglect can be beneficial to understanding the patient's experience and improving IBS outcomes.

Many women experience GI symptoms in pregnancy due to a surge in estrogen and progesterone as well as physical pressure from a growing fetus. Progesterone surges early in pregnancy and causes smooth muscle relaxation and decreases peristalsis. This combination leads to slowed gastric emptying and distension, both of which contribute to gastroesophageal reflux disease (GERD) as does the increase in intra-abdominal pressure from a growing fetus [14]. Thirty to fifty percent of pregnancies are complicated by GERD [39], and a food diary can help identify individual triggers. Decreased peristalsis can also lead to constipation and hemorrhoids, which is exacerbated by the pressure on the sigmoid colon from the fetus [14]. Along with common supplementation with calcium and iron and a decrease in exercise, constipation is the second most common GI symptoms in pregnancy after nausea [40]. Treatment for constipation in pregnancy should start with increasing fiber in the diet, having smaller frequent meals, and increasing fluid intake and

movement. Iron supplementation can be decreased to every other day if needed [41]. If these do not work, medications that are not systemically absorbed such as Metamucil and MiraLax are safe to use [42], [43]. Not all women with constipation in pregnancy will have IBS, though the Rome III criteria are still the best screening tool. If a pregnant patient presents with new diarrhea, she should be worked up for an infectious cause. If a patient with pre-existing IBS becomes pregnant, it is important to carefully review her medications as some IBS drugs are not safe in pregnancy. If GI symptoms are preventing your patient from getting enough to eat, it is important to work together to manage symptoms and find an appropriate diet.

Menopause occurs in women at an average age of 51. Many women report constipation with menopause, despite estrogens' known effect of slowed motility [16]. Many people eat less fiber and exercise less as they age, so constipation can be multifactorial. Dyssynergia, the inability to coordinate the nerves and muscles of defecation, or pelvic organ prolapse, is another anatomic cause of constipation in older women that should be considered. If a menopausal woman complains of alarm symptoms (Table 13.2), a further workup for colon cancer is indicated. Estrogen is known to promote mucosal health and tight junction integrity [17]. Mouse models have shown that decreasing estrogen leads to a temporal increase in intestinal permeability, which normalized over time [18]. While intestinal permeability may be exacerbated in menopause and is a predisposing factor for IBS, it is not diagnostic without the symptomatic criteria (Table 13.1).

Natural History

In most patients, IBS is a chronic relapsing disease in which symptoms may vary over time, exacerbated by multiple host and environmental factors. One systematic review demonstrated that over time, 2–18% of IBS patients worsened, 30–50% remained unchanged, and 12–38% improved [44]. Predictors of worse outcomes include previous surgery, longer duration of disease, higher somatic scores, history of trauma/abuse, pain as the predominant complaint, and comorbid anxiety and depression. Patients may also migrate between different IBS subtypes, and a change in bowel habit is not necessarily a cause for alarm.

Diagnosis

There is no currently accepted biomarker for IBS, but diagnostic criteria have evolved (Rome IV was created in 2016, revised from Rome III). The Rome IV criteria (Table 13.1) have a 69–96% sensitivity and 72–85% specificity for IBS and likely represent a more severe phenotype of IBS compared to Rome III patients [21, 45]. The Bristol stool chart is a helpful tool for patients to describe stool patterns and can be utilized to aid accurate history-taking.

A thorough initial history should include questions about recent travel, GI infections, life stressors, relation of symptoms to meals, and past medical history including mood disorders. "Alarm symptoms," which can indicate other disease processes (Table 13.2), are critical to explore. Obtaining a detailed medication list can help rule out medication-induced IBS, which can result from common medications such as opioids, metformin, antidepressants, and NSAIDs [23]. The

physical exam is typically normal in patients with IBS, but similar to asking about "alarm symptoms," an abnormal physical exam (lymphadenopathy, abdominal mass, the presence of anal fistulae, etc.) should prompt a more aggressive workup.

Once IBS is suspected, a thoughtful and focused workup can be pursued to screen for anemia, inflammation, and celiac disease (CBC, CRP, or fecal calprotectin, TTG IgA ± quantitative IgA). Upper or lower endoscopy is not required for the diagnosis of IBS, but patients should undergo all age-appropriate cancer screenings. *Clostridium difficile* infection should be excluded in patients with IBS-D who have recently received antibiotics. More invasive testing in the setting of typical IBS symptoms does not improve clinical outcomes or patient satisfaction [32].

Treatment Strategies

What can I do to make my symptoms better?

I don't like taking medication, is there anything non-medical for IBS?

A respectful patient-physician relationship is the cornerstone of successful IBS treatment [46]. Working to identify goals around quality of life and stress reduction in addition to addressing IBS symptoms may improve outcomes. Regular reassurance that even if symptoms are distressing, IBS is not a life-threatening condition, nor do symptoms lead to cancer or serious illness, can alleviate patient's concerns. Finally, establishing a secure and confident diagnosis of IBS is crucial to improving patient acceptance of the diagnosis.

Treatment for IBS can be just as varied as the causes of the disease itself. Treatment strategies of IBS can be both symptom-based and globally focused and will change depending on the patient's main complaint. For mild-to-moderate symptoms, over-the-counter medications targeted at regulating bowel movements, along with lifestyle changes, are first-line therapies given low-cost, low-risk, and widespread availability (Table 13.3). However, these first-line options often do little to improve the pain and bloating aspect of IBS. For moderate-to-severe symptoms, prescription medications (Table 13.3) are often utilized, but about half of patients with IBS use other approaches in addition to, or instead of, conventional medical therapy [47]. Most of these complementary and alternative approaches are unlikely to be seriously harmful, but some may exacerbate IBS symptoms (i.e., prebiotic supplements). While it is important to acknowledge patient efforts to self-educate and self-advocate, providers must inform patients about the unregulated nature of these products and lack of data supporting these approaches. That being said, there are several non-medical therapies and approaches that can be routinely recommended to patients, alone or in conjunction with other medical therapies. Finally, even short-term use of opiates should be avoided given the risk of narcotic bowel syndrome and potential for dependence.

Diet

Given that most patients experience GI symptoms in relation to eating, many patients attempt to restrict or modify their diets in some way to alleviate symptoms

[48, 49]. True food allergies are rare and food allergy testing is not indicated in IBS. Food sensitivities, however, are common and currently can only be diagnosed by elimination and subsequent reintroduction of the suspected food(s). Historically, most dietary trials have been small and of poor quality, suffering from bias and inadequate blinding due to the nocebo response (bias stemming from a perceived negative effect).

Gluten, the main protein found in wheat, barley, and rye products, has been implicated in symptom generation in IBS. The increased general awareness of gluten and gluten-free products [50] has led to widespread adoption of gluten avoidance in non-celiac individuals with IBS. Several studies have demonstrated improvement of IBS after gluten avoidance [51, 52] in select IBS populations. One double-blinded placebo-controlled trial in 34 subjects demonstrated worsening in overall IBS symptoms after ingesting wheat compared to placebo ($p = 0.047$), with similar significant trends seen in abdominal pain, bloating, and fatigue [53]. However, wheat contains fructans, alpha-amylase trypsin inhibitors, and other components that could be responsible for symptom generation in IBS. In fact, a subsequent study suggested that the symptom relief observed from gluten avoidance was likely secondary to the exclusion of poorly absorbed carbohydrates (fructans) rather than gluten itself [53]. Currently, the available evidence suggests that the prevalence of true non-celiac gluten sensitivity is small and has likely been previously overstated.

FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) are a family of osmotically active carbohydrates that are poorly absorbed in the small intestine. FODMAPs will then undergo fermentation in the large intestine, leading to gas, bloating, pain, and alteration in bowel habit. A diet low in FODMAPs has been shown to improve IBS symptoms, but the overall data are mixed. A recent meta-analysis identified seven randomized controlled trials comparing a low FODMAP diet with various control interventions and found the low FODMAP diet to be associated with reduced global symptoms compared to control interventions (RR = 0.69; 95% CI 0.54–0.88) [54]. The most robust studies, however, demonstrated the least magnitude of effect, and these authors rated the overall quality of the data "very low" mostly due to the low number of participants in the trials. Despite the limitations in the literature, a low FODMAP diet currently has the greatest evidence for efficacy in IBS. Providers recommending this diet should be mindful of the complexities of this approach as it requires individualized explanation, follow-up, and reintroduction by an experienced dietitian familiar with the low FODMAP concept.

Despite years of advising patients to alter their dietary and supplementary fiber intake, high-quality evidence surrounding the use of fiber for IBS is lacking with inconsistent data. Fiber undergoes partial or total fermentation in the distal small bowel and colon leading to the production of short-chain fatty acids and gas, thereby affecting gastrointestinal function and sensation. When fiber is utilized for IBS, a soluble supplement such as ispaghula/psyllium is best supported by the available evidence. To avoid side effects, fiber should be started at a nominal dose and slowly titrated up as tolerated over the course of weeks to a target dose of 20–30 g of total dietary and supplementary fiber per day.

Exercise

While the physical and mental benefits of exercise are readily apparent, increasing physical activity in somatic disease may have a positive impact on disease-related symptoms and quality of life as well. A randomized clinical trial found that an aerobic exercise intervention led to greater improvements in overall IBS symptoms than usual care [30]. Yoga, regular walking, and Tai Chi have all demonstrated improvement for IBS possibly through modulation of the brain-gut access. A recent systematic review of 14 randomized trials found that GI symptoms, QOL, anxiety, and IBS-related comorbidities showed better improvements with exercise therapy than with usual care or lifestyle maintenance in patients with IBS [31]. The safety profile, accessibility, and favorable cost associated with exercise makes it an attractive first-line therapy for this chronic disease.

Psychological Therapies

Given the overlap of mood disorders with IBS, psychological therapies (and antidepressant medications) may be beneficial not just for their effects on mood and coping but also for potential peripheral benefits on motility and visceral hypersensitivity. Although the beneficial effects may have been overstated due to lack of blinding and other methodological flaws, multiple meta-analyses have suggested that psychological treatments are effective for IBS, with the most recent study including 35 RCTs [55]. Cognitive behavioral therapy has the most data for efficacy in IBS, but other modalities that have shown efficacy include psychotherapy, hypnotherapy, and mindfulness-based therapy [32]. Logistical limitations, including variable third-party reimbursement, a lack of available clinicians, and poor patient and clinician acceptance, have limited the widespread adoption of these therapies in clinical practice, but this may improve with the development of book, Internet, or application-based behavioral programs.

Conclusions

While there is no cure for IBS, the majority of IBS patients endure mild-to-moderate symptoms which can be managed with a combination of the aforementioned approaches. The patient with refractory IBS that suffers severely reduced quality of life represents a clinical challenge. Pain is often the predominant complaint, with psychiatric comorbidity and a history of trauma or abuse invariably present. These patients are generally treated best via a multidisciplinary approach, utilizing mental health providers, registered dietitians, an effective provider-patient relationship, and ongoing follow-up.

Despite the high prevalence, the precise pathophysiology of IBS remains poorly understood likely due to the heterogeneity of IBS populations and the multifactorial etiology of this disorder. Future directions for IBS management include clarifying the efficacy and nuances of dietary therapy for symptom management. Given the

dysbiosis associated with IBS, modulation of the gut microbiota is an attractive approach, and further elucidation of the appropriate probiotic or antibiotic regimen is needed. The results of fecal microbiota transplant for IBS are thus far mixed, and further studies focusing on the mode of transplant and ideal patient phenotype are required. Finally, specific biomarkers may be useful not just for the diagnosis of IBS but for treatment planning and prognostic purposes as well.

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Chapter 14
Chronic Constipation

Arnold Wald

Questions

1. **I am a healthy 26-year-old woman who has a bowel movement once weekly on average. I have no straining or sense of incomplete evacuation. My family says this is very abnormal. Do I need a work-up or treatment?**

In a recent US survey, 96% of the sample reported between 3 and 21 bowel movements per week; 90% of women reported a BSFS from 2 to 6 (Mitsuhashi et al.). Therefore, this woman falls below the norm. However, she reports no defecatory symptoms such as excess straining and sense of incomplete evacuation or of anal blockage. Therefore, she does not fulfill the Rome criteria for chronic constipation (see Table 14.1); thus no work-up is needed nor is any treatment necessary.

2. **I have a bowel movement two to three times per week unless I use a laxative. I've been told that I should go every day to be healthy. Is there a safe laxative to take so I can do this?**

The concept of having a daily bowel movement is a holdover from concepts dating to the Victorian era and promoted by JW Kellogg, among others, at the turn of the nineteenth century. The "autointoxication" theory postulated that many diseases may arise via the absorption of poisonous substances from stools within the colon. In fact, many otherwise healthy adults have as few as three bowel movements per week, and this is especially true in women. Therefore, there is no biologically plausible reason to aim for a daily bowel movement to maintain optimal health, and therefore, a laxative is not necessary [2, 3].

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Table 14.1 Definition of chronic constipation

Presence of two or more of the following complaints present for at least 3 months in the previous year
With at least 25% of bowel movements: 1. Excessive or prolonged straining 2. Sensation of incomplete evacuation 3. Hard or lumpy stools 4. Sensation of anorectal obstruction 5. Manual maneuvers to facilitate defecation 6. Spontaneous and complete BM <3 per week
Implications: Infrequent defecation *alone* is insufficient for the diagnosis of chronic constipation

From Ref. [1]

3. **I have been told to drink at least eight glasses of water per day to maintain good bowel habits (I have four to five bowel movements a week). I empty my bladder a lot during the day and sometimes at night. Should I continue to do this?**

There is no evidence that constipation can be successfully treated by increasing fluid intake unless there is evidence of dehydration. Excessive water consumption results in more water absorption by the colon and, therefore, increased urinary output. If you urinate regularly and are not frequently thirsty, less fluid consumption will not adversely affect bowel habits [3].

4. **I often use a stimulant laxative to promote better bowel function. My doctor told me to stop doing this because I will become dependent on them over time. Should I stop taking them?**

The concept of dependency on laxatives with long-term use implies an addictive property that is misguided. While laxatives may be misused, there is no potential for addiction as they do not cross the blood-brain barrier. A proportion of patients with chronic constipation is dependent on laxatives to achieve satisfactory bowel function, and indeed, over time, a higher dose may be required to do so. However, we would not apply this term to patients using antihypertensive drugs or diabetics using hypoglycemic agents and who might require dose adjustments of these medicines from time to time. Finally, there is no evidence of "rebound constipation" after stopping laxative intake [3, 4].

5. **I've been constipated for many years and have used stimulant laxatives regularly. I'm 40 years old and was told that these laxatives can damage my colon and lead to colon cancer. Should I start having regular colonoscopies because of this?**

Although stimulant laxatives (senna and bisacodyl) can cause mild superficial damage to the colon, there is no known damage to the function of the nerves or muscles of the colon. The characteristic finding with senna and all anthraquinones is melanosis coli which is a benign dark pigmentation of the superficial colonic mucosa easily seen during colonoscopy.

Although chronic constipation itself is thought to slightly increase the risk of colon cancer, there is no evidence that the use of any laxatives available today do so, including senna and biscodyl. Therefore, there is no reason to alter the recommendations for colon cancer screening on chronic laxative use alone [3, 5].

6. **I have been constipated most of my life and often have bloating and cramps. A barium enema showed that my colon is very long and kinked. A surgeon advised that I have it shortened and straightened out. Do you agree?**

The term dolichocolon has been used to describe an elongated colon which may be folded upon itself. It is mainly congenital, and some have ascribed symptoms such as cramps and constipation to its presence. However, there is no evidence that such a colon is a cause of constipation or even symptoms. Surgery would be advised only in the case of volvulus or in the presence of severe and refractory slow transit constipation; in the latter case, a subtotal colectomy might be indicated regardless of the length of the colon [3, 6].

7. **I have always had trouble moving my bowels on a regular basis. I take a number of medications for my heart and for high blood pressure. Can these medications make my problems worse?**

There are many factors that may be associated with constipation and among them are many medications. Some of these medications are once used to treat high blood pressure or heart disease. Examples of such commonly used agents are shown on Table 14.2, although it is not a complete list. The decision to continue to use these agents is based upon the clinical indications for their use and the availability of suitable alternatives that do not worse constipation.

8. **I have been using opiate opioid drugs to reduce chronic back and neck pains. This has made me constipated, and no laxative has been very effective. Is there anything I can take to help my bowels move?**

Many patients who use opioids have constipation and other gastrointestinal adverse effects. Opioids delay gastrointestinal transit which promotes water absorption by working on opioid receptors in the gut as well as the central nervous system. This leads to constipation which may be resistant to most available laxatives.

Table 14.2 Some drugs associated with constipation

Anticholinergics	Diuretics
Anticonvulsants	5-HT3 antagonists
Antihypertensives (some)	Granisetron
Anti-Parkinson drugs	Ondansetron
Calcium channel blockers	***Opiates Opioids***
Cation-containing agents	Tricyclic antidepressants
Aluminum (antacids, sucralfate)	
Bismuth	
Iron supplements	

From Ref. [7]

Table 14.3 Available opioid antagonists (2018)

Drug	Receptor antagonism			BBB	Cost/month[a]
	Mu	Kappa	Delta		
Naloxone	+++	++	++	Yes	
Naltrexone	+++	++	++	Yes	
Methylnaltrexone (12 mg SC EOD) (450 PO daily)	+++	++	++	No	$2080 $2079
Naloxegol (12.5–25 mg daily)	+++	−−−	−−−	No	$427
Naldemedine (0.2 mg daily)	+++	−−−	−−−	No	$377

Mu, kappa, delta are opioid receptors in the gut
[a]Wholesale; Courtesy of Dr. Michael Hirsch, UWHC

Recent studies support the efficacy of a number of pharmacologic agents in the treatment of opiate-associated constipation—methylnaltrexone, naloxegol, and naldemedine. These agents work on the peripheral opioid receptors in the gut and not in the central nervous system, thus preserving the pain modulating effects of opiates opioids. The pharmacologic properties and the estimated whole cost of 1 month of drugs is shown on Table 14.3 [8].

9. **I strain a lot when I have a bowel movement, and I don't always think I feel empty. My gynecologist told me that I have a rectocele, and it can be repaired. Do you think this is a good idea?**

A rectocele is a bulging of the rectum through a defect or weakness of the anterior rectal wall into the posterior vagina. Rectoceles are common in asymptomatic women, and the finding of one in a patient with defecation straining does not imply causation. Surgery should be considered only for women who have retained barium during defecography *and* if digital vaginal pressure makes defecation easier and more complete. It would be wise to eliminate a defecation disorder with anorectal testing before performing a rectocele repair [9].

10. **I have been told that I have irritable bowel syndrome with frequent constipation. I eat lots of fiber and drink at least eight glasses of water per day. For the past several months, I have a great deal of bloating and cramps. Should I have a colonoscopy or a CT scan?**

Increasing dietary fiber often improves constipation. The recommended fiber intake is from 20 to 30 g in the form of vegetables or fruits, but one can supplement with fiber products such as psyllium, calcium polycarbophil, or wheat dextrin. However, many patients tolerate fiber poorly, at least in part due to fermentation of fiber by colonic bacteria which produce either hydrogen and/or methane gas. This is particularly so in the population with IBS-constipation predominance. In such patients, dietary fiber is best curtailed or used modestly. One can substitute PEG-based compounds which are inert or consider the use of secretory agents such as linaclotide, plecanatide, or lubiprostone. Many doctors have fallen off the "bran wagon" for treating constipation because of the intolerance that many patients experience [3, 10].

11. **I've been constipated for years, and my stomach is always distended. An X-ray showed a very large (mega)colon with lots of air and stool. I tried increasing fiber, Miralax, and every laxative including prescription agents, but nothing helps and I often feel worse. What can I do to feel better?**

Chronic megacolon is not a common condition and represents advanced colon failure that does not respond well to pharmacologic stimulation. The colon wall is often thin, and nerve cells are reduced. Eating lots of fiber or taking PEG or lactulose-based products simply increases stool and gas content and is analogous to a person consuming extra salt and water in the presence of dilated cardiomyopathy.

This condition is **not** treated like constipation. Rather, goals of therapy are to cleanse the colon, prevent stool buildup or fecal impaction, and minimize stool volume and gas (i.e., consume a low-fiber diet). Periodic enemas may be effective. If symptoms remain disabling, surgical exclusion or resection of the colon may be palliative [11].

12. **When I was young, my mother gave me mineral oil every day to help me be regular. I have been constipated for a while now. Should I start taking mineral oil again because my bowel movements are often large and hard?**

Mineral oil was a traditional approach to treating children with constipation but which has fallen out of favor. The biggest danger is that if it is aspirated or vomited, it can cause a severe (lipoid) pneumonia. In addition, mineral oil can sometimes seep out of the rectum. There are more palatable and safer products available. In children and adults, PEG-based products are a popular choice if fiber intake is inadequate and if inexpensive stimulant laxatives are unhelpful. Stool softeners are often used with no evidence that they are effective for constipation. These products make oral mineral oil an unattractive choice for constipation with the occasional risk of real harm.

13. **I have seen the Squatty Potty advertised on TV. Will it help my constipation and make me have better bowel movements?**

Squatting to defecate is practiced in many parts of the world. The natural squat position straightens the anorectal axis and relaxes the puborectalis muscle to better align the angle of defecation.

Although squatting theoretically makes defecation easier, there is no evidence that it produces a larger or more complete bowel movement.

If you want to use it, make sure that you sit on the toilet first, and then place the foot bench in place. Most importantly (especially for older individuals) retract the bench and place your feet on the floor before rising from the toilet [12].

14. **I have relapsing, remitting multiple sclerosis (MS) and have become constipated, with two to three bowel movements weekly with some straining. Magnesium citrate and Miralax help, but sometimes I have an urgent bowel movement and incontinence. Should I try one of the newer laxatives that are being advertised?**

In a large population survey, over 40% of individuals with MS reported constipation, and over 50% reported fecal incontinence (constipation and/or fecal incontinence in 68%). Studies have demonstrated frequent abnormalities of anorectal function, including impaired sense of the need to defecate and weak anal sphincter muscles. Laxatives may uncover subclinical abnormalities, lead to accidental passage of bowel movements, and therefore should be used judiciously.

Timed stimulation of defecation without liquifying stools is best accomplished by stimulant laxatives. Bisacodyl is effective orally or by suppository. Senna is effective only orally, and a glycerine suppository is an alternative to bisacodyl suppositories. Osmotic and secretory such as linaclotide, plecanatide, and lubiprostone can cause diarrhea, are more expensive, and are less optimal choices in the MS patient with constipation [13].

15. **I have had severe constipation for many years, and every laxative that I have tried has not worked. All of my tests (including a colonoscopy) have been normal. What is the reason for this, and do I need any more testing?**

Whereas most patients with constipation can find adequate relief, a small minority are resistant to all treatments. Broadly speaking, many patients have a problem with defecation, whereas others have a colon problem, referred to as slow transit constipation or colonic inertia.

The consensus among experts is that these patients should undergo anorectal manometry which includes testing to see if they can expel a water-filled balloon normally. If they cannot, they have a functional defecation disorder which can often be treated with pelvic muscle rehabilitation using instrument feedback. If defecation studies are normal, they should have a colon transit study which measures how radio-opaque (can be seen with an X-ray) markers pass through the colon over a 5–7-day period (depending on the protocol). If transit is very slow, they are thought to have a problem with the nerves or muscles of the colon, and this requires a different approach. The last pattern is seen almost exclusively in women [9].

16. **I have had severe constipation, but no laxatives give me sustained improvement. I had a sitzmark study, and I was told my colonic transit was very slow. A surgeon recommended that I have most of my colon removed and I won't need a bag. Should I have the surgery?**

The finding of very slow colonic transit does not necessarily mean that the colon is the primary problem. If you have a problem with defecation, the markers could be "backed up" into the proximal colon, and removing the colon would not solve the problem. That is why experts recommend anorectal manometry with timed balloon

expulsion from the rectum (BET) first. If this is abnormal, you may be successfully treated with biofeedback, and if the constipation markedly improves, no surgery should be done. If manometry is normal, you have isolated colonic inertia, and I would try misoprostol first in an attempt to stimulate the colon. Although there is little scientific evidence to support its use, it has worked in about 40% of my patients with colonic inertia in doses ranging from 400 to 1000 μg daily. If this fails and there is no evidence of poor motility elsewhere in the GI tract, and if abdominal pain is not a major complaint, subtotal colectomy can be useful in selected patients with severe slow colonic transit [9].

17. **I have been constipated for many years, and my husband and I want to start a family. What is the best laxative to take when I do become pregnant?**

In a comprehensive review of the safety of gastrointestinal drugs in pregnancy, PEG was judged to be the ideal laxative, although it is classified as Category C (no safety data available in animals or humans) by the FDA. This is due to its inert properties and minimal absorption from the adult GI tract. Senna is considered safe and effective for short-term use and may be given if PEG is not effective [14].

18. **I am a healthy person and had a screening colonoscopy last month. The doctor told me that the lining of my colon was dark and suggested that I was abusing laxatives. I have never used any laxative at all. Can you explain what is going on?**

The colonoscopy report states that you have melanosis coli which is a pigment in the lining of the colon often seen in individuals who use senna and similar substances. It is considered a harmless finding.

Many products sold in health stores for "bowel health" contain anthraquinones, which are derived from certain plants. These include senna, cascara sagrada, aloe, frangula (buckthorn), and rhubarb. If you are using such products, read the label to see if any of these plants are present. The pigment will generally disappear within 6–12 months after stopping the product [5].

19. **For many years, I have had constipation and have used stimulant laxatives or Miralax. I see ads for new agents for constipation—in particular, Linzess and Amitiza. Are these better or safer laxatives, and should I begin to use them?**

In the absence of any studies which compare older laxatives such as senna, bisacodyl, and PEG with newer agents such as lubiprostone, linaclotide, and plecanatide, most physicians are guided by efficacy, cost, and side effects when suggesting laxatives for constipation. If inexpensive and available laxatives are effective, there is no need to consider the newer and heavily promoted products.

While costs to patients will vary, Table 14.4 indicates the wholesale cost of one (1) month of the major laxatives which are available in the USA. The figures speak for themselves [8, 10].

Table 14.4 Cost comparison of constipation treatments[a]

Treatments	Cost per month, 2018 (USD)
Bulk agents	
Psyllium (10 g daily)	8.00
Non-absorbed substances	
Lactulose (20 g daily)	13.00
PEG 3350 (17 g daily)	9.00 31.00 (packets)
Stimulants	
Senna (17 mg daily)	7.00
Bisacodyl (10 mg daily)	5.00
Secretory drugs	
Lubiprostone (8–24 mcg bid)	445.00
Linaclotide (72–290 mcg daily)	509.00
Plecanatide (3–6 mg daily)	494.00

PEG 3350 polyethylene glycol 3350-electrolyte
[a]Lexicomp Online, Lexi-Drugs, Hudson, Ohio. January 14, 2018. Courtesy of Michael Hirsch, Pharm D, U of Wisconsin

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Chapter 15
Colorectal Cancer Screening and Women

Katherine Hu and Carrie Y. Peterson

Who is at risk for colon and rectal cancer?
Colorectal cancer (CRC) is one of the most commonly diagnosed cancers in the United States. Although most cases are diagnosed in adults over age 50, CRC is increasing in younger people in recent years for reasons we don't totally understand. Other people at high risk for developing CRC include those with personal history of polyps or CRC, family history of CRC, known familial CRC syndromes, or inflammatory bowel disease.

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer in the United States and the overall second leading cause of cancer death. Over 140,000 patients in the United States are expected to be diagnosed with CRC in 2018 [1]. Incidence of CRC is similar in women and men until age 35 but then increases for men; African-American men have the highest incidence and mortality rates compared with other racial and ethnic subgroups. For most adults, the most important risk factor for CRC is older age. Most cases are diagnosed in adults over age 50, with median age of diagnosis at 68 years [2].

Although the overall risk of CRC has declined, this is driven primarily by trends in older age groups, with accelerated decline in the early 2000s. In contrast, rates of CRC incidence are increasing in younger cohorts. Incidence of CRC in those younger than age 55 has increased by almost 2% per year from the mid-1990s to 2014 [1]. This difference between generations is especially pronounced in rectal cancer, with rectal cancer incidence in patients aged 20–29 increasing by 4% annually from 1974 to 2013, in contrast to a net decrease of 2.1% annually in adults aged 75 or older. Compared with adults born in the 1950s, those born in the 1990s have approximately double the risk of colon cancer and quadruple the risk of rectal cancer [3]. Similarly, although the overall mortality from CRC has declined by 52%

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from 1970 to 2015, death rates have increased since the 2000s in patients younger than 55 years [1, 4].

It is unclear why CRC incidence is rising in younger generations. Although early-onset CRCs are more likely to have a hereditary component than late-onset cancers, the majority of cases are sporadic [5]. An important measure to address the rising rates of young-onset CRC is education of the public and clinicians of the increased probability of disease in younger patients. Young patients are 58% more likely to be diagnosed with advanced disease, often due to delayed evaluation of symptoms, because CRC is not initially considered as a possible differential diagnosis. One study found that time from symptom onset to treatment for young patients with rectal cancer was more than four times longer compared to their older cohort, at 217 versus 58 days, respectively [6]. Additionally, these patients are too young to meet screening criteria based on current guidelines. CRC should be considered in patients who present with change in bowel habits, anemia, or bleeding, regardless of age [7].

Other individuals at increased risk for CRC include those with personal history of polyps, those who have previously undergone resection of CRC, and patients with family history or known genetic predisposition to CRC [8]. Approximately 20–30% of CRC is associated with a family history of CRC or polyps in at least one first-degree relative, and 3–5% of CRC is associated with a known germline mutation that confers an inherited predisposition to CRC [9, 10].

Finally, patients with inflammatory bowel disease (IBD), either ulcerative colitis (UC) or Crohn's disease, are at a higher risk for development of CRC. For both UC and Crohn's disease, duration and anatomic extent of disease are independent risk factors for development of CRC [11]. The risk of CRC in patients with IBD begins to increase 8–10 years after the initial onset of colitis [10]. It is important for these patients to undergo regular screening and random biopsies as cancer and dysplasia can occur in patients with quiescent disease and in areas of the colon that appear endoscopically normal [11].

Is colorectal cancer preventable?

Yes—colorectal cancer is preventable with screening measures, such as colonoscopy. Although some lifestyle changes, such as increased physical activity and increased dietary fiber, may further decrease risk, the primary way to prevent CRC remains screening and removal of polyps before they have the chance to turn into cancers.

CRC has a slow and predictable progression from precancerous polyps to malignancy. Thus, the primary means to prevent colon cancer are screening and early detection with colonoscopy. Since 2000, colonoscopy in US adults aged 50 years or older increased from 21 to 60% in 2015. This increased effort in screening is considered to be the primary cause of the accelerated overall decline in CRC incidence seen in older adults [1]. Other known lifestyle factors associated with increased CRC risk include obesity, cigarette smoking, and high consumption of processed meat and alcohol. One meta-analysis attributed a 60% increase in CRC risk in patients consuming the most alcohol compared to nondrinkers or light consumers.

Smoking, obesity, and high meat intake were each associated with a 20% increase risk of CRC [12]. Increased body mass index (BMI) has additionally been associated with an increase in both CRC incidence and long-term mortality [13]. In contrast, physical activity and high intake of whole grains and dietary fiber have been associated with reduced risk of CRC [12, 14].

Are My Children at Risk for Colorectal Cancer?

Having a family history of CRC does increase the risk—particularly for first-degree relatives such as parents, siblings, or children. There are a few known syndromes that dramatically increase CRC risk, most commonly Lynch syndrome and familial adenomatous polyposis (FAP), but overall only affect about 5% of patients with CRC. If a genetic syndrome is suspected, a detailed family history should be obtained, and the patient referred for genetic screening and counseling.

The minority of colorectal cancers, approximately 3–5%, are due to known germline mutations causing hereditary familial CRC syndromes. However, family history is a known risk factor for the development of CRC. Approximately 25% of patients with CRC have at least one first-degree relative with CRC [9, 10]. In one study, the relative risk for CRC cancer was 1.72 in patients with one first-degree relative with CRC and 2.75 if they had two or more relatives with CRC [10]. The two most common inherited CRC syndromes are familial adenomatous polyposis (FAP) and Lynch syndrome. Of particular significance to women, in addition to increased risk for breast cancer, *BRCA* mutations may also increase risk for colon cancer [15, 16]. If a hereditary colorectal cancer syndrome is suspected, it is essential to obtain a detailed history for each family member including current age, types of cancer diagnosed and age at diagnosis, age and cause of death, ethnicity, consanguinity, presence of any syndrome-specific features, birth defects, and details regarding any prior colonoscopies, pathology reports, and known inherited conditions [17].

Lynch Syndrome

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is the most common hereditary CRC syndrome and is estimated to account for ~3% of all CRCs [10]. Patients with Lynch syndrome have a 50–80% lifetime risk of developing CRC [15]. Lynch syndrome is characterized by autosomal dominant inheritance, early age of CRC onset, predominance of proximal colon cancers, and multiple primary colon tumors [10]. Patients with Lynch syndrome have additional increased risk for other cancers as well, including gastric, ovarian, hepatobiliary, urothelial, small bowel, brain, and pancreatic cancer. The most common extracolonic cancer is endometrial cancer, which is associated with a 40–60% lifetime risk in women with Lynch syndrome. Germline mutations in DNA

mismatch repair (MMR) genes lead to Lynch syndrome and include the following loci: *MLH1*, *MSH2*, *MSH6*, and *PMS2*. *MLH1* and *MSH2* mutations are most common, accounting for 90% of Lynch syndrome cases [15].

There are many screening criteria to identify these patients, including clinical criteria, such as the Amsterdam criteria and revised Bethesda guidelines, and various computational models, such as the MMRpredict, MMRpro, and $PREMM_{1,2,6}$ models. The Amsterdam criteria and Bethesda guidelines take into consideration number of family members with Lynch-associated cancers and age at diagnosis, whereas computational models additionally account for location of tumors, presence of synchronous disease, and history of any completed genetic testing [18]. In a project sponsored by the Office of Public Health Genomics at the Centers for Disease Control and Prevention, it was revealed that even under the most liberal screening criteria, up to 28% of Lynch syndrome patients could be missed. Although no testing strategy was specified, it was determined genetic testing should be offered to all individuals with newly diagnosed CRC [18, 19]. In many centers, patients with malignancies are routinely tested for microsatellite instability and abnormal MMR proteins present in tumor cells using immunohistochemistry. Confirmation testing to evaluate the germline mutations is needed to make the diagnosis of Lynch syndrome, as some sporadic tumors can develop microsatellite instability as well. Once the diagnosis of Lynch syndrome is made, further genetic counseling and testing can be offered to patients and their family members [18].

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant syndrome, characterized by the presence of tens to thousands of adenomas in the colon and rectum [10]. FAP is caused by germline mutation of the adenomatous polyposis coli (*APC*) tumor suppressor gene. Classic FAP is characterized by the presence of at least 100 synchronous adenomatous polyps throughout the colon and rectum. Approximately half of all patients with classic FAP will develop polyps by age 15 and 95% by age 35. In untreated patients, there is a near 100% risk of developing CRC, by an average age of 39 years old. Patients with attenuated FAP have 10–100 polyps and ~70% lifetime risk of CRC [20]. Polyp and CRC development is delayed by 10–20 years in patients with attenuated FAP compared to classic FAP [21].

FAP is also associated with extracolonic disease, including duodenal adenomas (present in 30–70% of patients) with lifetime duodenal adenocarcinoma risk of 4–10%, gastric polyps (present in 50% of patients), and desmoid tumors of the small bowel mesentery, abdominal wall, and extremities (present in 10% of patients) [20]. Genetic counseling and testing are indicated for all first-degree relatives of patients with known FAP, as well as anyone with a clinical diagnosis or suspicion for FAP. Approximately 20–30% of patients with FAP have no family history, with their disease arising from new spontaneous mutations [10].

BRCA Mutations

Mutations in *BRCA1* and *BRCA2* genes are well-known to increase susceptibility to breast and ovarian cancers. *BRCA* mutations have also been associated with other cancers, including lymphoma, leukemia, prostate, pancreatic, stomach, and colorectal cancer, though the magnitude of risk for these cancers is not clear. A recent prospective study of women with *BRCA* mutations demonstrated that *BRCA1* mutations were associated with an approximately fivefold increased risk of CRC in women younger than 50 years, but an association was not found in older women or those with *BRCA2* mutations [22]. This is consistent with prior retrospective studies demonstrating a 2–4× increase in in *BRCA1* mutation families, but not *BRCA2* [16]. This suggests women with *BRCA1* mutations should be counseled regarding their increased risk for early-onset CRC and undergo earlier screening colonoscopy.

What are the types of screening available?

Numerous screening methods for CRC exist; however, colonoscopy with polypectomy remains the gold standard and the confirmatory test performed when other screening options yield positive or suspicious results. Colonoscopy is so good because it allows us to diagnose cancers, treat some early cancer, and even prevent future cancer by removing the polyps at the same time. Other screening options include stool-based testing, flexible sigmoidoscopy, and CT colonography (Table 15.1).

Screening modalities for CRC can be divided into two main categories of stool-based testing and direct visualization tests. Direct visualization tests include flexible sigmoidoscopy and colonoscopy. Colonoscopy is the preferred, "gold standard" screening method with high sensitivity and specificity. It is the definitive test performed when other screening methods yield positive results and allows for detection, biopsy, and resection of lesions throughout the entire colon and rectum [23]. Colonoscopy with polypectomy is estimated to decrease incidence of CRC by 90% and CRC mortality by 53–68% [24–26]. Downsides to colonoscopy include cost and the need for full bowel preparation and sedation [23]. Additionally, there is risk for serious complications such as post-polypectomy bleeding and perforation [8]. Flexible sigmoidoscopy allows for limited bowel preparation in comparison to colonoscopy and has also been shown to decrease CRC mortality when compared to no screening. Sigmoidoscopy is limited to the distal colon and thus provides less mortality reduction, approximately 26–31%, compared to colonoscopy, but in selected patients it may be the most appropriate screening test [23].

CT colonography (CTC) is a noninvasive radiographic test that allows for screening with no sedation as well as extracolonic imaging evaluation. Although CTC may appeal to patients hesitant to undergo colonoscopy, it requires the same bowel preparation as colonoscopy in addition to the added risks of contrast reaction and radiation exposure [23]. Additionally, while overall sensitivities of CTC and colonoscopy for detection of CRC are similar, CTC has decreased sensitivity for polyps <8 mm in size, and any positive CTC findings still require follow-up colonoscopy [27, 28]. CTC is often employed when endoscopists are unable to complete the colonoscopy (e.g., due to redundancy and looping) to evaluate the proximal colon for significant lesions.

Table 15.1 Screening options for colorectal cancer

Screening method	Frequency	Description
Colonoscopy	Every 10 years	"Gold standard" endoscopic screening of entire colon Allows for screening and intervention (biopsy, polypectomy) Requires full bowel preparation and sedation Small risk of serious complication (perforation, bleeding)
Flexible sigmoidoscopy	Every 5 years Every 10 years if combined with FIT	Evaluation limited to distal colon and rectum Can be performed with limited bowel preparation and less sedation compared to colonoscopy Provides less mortality reduction compared to colonoscopy but may be more appropriate test for select patients
CT colonography	Every 5 years	Noninvasive, imaging-based test Decreased sensitivity for small polyps (<8 mm) No sedation required but still requires full bowel preparation Positive findings require follow-up colonoscopy
Fecal occult blood test (FOBT)	Every year	Stool-based test Assesses for peroxidase activity of heme Limited by low specificity, positive predictive value Red meat and plant peroxidases can confound results Positive findings require follow-up colonoscopy
Fecal immunochemical testing (FIT)	Every year	Stool-based test identifying human hemoglobin No cross-reactivity with food peroxidases Requires fewer samples compared to FOBT Positive findings require follow-up colonoscopy
Stool DNA testing	No consensus guidelines, variable by manufacturer	Stool-based test identifying abnormal DNA debris shed by tumor cells New technology—first test approved in 2014 Sensitivity is dependent on selection of genetic markers included in the test panel, which varies by brand Limited data regarding efficacy

Stool-based testing includes guaiac-based fecal occult blood testing (FOBT), fecal immunochemical testing (FIT), and stool DNA testing. FOBT detects blood in the stool using chemical reactions based on the peroxidase activity of heme [23].

Several studies have shown an approximate 32–33% decrease in CRC mortality with annual or biennial FOBT testing [29, 30]. A major limitation of FOBT is its low specificity and low positive predictive value of 3–10%. Additionally, any dietary sources of peroxidase, such as plant peroxidases or red meat, have the possibility of confounding the test results [23]. FIT functions by identifying intact human hemoglobin in stool with an antibody that does not cross-react with food peroxidases. FIT is more sensitive and specific than FOBT in detection of CRC [31]. It should be noted that both stool-based tests are significantly limited in their detection of polyps, and any positive screening requires a follow-up colonoscopy for further evaluation. Stool DNA tests identify abnormal DNA molecular debris in stool shed by tumor cells. It is a relatively new screening technology; the first multitarget test was approved for CRC screening in 2014 [23]. Data supporting efficacy of stool DNA testing is limited due to variability between brands of tests and relative newness of the technology. Additionally, stool DNA sensitivity is based on the panel of markers included in the test, which may identify most, but not all cancers [8].

Who Should be Screened for Colorectal Cancer and When?

Patients of average risk, with no personal or family history of CRC, should begin screening at age 45. Those with increased risk, such as patients with personal or family history of CRC or inflammatory bowel disease, will require earlier and more frequent screening and surveillance (Table 15.2).

Average-Risk Patients

For average-risk patients, current United States Preventive Services Task Force (USPSTF) guidelines recommend screening for CRC beginning at age 50 and continuing until age 75 [2]. Of note, given the rising burden of disease in individuals younger than age 50, the American Cancer Society (ACS) recently published updated guidelines recommending earlier routine screening beginning at age 45 for average-risk patients [32]. For patients aged 76–85 years, screening should be evaluated on an individual basis, taking into consideration the patient's overall health, prior screening history, and life expectancy. Screening would be most appropriate for adults healthy enough to undergo treatment in the event cancer is detected and who do not have comorbidities that significantly limit life expectancy [2].

The USPSTF recommends stool-based screening (FOBT or FIT) to be repeated every year. Flexible sigmoidoscopy should be repeated every 5 years, CT colonography every 5 years, and colonoscopy every 10 years. Frequency of flexible sigmoidoscopy can be extended to every 10 years when performed in conjunction with annual FIT [2]. The recommended frequency of stool DNA analysis is

Table 15.2 Overview of colorectal cancer screening by risk profile

Risk profile	Screening recommendations
Average risk	Screening beginning at age 45 (American Cancer Society) or age 50 (USPSTF) Continue screening until age 75 For patients age 76–85, continue screening depending on overall health, life expectancy, prior screening history
Family history of CRC	For patients with first-degree relative diagnosed with CRC or polyps before age 60 or two or more first-degree relatives at any age: Screen at age 40 or 10 years prior to youngest diagnosis of CRC For patients with first-degree relative diagnosed with CRC or polyps ≥60 years or two more second-degree relatives with CRC: Screen at age 40
Familial adenomatous polyposis	Begin screening with annual colonoscopy or flexible sigmoidoscopy at age 10–15 Continue screening until decision made to undergo surgery *Extracolonic screening:* Endoscopic evaluation for gastric and duodenal malignancy beginning at age 20–25
Lynch syndrome	Begin screening at age 20–25, or 10 years prior to youngest age of CRC diagnosis in immediate family Continue screening every 1–2 years *Extracolonic screening:* Endometrial and ovarian cancer screening—annual gynecologic exam, pelvic ultrasound, aspiration biopsies beginning age 30–35 Consider screening for urinary tract, gastric malignancy beginning age 30–35 depending on family history
Inflammatory bowel disease	Screening colonoscopy beginning 8–10 years after initial onset of symptoms Continue surveillance every 1–2 years

controversial, as the tests are relatively new. Many specialty organizations have issued separate consensus guidelines regarding screening for CRC, with slight variations. Of note, these recommendations apply only to average-risk patients with negative findings on screening tests and no personal history of CRC. Surveillance after previous CRC treatment or positive screening results will vary based on colonoscopy findings and history [8].

Patients with Family History of CRC

For patients with a first-degree relative diagnosed with CRC or adenomatous polyps before age 60, or two or more first-degree relatives at any age, screening colonoscopy should start at either age 40 or 10 years before the youngest CRC case in immediate family members. For patients with a first-degree relative diagnosed with CRC or polyps ≥60 years, or two or more second-degree relatives with CRC, screening should begin at age 40 [8].

Patients with Hereditary CRC Syndromes

Screening recommendations vary based on type of inherited syndrome. For patients with known or suspected Lynch syndrome, screening colonoscopy should begin at age 20–25 or 10 years before the youngest age of CRC onset in immediate family members. Surveillance should occur every 1–2 years thereafter [8, 17]. Annually starting from age 30 to 35, women with Lynch syndrome should undergo gynecologic exam, pelvic ultrasound, and aspiration biopsies. Prophylactic hysterectomy and salpingo-oophorectomy should be considered when childbearing is complete. Further screening for urinary tract and gastric cancers should be considered beginning at age 30–35 depending on specific family history [20, 33].

For patients with known familial adenomatous polyposis (FAP), screening for CRC should begin between ages 10 and 15 with annual colonoscopy (preferred) or flexible sigmoidoscopy. Once polyps are detected, patients should continue undergoing annual colonoscopy until a decision is made to undergo surgery. Patients with attenuated FAP and small adenoma burden can be managed with annual colonoscopy and polypectomy. However, once adenoma burden reaches a point where polypectomy can no longer eliminate all disease, patients with attenuated FAP will also need to undergo surgery. FAP patients additionally require endoscopic screening for duodenal and gastric cancer beginning at age 20–25 [17, 21].

Patients with Inflammatory Bowel Disease

Patients with IBD should undergo screening colonoscopy with biopsies to evaluate for dysplasia and cancer 8–10 years after initial onset of colitis symptoms. Surveillance colonoscopies should be repeated every 1–2 years [8, 11].

What are the signs and symptoms of colon and rectal cancer?
The most common symptoms of CRC include changes in bowel habits and bleeding, though many patients may be asymptomatic. Complaints of rectal bleeding require thorough investigation and should not be assumed to be secondary to hemorrhoids. Furthermore, iron deficiency anemia is often associated with cancers in the beginning part of the colon and should be investigated when found. Less commonly, patients may present with pain or obstruction, which are often signs of advanced cancers.

Many patients may not have any symptoms at all, but a change in bowel habits is the most common complaint, which can be subtle and go unnoticed for a long period of time. Typically, distal cancers tend to create more noticeable symptoms due to the narrower lumen and firmer stools in the distal colon compared to proximal, as well as the presence of other symptoms such as bleeding, pain, and tenesmus [10]. Bleeding is the second most common symptom of CRC and can be occult or present as overt melena or hematochezia. If both blood and mucus are present in stool, further investigation is needed as the combination of blood and mucus is highly suggestive of malignancy [10]. Rectal bleeding may frequently be

attributed to hemorrhoids, especially if patients have a known history of hemorrhoids. It is important to carefully investigate bleeding so that cancers are not misdiagnosed as hemorrhoids, resulting in potentially devastating treatment delays.

Most patients do not present with pain. Pain from distal rectal cancers may be secondary to invasion into the anal canal or sphincters and is usually associated with more advanced disease. Obstructing lesions may cause colicky abdominal pain, distention, nausea, and vomiting. Approximately 5–15% of patients will have obstruction as a presenting symptom. Uncommon presentations include peritonitis secondary to perforation, *Streptococcus bovis* septicemia, intussusception, and cutaneous manifestations [10].

What are the next steps to take after cancer has been identified on colonoscopy?

Once CRC has been identified, the next step involves determining if the tumors have spread to other areas of the body, usually with various scans. Depending on the results, additional treatments may be needed.

For both colon and rectal cancers, work-up should begin with pathology review and, if not already performed, a complete colonoscopy. Laboratory testing includes complete blood count (CBC), chemistry profile, and carcinoembryonic antigen (CEA) level. CT imaging of the chest, abdomen, and pelvis should be obtained to complete clinical staging. PET/CT imaging is not typically indicated [34, 35]. For rectal cancers, patients should additionally undergo pelvic MRI with contrast. MRI is the preferred imaging modality for local staging of the pelvic tumor; however, if contraindicated or unavailable, patients can alternatively undergo endorectal ultrasound [35]. Further treatment and surgical planning are dependent on clinical stage and results of initial work-up. Patients may need additional referrals to medical oncology, radiation oncology, or an enterostomal therapist [34, 35]. All patients should be counseled and evaluated for family history of CRC. Patients with a personal or family history of a known genetic mutation predisposing to CRC or those with suspected Lynch or polyposis syndromes should be referred for further genetic testing and counseling [17].

What if a woman is diagnosed with colorectal cancer during pregnancy?

Colorectal cancer diagnosed during pregnancy is rare but important to consider as CRC becomes more common in younger populations and as women delay pregnancy until later ages. Pregnancy should not delay treatment; however, decision-making is complex, with significant emotional and ethical factors to consider. Each case should be considered on an individual basis and approached from a multidisciplinary standpoint.

Although a new cancer diagnosis during pregnancy remains uncommon, it is becoming more frequent as more women wait to have children until later in life. The most common cancers in women of reproductive age include breast, melanoma, thyroid, cervical cancer, and lymphomas [36]. Colorectal cancer during pregnancy is rare, with an estimated incidence of 0.002%, but is important to consider as CRC becomes more prevalent in younger populations. The median age of colon cancer

diagnosis in pregnant women is 32. Stratified by stage, prognosis in pregnant patients is similar to that for nonpregnant patients; however, pregnant women tend to be diagnosed at a more advanced stage [37].

The symptoms of colorectal cancer may be easily overlooked as they are similar to common pregnancy-related symptoms (nausea, vomiting, and changes in bowel habits) or misdiagnosed as hemorrhoidal bleeding [38]. Work-up for suspected colorectal cancer in pregnancy remains largely the same. Once cancer is suspected, patients should undergo colonoscopy and CEA level measurement. Either MRI or CT scan can be used for staging evaluation and evaluation of tumor burden [37]. Although metastases to the placenta are extremely rare, ovarian metastases are more common in pregnancy-associated colon cancer (23% vs 8% in nonpregnant women) [36].

Depending on gestational age at time of diagnosis, surgical treatment options include surgical resection while pregnant, surgical resection with termination of pregnancy, or surgical resection with delivery if the fetus is at a gestational age with acceptable prematurity outcomes [36]. There are no guidelines regarding best course of treatment during pregnancy, and data regarding outcomes is limited to retrospective case reports and some animal studies. Factors impacting decision-making include cancer stage, balancing risks to the fetus against the benefit of treatment for the mother, risks associated with delaying treatment, and teratogenic effects of treatment [39]. Given the ethical and safety concerns, as well as the emotional impact of decision-making, treatment decisions should be made on an individual basis with the patient and her family.

Chemotherapy is not recommended during the first trimester, but the standard first-line regimen of FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) can be given in the second and third trimesters and is generally considered to be well-tolerated by the fetus, though little is known regarding long-term outcomes [39, 40]. Newer targeted immunotherapy agents, such as bevacizumab and pembrolizumab, should not be given during pregnancy due to their anti-angiogenic properties and ability to cross the placenta, respectively [41, 42]. In regard to obstetrical outcomes, there is increased risk for preterm labor and cesarean delivery for pregnant women with colorectal cancer, especially those with extensive disease or those undergoing systemic chemotherapy. Although vaginal delivery is possible, cesarean section is suggested by some expert opinion recommendations and may be mandatory for patients with bulky tumor burden [43]. In summary, diagnosis of colorectal cancer during pregnancy poses difficult treatment planning decisions. There is limited data available given the rarity of diagnosis, as only a few hundred cases have been reported in the literature. Each case should be considered individually and approached from a multidisciplinary management approach.

How does colorectal cancer treatment affect fertility?

Surgery, chemotherapy, and radiation therapy for the treatment of CRC all may negatively impact women's fertility, with effects ranging from decreased ability to conceive to premature menopause and sterilization. This can significantly impact

quality of life and self-esteem. All women of childbearing age who require CRC treatment should be counseled regarding the impact of treatment on fertility and options for fertility preservation or assisted reproduction. They may additionally require referral to a counselor to address the stress and negative emotions associated with their cancer diagnosis and prospect of infertility.

The components of treatment for colorectal cancer—surgery, chemotherapy, and/or radiation—may all cause compromised female fertility. In addition, women in Western societies are more frequently delaying childbearing until later in life, further increasing the risk for premature ovarian failure [44]. Despite this, adequate counseling regarding the impact of cancer treatment on fertility and options for fertility preservation is often not offered to patients. In one series, 38% of women of childbearing age reported difficulty with pregnancy or menses after colorectal cancer treatment, but less than 20% had documented counseling for posttreatment infertility [45].

There are no specific studies associating surgical procedures for colorectal cancer with impaired female fertility or fecundity. However, for resections below the peritoneal reflection, impaired fertility after low anterior or abdominoperineal resection can be extrapolated from numerous studies clearly indicating impaired fertility after pelvic surgery, such as ileal pouch-anal anastomosis (IPAA) for inflammatory bowel disease or FAP [46, 47]. The main hypothesis for the etiology of postoperative infertility is formation of adhesions, distorting normal fallopian tube and ovary anatomy, and hindering ovum rupture and conception [44]. In these situations, in vitro fertilization (IVF) can be especially helpful to aid conception. One retrospective study demonstrated patients with ulcerative colitis who have undergone IPAA are able to achieve similar live birthrates following IVF compared to women without IPAA and women without an IBD diagnosis [48]. However, patients undergoing surgery for cancer may experience less success, as they are likely to undergo other cancer treatments that may negatively impact their fertility.

Chemotherapy-induced ovarian damage is variable dependent on age, treatment protocol, dose, and type of chemotherapeutic agent utilized. The components of FOLFOX have mixed effects on fertility. 5-fluorouracil (5-FU) has mild or no gonadotoxic potential, whereas oxaliplatin can cause both ovarian failure and birth defects if given in the first trimester. The role of newer targeted agents, such as capecitabine, bevacizumab, and pembrolizumab, on female fertility is relatively unknown [44]. Bevacizumab may transiently induce ovarian damage, with effects disappearing with drug clearance; however, it is unknown if frequent or prolonged exposure may increase toxicity [41]. There is no data evaluating the effect of pembrolizumab on fertility, though animal studies have revealed no negative effects [42].

The effect of radiation therapy on fertility is dependent on dose, patient age, and field of radiation. Radiation can cause ovarian damage, premature menopause, and permanent infertility. Women under the age of 40 are less sensitive to radiation-induced ovarian damage compared to older women. Pelvic radiation, utilized in the treatment of locally advanced rectal cancer, exposes the ovaries to particularly high

Table 15.3 Overview of fertility preservation options

Preservation option	Special considerations
Embryo or oocyte cryopreservation	Requires delay in treatment for ovarian stimulation and egg retrieval Success rate varies depending on patient age and baseline ovarian function
Ovarian tissue cryopreservation	Experimental therapy Possible option for women who cannot delay treatment for oocyte or embryo freezing Contraindicated if there is a high risk of ovarian metastasis Success rate varies depending on patient's baseline ovarian function
Ovarian transposition (oophoropexy)	Variable functional preservation depending on accuracy of shielding and radiation field calculation Uterus remains unprotected May still require other reproductive assistance techniques

doses of radiation that causes permanent ovarian failure [49]. In addition to the ovaries, the uterus may also be damaged by radiation, resulting in miscarriage, low birthweight, or premature delivery due to impaired uterine blood flow and reduced uterine volume [44].

Options for fertility preservation in women include oocyte (egg) and embryo freezing, ovarian tissue preservation, and ovarian transposition (Table 15.3) [44, 50]. Embryo and oocyte cryopreservation are well-established methods for fertility preservation in women requiring cancer treatment [51]. Embryos are more resilient to freezing, with post-thaw survival rates of 35–90%. When multiple embryos are available, cumulative pregnancy rates of up to 60% have been reported [44]. Embryo cryopreservation requires the availability of a fertile male partner or sperm donor for fertilization; oocyte preservation is an option for patients with no male partner and who do not wish to utilize donor sperm. Oocytes are more susceptible to damage from cryopreservation and yield lower pregnancy rates with IVF compared with preserved embryos. Recent improvements in freezing and thawing techniques have increased implantation rates of up to 40% in some series [52, 53]. Both embryo and oocyte preservation require delay in initiation of treatment, which may not be possible. Hormonal-based ovarian stimulation is also required for retrieval, which may result in progression of estrogen-sensitive malignancies and may be less successful in cancer patients [44]. Additionally, success rates are dependent on patient age and baseline fertility, with success rates >40% reported in women younger than age 35 compared to <20% in women over age 40 [51].

Ovarian tissue cryopreservation is an experimental technique to preserve fertility in women who require gonadotoxic treatment but are unable to delay treatment to preserve oocyte or embryo freezing [50]. Thus far, the overall reported pregnancy rate is approximately all 25%, with 40 live births reported in cancer patients utilizing this technique. This technique should not be used in patients where there is a high risk for ovarian metastasis and will be less successful in women with decreased baseline ovarian reserve [51].

Table 15.4 Resources available online for more information

Resource	Website
American Cancer Society	www.cancer.org/cancer/colon-rectal-cancer.html Information for both patients and providers
American Society of Colon and Rectal Surgeons (ASCRS)	https://www.fascrs.org/patients/disease-condition/colon-cancer Information about colon cancer for patients https://www.fascrs.org/patients/disease-condition/rectal-cancer Information about rectal cancer for patients
National Comprehensive Cancer Network (NCCN)	www.nccn.org/professionals/physician_gls/default.aspx Clinical practice guidelines for providers www.nccn.org/patients/guidelines/colon/ Colon cancer guidelines for patients https://www.nccn.org/patients/guidelines/rectal/index.html Rectal cancer guidelines for patients

Ovarian transposition (oophoropexy) involves surgical transposition of the ovaries out of the field of irradiation to preserve ovarian function. Results are variable, with rates of function preservation ranging from 16% to 90%, due to inaccuracies in calculating radiation fields and preventing radiation scatter [44]. Additionally, ovarian transposition does not protect the uterus from radiation and may require separation of the fallopian tubes from the uterus, potentially requiring further reproductive assistance or a surrogate carrier [50].

It is important for female patients of childbearing age who are diagnosed with colorectal cancer to receive counseling regarding the negative impact cancer treatment may have on their fertility, as well as assisted-reproductive options available to them, such as egg harvest and storage and in vitro fertilization. They may additionally need referral to psychosocial providers to address feelings of stress, loss of control, depression, and low self-esteem that may be brought on by both their cancer diagnosis and the prospect of infertility [49].

Where can I get more information?

Your doctors can answer questions and help guide you toward resources for more information. There is also information available from online from major organizations such as the American Cancer Society, American Society of Colon and Rectal Surgeons, and the National Comprehensive Cancer Network.

The American Cancer Society (ACS), American Society of Colon and Rectal Surgeons (ASCRS), and the National Comprehensive Cancer Network (NCCN) provide resources for patients on their websites. Clinical practice guidelines for providers are also available through the NCCN website (Table 15.4).

Conclusions

CRC is the fourth most common cancer diagnosed in the United States and the second leading cause of cancer death. Although overall CRC incidence and mortality rates are decreasing, this is primarily driven by improved screening in older adults. In younger patients, CRC rates are rising, as is mortality [3, 4]. Diagnosis in this group is often delayed as patients are often too young to meet current age-based screening guidelines, and CRC is often not considered early on as a possible differential diagnosis. The most common presenting symptoms for CRC are change in bowel habits and rectal bleeding, though many patients may be asymptomatic [10]. It is important to investigate and consider CRC in any reported change in bowel habits, bleeding, and anemia, regardless of patient age.

Screening for CRC by colonoscopy with polypectomy has been demonstrated to reduce incidence of cancer by ~90% and mortality by ~60% [25, 26]. Screening for average-risk patients should begin at age 45, with earlier screening for patients with personal or family history of CRC, known history of familial CRC syndromes, or inflammatory bowel disease. Alternatives to colonoscopy include flexible sigmoidoscopy, CT colonography, and stool-based testing [2]. Although these options may be appropriate for select patient populations, any abnormal findings require a full colonoscopy for further evaluation. Patients with hereditary CRC syndromes such as Lynch syndrome and FAP require additional screening for extracolonic malignancies [17].

Of special consideration for female patients are the impact of a CRC diagnosis and treatment on pregnancy and future fertility. Diagnosis in pregnancy may be delayed due to the similarity of symptoms between presentation of CRC and common pregnancy discomforts, such as nausea, vomiting, changes in bowel habits, and hemorrhoidal bleeding [38]. There are no guidelines regarding treatment of CRC during pregnancy, and decision-making is difficult, requiring balance of risks to the fetus against the benefit of treatment for the mother, as well as the significant emotional weight attached to a cancer diagnosis during pregnancy. Each case should be evaluated on a case-by-case basis with the patient, her family, and a multidisciplinary care team. Additionally, CRC treatment will likely negatively impact future fertility. All female patients of childbearing age should receive counseling regarding the possible posttreatment infertility, as well as options for fertility preservation and assisted reproduction [44, 51].

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Part II
Gastrointestinal/Liver Diseases During Pregnancy

Chapter 16
Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum

Sumona Saha

I Have Heard the Terms, "Morning Sickness," "Nausea and Vomiting of Pregnancy," and "Hyperemesis Gravidarum." What Do They All Mean? How Do They Differ? Which One Do I Have?

Nausea and vomiting of pregnancy (NVP) is one of the most common GI disorders of pregnancy, affecting 70–80% of pregnant women [1]. It is characterized by nausea and vomiting which typically begin within 4 weeks of the last menstrual period, peaks between 10 and 16 weeks gestation, and resolves after 20 weeks gestation [2]. NVP is often erroneously referred to as "morning sickness" as NVP is limited to the morning in less than 2% of women and more commonly persists throughout the day [2]. Women with severe symptoms may have hyperemesis gravidarum (HG), a condition associated with fluid, electrolyte and acid-base imbalance, nutritional deficiency, and weight loss [3]. HG is much less common than NVP, affecting only 0.3–3.6% of all pregnancies worldwide [4]. While there are no strict criteria for HG, it is commonly defined as the occurrence of greater than three episodes of vomiting per day with accompanying ketones in the urine and weight loss of more than 3 kg or 5% of body weight [5].

Although NVP and HG exist on a continuum and share the classic symptoms of nausea and vomiting, they are distinct conditions and pose different risks to mother and fetus. It is important that pregnant women who are nauseous and vomiting be accurately classified as having NVP or HG so their treatments can be tailored to their disease severity and maternal and fetal outcomes can be optimized.

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How Did I Get This?

Multiple risk factors have been identified for the development of NVP and HG. These include history of HG in a prior pregnancy, multiple gestations, female gender of the fetus, history of psychiatric illness, high and low prepregnancy body mass index, young age, black or Asian ethnicity, and Type I diabetes [6–9]. Interestingly, smoking has been associated with a decreased risk of HG [10].

The exact cause of NVP and HG has not been determined; however, several factors have been proposed to contribute to their development including genetics, psychological factors, hormones, infection with *Helicobacter pylori*, and altered gastrointestinal tract motility. With regard to genetic factors, history of NVP in a woman's mother or sister has been long noted to be a risk factor for NVP [11, 12]. Furthermore, a twin study found that monozygotic twins had twofold increased risk of having NVP compared to dizygotic twins [13]. Two potential candidate genes, GDF15 and IGFBP7, both of which have roles in early pregnancy, have been associated with HG [14].

It has been noted by numerous investigators that psychiatric disturbances are common in women with NVP and HG, and many have queried whether depression and anxiety may contribute to their development [15–17]. Furthermore, HG has been hypothesized to be some to be a psychosomatic illness or a conversion disorder underlying a subconscious wish for an abortion [18]. HG has also been linked with abnormal personality traits and with unhealthy bonds between the pregnant woman and her mother [19]. Depression, anxiety, and other psychiatric disorders associated with HG are more likely to be secondary to HG rather than contributing factors [20, 21].

With regard to hormonal factors, beta human chorionic gonadotropin (β-hCG) has been most strongly implicated in the pathogenesis of NVP as serum concentrations of β-hCG and the symptoms of NVP peak at the same time. Furthermore, conditions associated with a higher risk for HG including multiple gestations, Down's syndrome, carrying a female fetus, and molar pregnancy are also characterized by higher β-hCG levels [22]. It is hypothesized that hCG levels may directly affect nausea centers in the brain or may indirectly induce symptoms by leading to increases in other hormones (e.g., thyroid hormones, estradiol) which affect nausea [23]. It should be noted, however, that some studies have not found high level of β-hCG in affected women [3, 24, 25].

Other hormones which have been implicated in the development of NVP and HG include progesterone, estrogen, thyroid hormones, and leptin; however, studies evaluating their role in these conditions have not been conclusive [26–31]. It is thought that the ovarian hormones progesterone and estrogen may cause nausea and vomiting by affecting gastric smooth muscle and impairing gastric motility [32]. Thyroid hormones have also been implicated due to the shared alpha subunit between thyroid-stimulating hormone (TSH) and β-hCG and which allow β-hCG to cross-react with the TSH receptor and stimulate free thyroxine (T4) production [33]. Thyroid hormone abnormalities (typically high-free T4 and low TSH levels)

have been found in 30–60% of women with HG; however, despite these laboratory abnormalities, women with HG are generally euthyroid and nearly always return to normal TSH levels by 20 weeks gestation without intervention [33–37]. Lastly, leptin is a hunger regulatory hormone that has recently been shown to be secreted by the placenta [38]. Lower levels of leptin have been reported in a small study of women with HG compared to controls; however, other studies have not shown this association [31, 39].

Infection with *Helicobacter pylori* (*H. pylori*) may contribute to the development of HG. Two meta-analysis have found higher rates of *H. pylori* infection in women with HG compared to controls [40, 41], and several small case reports have reported that treatment of *H. pylori* improved symptoms [42, 43]. What has confounded determining causality between *H. pylori* and HG is the mode of diagnosing *H. pylori* as many studies use serum IgG antibodies as a marker of infection despite the fact that seropositivity for the *H. pylori* IgG is not a direct marker for active infection and may reflect cleared infection.

Abnormalities in gastric emptying and lower esophageal sphincter (LES) resting pressure have been proposed to be mechanisms for the development of NVP and HG; however, as in studies evaluating hormonal causes, results have been mixed. In one study by Koch et al. which evaluated the gastric myoelectric activity in pregnant women, with and without nausea gastric dysrhythmias were demonstrated in all nauseated women, while normal 3-ccylce per minute patterns were seen in all of the women with minimal to no nausea [44]. However, other studies of gastric transit have not found abnormalities in women with HG compared to controls [29]. Lower resting LES pressure and reduced percentage of transmitted contractions in the esophagus have been found during pregnancy [45]. This likely accounts for the high prevalence of gastroesophageal reflux disease (GERD) during pregnancy [46–48]. Although decreased LES pressure is most likely to produce heartburn, GERD may also manifest as including nausea and vomiting [49].

How Do You Diagnose NVP and HG?

NVP and HG are clinical diagnoses which are characterized by the development of nausea and vomiting, typically in the early first trimester [2]. Some women may also experience ptyalism (i.e., excess salivation) or GERD symptoms such as heartburn and non-cardiac chest pain [50]. The onset of nausea and vomiting more than 8 weeks after the last menstrual period is atypical for NVP and should prompt investigation for other conditions which can cause nausea and vomiting in pregnancy (see Table 16.1) [50, 51].

Most women with NVP have normal vital signs and a benign physical exam. Women with HG, however, may show signs of dehydration and be orthostatic. HG may also lead to muscle wasting and weakness, peripheral neuropathies due to vitamin B6 and B12 deficiencies, mental status changes, and cognitive malfunction [52].

Table 16.1 Differential diagnosis of NVP and HG

Gastrointestinal conditions	Gastroenteritis Gastroparesis Achalasia Biliary tract disease Hepatitis Intestinal obstruction Peptic ulcer disease Pancreatitis Appendicitis
Genitourinary tract conditions	Pyelonephritis Uremia Ovarian torsion Nephrolithiasis Degenerating uterine leiomyoma
Metabolic conditions	Diabetic ketoacidosis Porphyria Addison's disease Hyperthyroidism Hyperparathyroidism
Pregnancy-unique conditions	Acute fatty liver of pregnancy Preeclampsia
Other	Drug toxicity or intolerance Psychologic conditions

Adapted from Goodwin TM. Hyperemesis Gravidarm. Obstet Gynecol Clinics 2008;3:401–17

A complete physical exam should always be done to rule out peritonitis and evaluate for other causes of nausea and vomiting.

No specific laboratory or radiographic studies are needed for the diagnosis of NVP. Tests which may be helpful in ruling out other causes of nausea and vomiting in a pregnant woman include a white blood cell count, liver function tests, fasting serum glucose, and TSH. Women with suspected HG laboratory studies should undergo laboratory testing to evaluate the severity of the disease. Labs to consider include a serum blood urea nitrogen, creatinine, and hematocrit which may all be elevated due to volume depletion. Urinalysis should also be obtained to assess specific gravity and evaluate for ketones. Additionally, electrolytes should be checked to assess for deficiencies in sodium and potassium levels and to check acid-base status as should prealbumin, vitamin B1 (thiamin), iron, calcium, and folate as deficiencies are possible [53–55].

Liver function tests are commonly abnormal in women with HG [51]. Specific abnormalities include mild hyperbilirubinemia (bilirubin <4 mg per deciliter), elevations in alkaline phosphatase to twice the upper limit of normal, and elevated alanine aminotransferase (ALT) levels and aspartate aminotransferase (AST) levels [56] with the latter being most common. The transaminase elevation is usually modest and within two to three times the upper limit of normal [57]. Liver test abnormalities typically resolve once vomiting subsides. Serum amylase and lipase levels are less commonly elevated compared to liver function tests; however, elevations in these enzymes occur in 10–15% of women [30].

What Can I Do to Feel Better?

Dietary Modifications

Women who are able to tolerate oral intake should consume small frequent meals that are high in protein, bland in flavor, and low in odor [58–61]. Small frequent meals can help prevent hypoglycemia and gastric over-distention [62].

Women with HG should be encouraged to eat any pregnancy-safe food or beverage they can tolerate. If hospitalization is required to manage HG, the diet order should be regular as tolerated. A focus on adequate calories, as opposed to proper macronutrient distribution, is advised. A dietitian should elicit the patient's food choices to identify types of foods preferred and tolerated which will help drive further dietary suggestions.

Dietary advice for women with NVP and HG is summarized in Table 16.2.

Complementary and Alternative Medicine

Women with mild symptoms may respond to treatment with ginger, acupressure, or acupuncture. Ginger has been found to improve mild to moderate nausea and vomiting compared to placebo across several studies and meta-analyses [63–68]. Although its exact effects are not known, ginger may reduce nausea via antagonistic effects on serotonergic 5-HT3 and cholinergic receptors and/or by improving GI tract motility and increasing bile and gastric acid secretion [63, 69–71]. It can be taken in various forms including fresh, candies, teas, and capsule and syrups. The dose of ginger found to be effective in a crossover study of women with HG was 1 g/day [66]. With regard to acupressure, stimulation of the median nerve at the Pericardium 6 (known as P6 or Neiguan) acupuncture point by placing pressure on the ventral aspect of the wrist has been shown to decrease symptoms in several studies of NVP as well as in a systematic review of 26 trials which included a variety of conditions which cause

Table 16.2 Dietary recommendations for NVP and HG

Eat small meals every 2–3 h (about 1–1.5 cups)
Choose bland foods like toast, rice, baked chicken
Avoid high-fat/greasy foods
Choose low-fat high-protein foods like lean meats, eggs, and beans
Separate liquids and solids. Drink liquids 20–30 min before or after eating
Avoid foods with strong odors like fish and cauliflower
Explore different food characteristics such as salty versus sweet, hot versus cold, and crunchy versus soft or combinations that may be complementary
Try ginger (tea, lollipops, capsules)
To reduce bitter or metallic taste, try candies and colder fluids

Adapted from: Austin K, Wilson K, Saha S. Hyperemesis Gravidarum. Nutr Clin Prac 2018; 0:1–16

nausea and vomiting (e.g., chemotherapy, postoperative state, pregnancy) [72–74]. Acupuncture has been rigorous than acupressure in women with NV; however, small studies have suggested that traditional and P6 treatments may be beneficial [75].

Pharmacotherapy

Pharmacologic treatments include vitamin B6 (pyridoxine) alone or in combination with doxylamine, antihistamines, metoclopramide, and ondansetron. Randomized controlled trials have shown that vitamin B6 taken at doses of 10–25 mg every 8 h reduces symptoms among women with NVP [76, 77]. Vitamin B6 has also been found to be effective when used in conjunction with doxylamine. The combined formulation of vitamin B6 and doxylamine, Diclegis (Duchesney, Bryn Mawr, PA), is currently the only FDA-approved medication for NVP [58, 78]. Antihistamines are thought to reduce nausea and vomiting by indirectly affecting the vestibular system and decreasing stimulation of the vomiting center and/or by inhibition of muscarinic receptors [79]. First- and second-generation histamine antagonists such as dimenhydrinate, diphenhydramine, hydroxyzine, and meclizine have long been used for treatment of NVP, and many studies have found them to be effective [80]. Their safety was also recently established in systematic review of 37 studies which found no increased risk for spontaneous abortions, prematurity, stillbirth, or low birthrate when used for a variety of indications during pregnancy including seasonal allergies, asthma, and NVP [81].

Dopamine antagonists used in the treatment of NVP and HG include metoclopramide and several phenothiazine derivatives (e.g., promethazine, prochloroperazine, and chlorpromazine). Metoclopramide is thought to improve nausea and vomiting by antagonizing D2 receptors in the chemoreceptor trigger zone within the central nervous system and at higher doses by antagonizing 5-HT3 receptors [82]. Phenothiazinee derivatives work as D2 antagonists and have antihistamine activity by blocking H1 receptors [83, 84]. While case reports have suggested an association between phenothiazines and birth defects, multiple prospective cohort, retrospective cohort, case-control, and record linkage studies have been reassuring [85]. When used continuously into the third trimester, newborns should be monitored for withdrawal, including extrapyramidal effects [86]. Metoclopramide has not been associated with an increased risk for major congenital malformations, low birth weight, preterm delivery, or perinatal death [87–89]. It does, however, carry an FDA-issued black box warning due to the risk of tardive dyskinesia with high cumulative doses. To minimize this risk, it is generally recommended that metoclopramide use be limited to less than 12 weeks.

Serotonin antagonists such as ondansetron prevent nausea and vomiting by acting peripherally on the vagus nerve and centrally by blocking chemoreceptors in the area postrema of the brain. Randomized controlled trials support the use of ondansetron for NVP with greater symptom improvement compared to metoclopramide

and to vitamin B6-doxylamine [90–93] and better side effect profile. Multiple case reports, a nationwide historical cohort study, and a prospective comparative observational study have reported no increased risk for adverse pregnancy outcomes with ondansetron use which showed no significant differences between the rates of live births, miscarriages, stillbirths, therapeutic abortions, gestational age, or risk of major malformations among infants of mothers who had taken ondansetron compared to those who had not taken any medications during pregnancy [94, 95]. However, one study reported an increased rate of cleft palate in infants born to mothers who had taken ondansetron, and another large Danish study reported an increased risk for cardiovascular birth defects (specifically cardiac septum defects) with an odds ratio of 1.62 (1.04–2.14) but no increased risk when all major adverse birth defects were pooled OR 1.11 (0.81–1.53) [96, 97].

Corticosteroids are frequently co-administered with 5-HT3 antagonists to treat chemotherapy-induced nausea and vomiting [98]. Several small, randomized controlled trials evaluated the role of corticosteroids in the treatment of HG. Two such studies comparing corticosteroids to promethazine were negative [99, 100]. A third study of women with HG admitted to the intensive care unit compared hydrocortisone to metoclopramide and found that patients treated with corticosteroids had a greater reduction in vomiting within 3 days of treatment [101]. Given these conflicting results and the potentially increased risk for oral clefts (cleft lip and cleft palate) with first trimester corticosteroid use, it is recommended that corticosteroids be reserved for refractory case and that its use be minimized in the first trimester [102, 103].

Lastly, gabapentin has been shown to be beneficial in reducing chemotherapy-induced nausea and vomiting and in one small open label study to be effective in the treatment of HG [104, 105]. A larger, controlled trial is currently underway to further assess the effectiveness and safety of gabapentin in HG.

Pharmacologic treatments for HG are summarized in Table 16.3.

Intravenous Fluids

Patients with HG who cannot tolerate oral liquids or are clinically dehydrated should be treated with intravenous (IV) fluids [58]. IV hydration not only improves fluid status but also the symptoms of nausea and vomiting. Normal saline has been shown to be an effective route of rehydration in one-controlled study although 5% dextrose normal saline (D5NS) is also a reasonable alternative [106]. It is important to note, however, that Wernicke's encephalopathy may develop when dextrose-based solutions are given prior to thiamin repletion [107–110]. Thiamin deficiency can occur within 2–3 weeks of persistent vomiting; thus thiamin should be repleted intravenously before D5NS is administered [107, 111, 112]. As women with HG are also at high risk for electrolyte imbalances, serum potassium, magnesium, and phosphorus levels should be monitored and repleted as needed in the patient requiring IV rehydration [113].

Table 16.3 Pharmacologic treatments for NVP and HG

Treatment	Dose	Possible side effects	Contraindications
Ginger	250 mg up to 4 times daily	Heartburn	None
Vitamin B6 (pyridoxine)	10–25 mg 3–4 times daily	Numbness, paresthesia, unsteady gait	None
Antihistamine/B6 combination	10–12.5 mg doxylamine +10 mg B6 up to four times daily	Fatigue, epigastric pain, constipation, impaired coordination, paresthesia	None
Metoclopramide	10 mg up to 4 times daily	Fatigue, anxiety, headache, dizziness, depression, galactorrhea, extrapyramidal symptoms, dystonia	Hypertension, seizure disorder, Parkinson's disease, history of tardive dyskinesia, depression
Phenothiazine derivatives (promethazine, Compazine, Thorazine)	10–25 mg up to 3 times daily	Tissue damage, seizures, respiratory depression, hallucinations, sedation, extrapyramidal symptoms, dry mouth	Respiratory depression, seizure disorder
Ondansetron	Up to 24 mg/day in 3–4 divided doses	Headache, constipation, urinary retention, dizziness, possible increased risk for birth defects	Congenital long QT interval
Corticosteroids	Hydrocortisone 100 mg twice daily IV, converted to prednisone 40 mg and taper to lowest effective dose	Possible increased risk for oral clefts,	Corticosteroids
Clonidine	5 mg patch	Hypotension, headache, sedation, contact dermatitis, dizziness, constipation	Recent myocardial infarction, depression, hemodynamic instability, renal impairment
Gabapentin	300–900 mg up to three times daily	Fatigue, depression with abrupt withdrawal	Renal impairment, depression

Adapted from Austin K, Wilson K, Saha S. Hyperemesis Gravidarum. Nutr Clin Prac 2018; 0:1–16

Enteral and Parenteral Nutrition

Nutrition support should be initiated in women with HG who continue to lose weight and are unresponsive to pharmacological and non-pharmacological treatments. The decision to start enteral nutrition (EN) or parenteral nutrition (PN) must be individualized and take into account the patient's gestational age, comorbidities, and preferences as well as institutional resources and expertise. In most cases, EN is preferred over PN given the increased health risks with PN during pregnancy. EN

is also more cost-effective and less intensive than PN. Nasogastric or nasoenteric tubes are preferred for an anticipated duration of 4–6 weeks, whereas longer-term needs require gastrostomy or jejunostomy placement. While gastric feedings hold a higher risk of aspiration, jejunostomy tube placement typically involves exposure to radiation, and tube dislodgement with retraction into the stomach is common. There are no studies comparing gastric to intestinal feedings, nor polymeric to elemental formulas, in the treatment of HG. Antiemetics should be co-administered with nutritional support to minimize symptoms, risk of aspiration, and tube dislodgement from retching.

PN should be reserved for those with ongoing weight loss who have failed a trial of EN or have contraindications given the increased risks associated with centrally placed catheters in pregnant women which include bacteremia/sepsis and venous thrombosis [114, 115].

What Is the Impact of NVP and HG on My Fetus and on My Own Health? What Are the Societal Costs?

NVP is associated with a favorable outcome for the fetus. In a prospective study of 16,398 women, no difference was found in congenital abnormalities between those with and without NVP [116]. A meta-analysis of 11 studies found a decreased risk of miscarriage (common odds ratio = 0.36, 95% CI 0.32–0.42) and no consistent associations with perinatal mortality [117] in women with NVP. Moreover, women without NVP have been found to deliver earlier compared to women with NVP [118]. NVP, however, causes substantial psychosocial morbidity in the mother. NVP impairs employment, performance of household duties, and parenting [119]. It is also associated depression, consideration of termination of pregnancy, and impaired relationships with partners.

HG, in comparison, is associated with both adverse maternal and fetal outcomes. In a study of over 150,000 singleton pregnancies, women with HG had increased rates of low pregnancy weight gain (<7 kg), low birth weight (LBW) babies, small for gestational age (SGA) babies, preterm birth, and poor 5-min Apgar scores [120].

Common maternal complications include weight loss, dehydration, micronutrient deficiency, and muscle weakness. More severe, albeit rare, complications include Mallory-Weiss tears, esophageal rupture, Wernicke's encephalopathy with or without Korsakoff's psychosis, central pontine myelinolysis due to rapid correction of severe hyponatremia, retinal hemorrhage, spontaneous pneumomediastinum [121], and vasospasm of the cerebral arteries [122]. HG may also lead to psychological problems and result in termination of an otherwise wanted pregnancy and decreased likelihood to attempt a repeat pregnancy [123].

Some studies have found no increased risk for adverse fetal outcomes in women with HG [124]. However, many have found an association between HG and fetal growth retardation, preeclampsia, and SGA [125]. In a retrospective study of 3068 women, HG was associated with earlier delivery and lower birth weight [126].

Similarly, Dodds et al. found higher rates of LBW, preterm birth, and fetal death in women with HG who gained less than 7 kg overall during pregnancy [120].

Various congenital malformations have been observed more in women with HG [126]. These include Down's syndrome, hip dysplasia, undescended testes, skeletal malformations, central nervous system defects, and skin abnormalities. Fetal coagulopathy and chondrodysplasia have been reported from vitamin K deficiency [127] with third trimester fetal intracranial hemorrhage [128].

It is also worth noting that NVP is one of the most common indications for hospitalization throughout pregnancy and that HG is the most common cause of hospitalization in the first half of pregnancy, accounting for over 59,000 hospitalizations annually [129, 130]. Apart from requiring hospitalization, HG leads to extra doctors' visits and emergency room visits throughout pregnancy [131]. Conservative estimates put the total economic burden posed by NVP in 2012 to be over 1.7 billion dollars annually in the United States, with over 1 billion dollars in direct costs [132]. Indirect costs which include lost time from work and caregiver time are also substantial and difficult to fully estimate in cost models.

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Chapter 17
Viral Hepatitis: Hepatitis B, D, and E Viruses

Aiman Ghufran

Abbreviations

AASLD	American Association for the Study of Liver Diseases
ALT	Alanine transaminase
AVT	Antiviral therapy
cccDNA	Covalently closed circular DNA
HBcAb	Hepatitis B core antibody
HBcAg	Hepatitis B core antigen
HBeAb	Hepatitis B envelope antibody
HBeAg	Hepatitis B envelope antigen
HBIg	Hepatitis B immunoglobulin
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HDAg	Hepatitis D antigen
HDV	Hepatitis D virus
HEV	Hepatitis E virus
IgM	Immunoglobulin M
IU/mL	International units per milliliters
MTCT	Mother-to-child transmission
PAN	Polyarteritis nodosa
RT-PCR	Reverse transcriptase-polymerase chain reaction

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Introduction

Viral hepatitis is the one of the most common causes of liver disease worldwide. The burden of disease has increased in recent years and has climbed from being the tenth leading cause of death in 1990 to seventh leading cause of death in 2013 worldwide [1].

The focus of this chapter will be to discuss the presentation and management of hepatitis B, D, and E from a women's health perspective, specifically during pregnancy and lactation.

Hepatitis B

Question: What is hepatitis B?

Answer: Hepatitis B is a virus that primarily infects the liver.

Explanation: Hepatitis B is a partially double-stranded circular DNA virus belonging to the *Hepadnaviridae* family [2]. The infectious hepatitis B virus is called the Dane particle. The viral genome is repaired in the host cell nucleus to form the covalently closed circular DNA (cccDNA). The cccDNA is then used to transcribe the various proteins along with replication of the genome necessary for formation of the hepatitis B virus [3].

The hepatitis B virus DNA, broadly speaking, has three layers of protection [2]. The outer or surface layer produces the surface antigen (sAg), the innermost or the core layer encapsulates the viral DNA and produces the core antigen (cAg), and the layer in between the envelope antigen (eAg). The functions of these antigens and the antibodies produced in response to these proteins are described below.

Question: *How did I get infected with hepatitis B?*

Answer: Hepatitis B is transmitted via infected bodily fluids through injections, transfusions, or minor skin breaks. Hence it is typically acquired at the time of birth from an infected mother, sharing razors and toothbrushes, and during sexual contact with an infected person. Casual contact like hugging and kissing does not increase this risk.

Explanation: The hepatitis B virus is primarily transmitted parenterally via infected bodily fluids [4]. The most common route of transmission worldwide is perinatal, though infected blood transfusions, use of infected syringes in IV drug users, and use of infected dialysis machines are other routes of transmission. The hepatitis B virus can survive for up to 7 days outside the human body. Once it enters the host, the hepatitis B virus incubation period can range from 30 to180 days [2].

Hepatitis B virus is a highly infectious virus, though the infectivity does appear to depend on circulating viral load and HBeAg status [2, 5].

Question: *How do I find out whether I have been exposed to hepatitis B?*

Answer: Several blood tests can be ordered by your physician in a step-by-step fashion to determine if there has been a current or past exposure to the hepatitis B virus. Once exposure is confirmed or suspected with blood tests, further blood tests and occasionally a liver biopsy can be obtained to confirm whether there is persistent infection.

Explanation: As described above, *Hepatitis B virus* produces several antigens. The host immune system then reacts against these proteins to form corresponding antibodies. These antigens and antibodies then serve as markers of exposure and/or immunity to hepatitis B.

The primary function of the HBsAg is to attach itself to the host cell membrane and which then allows the Dane particle to enter the cell [2]. The surface antibody (sAb) produced in response to the sAg attaches to the protein, thereby neutralizing the ability of the virus to enter the host cell. The sAb, therefore, provides immunity against hepatitis B infection. The sAg is therefore the protein used in various commercially available vaccines.

Hepatitis B core antigen, on the other hand, aids in replication and regulation of transcription of the hepatitis B virus genome [6]. While the antibody produced against the core antigen serves as a marker of prior exposure to hepatitis B, it does not confer immunity against hepatitis B infection. Hepatitis B eAg has been shown to have an immunoregulatory role, modulating the host immune response [7]. It therefore can serve as a marker of virulence of hepatitis B infection. The eAb, like the cAb, does not provide immunity against hepatitis B infection (Table 17.1).

There is a fourth protein produced by the *Hepatitis B virus* called the X antigen [8]. The function of this protein (xAg) remains poorly defined but is shown to be vital in interactions between various proteins of the hepatitis B virus and host cell

Table 17.1 Interpretation of serological markers in hepatitis B

	sAg	sAb	cAb IgM	cAb total	eAg	eAb	Viral DNA load
Vaccinated and immune	–	+	–	–	–	–	–
Prior exposure with functional cure[a]	–	+	–	+	–	+	–
Acute infection	+	–	+	+/–	+/–	+/–	+
Chronic infection	+	–	–	+	+/–	+/–	+/–
Chronic infection with pre-S mutant	–	–	–	+	+/–	+/–	+/–
Chronic infection with pre-core mutant	+	–	–	–	–	–	+/–

[a]Some combination of antibodies being positive

and modulating signal transduction [2], thereby possibly contributing to the oncogenic property of the hepatitis B virus.

Question: *What health problems am I at risk of from hepatitis B infection?*

Answer: Hepatitis B infection can cause liver and non-liver-related problems. Within the liver, it can cause acute infection with liver failure, chronic infection with cirrhosis, and liver cancer. In rare circumstances it can also cause non-liver-related problems like skin rash, joint pains, and damage to the blood vessels and kidneys.

Explanation: Hepatitis B can lead to acute and chronic infection and risk of reactivation in immunosuppressed states. After getting exposed to the hepatitis B virus and following the incubation period, patients can develop acute hepatitis B infection. While sometimes asymptomatic, patients often experience vague nonspecific symptoms of fatigue, nausea, vomiting, abdominal pain, and jaundice. These symptoms then gradually resolve over the next several weeks, with about 90–95% of the individuals acquiring infection in adulthood attaining spontaneous immunological clearance or functional cure [9]. Conversely, approximately 90% of the infants that acquire hepatitis B infection perinatally progress to developing chronic hepatitis B infection. Rarely, acute infection with hepatitis B infection can lead to acute liver failure in 1% of the patients [2] which has a relatively poor prognosis, with 25–50% survival rate in the absence of a liver transplant [10]. Chronic infection with hepatitis B can lead to cirrhosis along with its complications [11] and development of hepatocellular carcinoma (HCC).

Chronic hepatitis B has conventionally been recognized to have four distinct phases. These phases are distinguished by the serological markers, circulating viral load, and the level of inflammation as determined by biochemical and histological data (Table 17.2). This classification helps to determine need for therapy and further management. It is, however, important to recognize that patients may often clinically fall into gray zones and therefore require close monitoring, and occasionally a liver biopsy is required before determining the actual phase of chronic infection and need for antiviral therapy. All patients with chronic hepatitis B infection have hepatitis B surface antigen positivity, except in the rare case of the pre-S mutant virus which does not produce the surface antigen [12].

Table 17.2 Phases of chronic hepatitis B infection: Modified from 2016 AASLD guidelines [11]

	ALT	HBV DNA	Histology
Immune-tolerant	Normal	Elevated	Minimal necroinflammation/ fibrosis
HBeAg-positive immune active	Elevated	Elevated	Moderate to severe necroinflammation or fibrosis
Inactive	Normal	Low or undetectable	Minimal necroinflammation, variable fibrosis
HBeAg-negative immune reactivation	Elevated	Elevated	Moderate to severe necroinflammation or fibrosis

Hepatitis B has been well-recognized as a carcinogenic virus. It accounts for approximately half of all cases of hepatocellular carcinoma diagnosed worldwide [13] even in the absence of underlying cirrhosis. Hepatocellular carcinoma is the sixth most common cancer worldwide and the second leading cause of cancer death globally [14, 15].

Hepatitis B also has several extrahepatic manifestations, which can lead to significant morbidity and mortality [16]. The most serious of these is polyarteritis nodosa (PAN). Like almost all other extrahepatic manifestations of hepatitis B, PAN is immune-mediated necrotizing inflammation of medium- and small-sized arteries. It leads to diffuse aneurysmal dilation of the arteries, along with marked systemic inflammatory response. When caused by hepatitis B infection, antiviral therapy is vital in combination with immunosuppressive agents to achieve clinical remission of PAN [16, 17]. Furthermore, hepatitis B may also be associated with mixed cryoglobulinemia-associated vasculitis though is far less infrequent. Glomerulonephritis is another extrahepatic manifestation of chronic hepatitis B infection [18]. It typically occurs in the pediatric population and is usually self-limited with only rare progression to renal failure [16]. Approximately one third of patients with chronic hepatitis B may develop a serum sickness with skin and joint involvement.

Question: *Do I need to be treated for hepatitis B?*

Answer: Possibly. Not all patients with chronic hepatitis B infection require treatment but need to be monitored closely so that when the need arises, appropriate therapy may be started. It is very important to get regular tests and follow-ups to make that determination to reduce the risk of development of cirrhosis and liver cancer.

Explanation: The principles of treating chronic hepatitis B infection largely revolve around presence of advanced fibrosis, level of inflammation as often reflected by transaminase elevation, the viral load, and presence of hepatic and non-hepatic complications [11, 19]. As per current AASLD guidelines, all patients with chronic hepatitis B infection, low-level viremia, and underlying cirrhosis should be considered for treatment, regardless of the transaminase level due to the high risk of reactivation with acute liver failure in patients with cirrhosis.

However, if there is no evidence of advanced fibrosis, treatment is advisable in patients who have immune-active or immune-reactive chronic hepatitis B infection [11]. Occasionally, patients would fall into "gray zone," with discrepant data. In these cases, close monitoring of ALT and viral load is advised for 3–6 months, followed by a liver biopsy if the phase remains indeterminate.

The current available treatment options can be broadly classified into injectables (interferon and pegylated interferon) and oral medications. Oral medications are then subclassified into nucleosides (lamivudine and entecavir) and nucleotides (tenofovir, adefovir, and telbivudine) (Table 17.3). These medications have varying levels of efficacy and side effect profile. Interferon used to be the preferred agent in patients with HBeAg-positive and intact hepatic function due to the finite nature of

therapy, with a goal of achieving seroconversion in 1 year. However, it has fallen out of favor due to the severe side effect profile (Table 17.3) and lower efficacy compared to the oral agents. Entecavir and tenofovir are currently the preferred therapeutic agents for use due to their favorable side effect profile and low risk of resistance development. Also, if there is concern for resistance development, the patients can be treated either with dual therapy or by switching over to the other one [11, 19].

Question: *Do I need to be monitored for liver cancer?*

Answer: Yes. The time to start surveillance depends on presence of cirrhosis, ethnicity, and gender.

Explanation: Presence of cirrhosis is the strongest risk factor for development of liver cancer. Therefore, all patients with underlying cirrhosis should be screened for liver cancer, irrespective of the underlying cause of cirrhosis [20]. These patients should be screened with some form of liver imaging (ultrasound or CT scan or MRI scan) with or without alpha-fetoprotein (AFP) every 6 months (AFP) [20].

Hepatitis B is a well-recognized carcinogen, and patients with chronic hepatitis B are at risk for developing liver cancer even in the absence of underlying cirrhosis. This risk appears to be highest in the setting of hepatitis B eAg positivity and the viral load [20, 21]. It is therefore advised to regularly screen patients with chronic hepatitis B infection, depending on their race and gender (Table 17.4).

Question: *I just found out I am pregnant and have chronic hepatitis B infection. Do I need treatment, and is my unborn child at risk of getting infected?*

Table 17.3 Medications approved for treatment of chronic hepatitis B

	Medication	Common side effects	Pregnancy class
Injectables	Interferon and PEG-interferon	Mood disorders and flu-like symptoms	C
Nucleoside agonists	Lamivudine	Lactic acidosis	C
	Entecavir	Lactic acidosis	C
Nucleotide agonist	Tenofovir	Lactic acidosis	B
	Adefovir	Lactic acidosis, renal failure, Fanconi syndrome, nephrogenic diabetes insipidus	C
	Telbivudine	Lactic acidosis, peripheral neuropathy, and myopathy	B

Table 17.4 Screening for hepatocellular carcinoma patients with chronic hepatitis B

All patients with cirrhosis
Asian males over the age of 40
Asian females over the age of 50
Africans and African-Americans over the age of 20
Patients with family history of hepatocellular carcinoma

Answer: There is a significant risk of your baby getting infected at the time of birth. Close monitoring with blood testing should be done throughout your pregnancy in collaboration with a hepatologist and a high-risk obstetrician. This risk can be reduced significantly with appropriate immunization of the baby at the time of birth and subsequent follow-up, and, if indicated, antiviral medication for mothers during the third trimester.

Explanation: The mother-to-child transmission (MTCT) of hepatitis B is the most common route of transmission worldwide [4]. The risk of MTCT appears to increase with the circulating viral load and HBeAg, with 70–90% of babies born to HBeAg-positive mothers getting infected if appropriate prophylaxis is not administered [22, 23], compared to only 10–20% of HBeAg-negative mothers [22]. The rates of transmission from vaginal versus cesarean delivery appear to be similar, and there is no clear cause to push for cesarean section unless there are other obstetrical indications [24]. The most effective way to reduce the risk of MTCT is with administration of immunoglobulins and immunization within 12 h of birth [19, 23, 24], followed by completion of the immunization schedule based on the birth weight of the infant and whether the delivery was at term or not (Table 17.5). There is strong evidence to suggest that the risk of MTCT increases with delay in HBIg administration.

There is also evidence to suggest that higher viral load is associated with increased risk of hepatitis B MTCT. Different societies have slightly differing recommendations for the viral load, time to start therapy, and time to stop therapy [24]. However, broadly speaking, if the circulating viral load is 200,000 IU/mL or higher,

Table 17.5 Protocol for prevention of MTCT of hepatitis B infection

	Mother	Term and normal birth weight infant	Pre-term or low birth weight infant
Third trimester	Start antiviral therapy if viral load >200,000 IU/mL	–	–
At birth	May stop or continue AVT[a]	100 IU of HBIg within 12 h of delivery and first dose of recombinant hepatitis B vaccine	100 IU of HBIg within 12 h of delivery and first dose of recombinant hepatitis B vaccine
At 1 month	Stop AVT[a]	Second dose of recombinant hepatitis B vaccine	Second dose of recombinant hepatitis B vaccine
At 2 months	–	–	Third dose of recombinant hepatitis B vaccine
At 3 months	–	–	–
At 6 months	–	Third dose of recombinant hepatitis B vaccine	–
At 7 months	–	–	Fourth dose of recombinant hepatitis B vaccine

[a]Antiviral therapy may be stopped anywhere from the time of delivery up to 1 month post-partum, provided there are no other indications for continued antiviral therapy

therapy should be initiated at third trimester. Antiviral therapy can then safely be discontinued at the time of delivery up to 1 month postpartum as per current AASLD Guidelines, provided there are no other indications to remain on therapy (Table 17.5).

Question: *I am on hepatitis B therapy, and I just found out I am pregnant. Is it safe for me to continue taking my antiviral therapy?*

Answer: Some hepatitis B medications are safe for use during pregnancy. Consult with your hepatologist and/or obstetrician immediately, so they may assess the safety of your medication during pregnancy.

Explanation: Of all the antivirals available, tenofovir and telbivudine are the only Category B medications for treatment of hepatitis B during pregnancy (Table 17.3). All the rest are pregnancy Class C medications. This data for safety of tenofovir is primarily derived from use in HIV patients [25, 26], but there is primary data from Chinese studies on safety and efficacy of tenofovir and telbivudine in reducing the risk of MTCT of hepatitis B infection [27–30].

Question: *Can I breastfeed my child if I have hepatitis B infection?*

Answer: Yes, breastfeeding in hepatitis B infection is safe.

Explanation: A study published in 1975 in Lancet demonstrated that breastfeeding does not increase the risk of transmission of infection [31]. This has been re-demonstrated in multiple studies since then and confirmed in a meta-analysis [32].

Hepatitis D

Question: *What is hepatitis D infection and how did I get it?*

Answer: Hepatitis D is a virus that primarily affects the liver and is acquired via infected bodily fluids.

Explanation: Hepatitis D is a defective circular RNA virus with a single antigen that is surrounded by a lipoprotein envelope that is made of proteins from the hepatitis B virus [33]. It is a hepatotropic virus that is transmitted parenterally by infected body secretions. The most common routes of transmission appear to be via intravenous drug use (IVDU) and sexual intercourse [34]. However, unlike hepatitis B, MTCT, nosocomial transmission, and spread in men-who-have-sex-with-men seem to be very low [34].

Question: *Who should be tested for hepatitis D?*

Answer: Anyone with chronic hepatitis B infection should be screened for the presence of hepatitis D infection.

Explanation: Hepatitis D is a defective virus that can replicate utilizing the host polymerase but requires active hepatitis B infection for assembly and secretion [33,

35]. The prevalence of hepatitis D, however, does not follow that of hepatitis B, as regions with endemic HBV may be nearly free of HDV with very low prevalence in Hong Kong [36] and Japan [37]. HDV coinfection in patients with chronic hepatitis B does accelerate the rate of progression to cirrhosis [37].

Hepatitis D genome codes for a single protein, called the hepatitis D antigen (HDAg) [33, 37]. Hepatitis D antigen may be measured in serum for diagnosis; however, it is only briefly measurable and therefore not reliable as a diagnostic tool. Commercial testing of HDAg is currently not available in the United States, and antibody against this antigen is used to make a diagnosis of concomitant exposure to hepatitis D. An RNA viral load may be tested for by reverse transcriptase-polymerase chain reaction (RT-PCR)-based assays.

Question: *Do I need treatment for hepatitis D?*

Answer: Possibly. Check with your hepatologist.

Explanation: It is important to differentiate acute hepatitis B and D coinfection from chronic hepatitis B superinfection with hepatitis D due to the differing prognosis of the two [38]. Chronic superinfection has poorer outcomes with more rapid progression to cirrhosis, liver failure, and increased risk of hepatocellular carcinoma.

The only agent shown so far to have some efficacy against HDV is interferon. Interestingly, treatment of hepatitis B with adequate suppression, even in cases of HBsAg clearance with antivirals, has not been shown to be effective in treatment of HDV [38].

Question: *I have HDV/HBV coinfection, and I just found out I am pregnant. Is my child at risk of acquiring hepatitis D?*

Answer: No. Your child should, however, receive immunization against hepatitis B at the time of birth to reduce the risk of hepatitis B infection.

Explanation: Unlike hepatitis B, MTCT of HDV seems to be very low [34, 39]. Furthermore, there is no vaccine currently available against hepatitis D.

Hepatitis E

Question: *What is hepatitis E and how did I get infected by it?*

Answer: Hepatitis E is a virus that can cause inflammation in the liver. It is primarily transmitted through eating and drinking contaminated food and water, though transmission via infected blood products can also occur.

Explanation: Hepatitis E virus (HEV) is a non-enveloped RNA virus in the *Hepeviridae* family [40]. It is primarily transmitted enterically though has been

shown to also be transmitted via infected blood products [41], MTCT [42], and possibly lactation [43].

Two separate patterns of enteric transmission of hepatitis E have been recognized based on the genotype: waterborne for genotypes 1 and 2 and via contaminated food (zoonotic) for genotypes 3 and 4 [44]. Waterborne transmission is endemic in developing countries [44], while zoonotic transmission especially from pigs serving as the reservoir is more common in the developed world [45].

Question: *How do I know if I have hepatitis E infection?*

Answer: Infection with HEV can cause vague symptoms like abdominal pain, nausea, vomiting, and jaundice. Blood tests can be done to confirm the diagnosis.

Explanation: Patients with acute HEV infection usually are asymptomatic or have very mild disease with vague abdominal symptoms and jaundice with marked elevation in transaminases into the thousands. Jaundice and other symptoms may last 2–6 weeks before they gradually subside. The diagnosis is made by first obtaining serum IgM and IgG antibodies against HEV and then confirmed with obtaining HEV RNA PCR. It is important to recognize that serology may be negative in handful of a subset of patients, and a high index of suspicion is necessary to make the diagnosis.

Question: *What does infection with hepatitis E virus do?*

Answer: Infection with hepatitis can cause acute hepatitis, renal disease, thyroid and pancreas inflammation, and neurological problems. In rare circumstances it can lead to acute liver failure, especially during pregnancy.

Explanation: Infection with HEV typically leads to self-limited acute hepatitis with jaundice. However, 0.5–4% of patients may develop acute liver failure [46], with pregnant females in endemic regions at particularly increased risk in their third trimester [47]. The mortality in pregnancy can be as high as 15–25%. This increased risk is thought to be secondary to a reduced state of immunity with defective toll-like receptor signaling, a reduced CD4 to CD8 cell ratio, and increased steroids level [48], thereby potentiating viral replication and damage to the hepatocytes.

In addition to acute hepatitis, HEV may also cause chronic hepatitis in patients who are immunosuppressed.

HEV can also cause extrahepatic manifestations involving multiple different organ systems [49]. Pancreatitis [50], membranous glomerulonephritis, thyroiditis, pancytopenia, and Guillain-Barre syndrome are a few such recognized complications.

Question: *Can I get a chronic infection from hepatitis E?*

Answer: Typically, no. However, it is now well-recognized that chronic hepatitis E may occur in immunocompromised individuals, especially those who have undergone solid organ transplant.

Explanation: Hepatitis E has classically been recognized as a virus that causes acute infection. However, over the past decade, HEV-associated chronic hepatitis in immunosuppressed individuals has been well-documented, especially those who undergo solid organ transplant [51–53]. Presence of HEV RNA in serum or stool for longer than 6 months is defined as chronic hepatitis E. Approximately 70% of the patients who get acutely infected with HEV after a solid organ transplant go on to develop chronic hepatitis E infection [54]. Patients with chronic hepatitis E are typically asymptomatic except for mild elevations in transaminases or presentation with cirrhosis, with negative etiological evaluation other than presence of hepatitis E virus [53]. Ribavirin is an effective therapy for patients with chronic hepatitis E virus and can lead to sustained virologic response [55, 56].

Conclusion

Viral hepatitis has a significant global disease burden, especially in female patients during pregnancy and lactation. It is vital that these illnesses are identified early on especially in pregnancy to reduce the risk of significant, possibly lifelong, complications to both the mother and child.

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Chapter 18
Pregnancy-Specific Liver Disorders: Preeclampsia and HELLP Syndrome

Ashina Singh

Abbreviations

CI	Confidence interval
CT	Computed tomography
DIC	Disseminated intravascular coagulation
HTN	Hypertension
Mg	Milligrams
MHC	Major histocompatibility complex
Mmol	Millimol
MR	Magnetic resonance
NK	Natural killer
PGI2	Prostacyclin
PlGF	Placental growth factor
PP13	Placental protein 13
sFLT1	Soluble FMS-like tyrosine kinase receptor 1
TXA2	Thromboxane

Introduction

Central to understanding these two disorders of pregnancy is being aware of the normal physiology and hemodynamics of pregnancy. Cardiac output increases greatly during pregnancy, especially in the first two trimesters [1–3]. After the second trimester, cardiac output typically will stay steady and level off. In pregnancy as the cardiac output increases, the peripheral vascular resistance decreases. The

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mother's blood plasma volume also increases by around 30–50% during gestation [2, 4]. With all of these dramatic physiologic changes, it is important to note that the absolute hepatic blood flow does not change, but the percent of cardiac output to the liver decreases [2, 3].

In the pregnant state, several changes must occur, not only physically and physiologically in order for the body to accept and allow the fetus to grow, but there is also significant immunologic adaptation that must occur on the part of both mother and fetus. Our current understanding of the precise immunologic adaptions that occur is still under investigation. It seems likely that through a multifactorial process, adaptations occur at the maternal-fetal interface so that a tolerogenic state exists. It is known that the fetal trophoblast cells lack HLA-A and HLA-B antigens [5]. They do however have HLA-C, HLA-G, and HLA-E nonclassical antigens [5]. These nonclassical antigens are major histocompatibility complex (MHC) Class I molecules. Thus they act as tolerogenic ligands for inhibitory receptors expressed by maternal natural killer (NK) cells. It is important to note that fetal trophoblast cells completely lack MHC Class II molecules [5]. MHC Class II molecules are important in complexing with antigen presenting cells in order to introduce foreign entities to the body's immune system. As the fetal trophoblast cells lack these, it allows them to be more tolerogenic and less likely to attack the maternal cells. Additionally these immunologic adaptations occur in response not only to maternal antigens but also to paternal antigens. Seminal fluid exposure will in a dependent manner induce regulatory T cells [1, 5]. This is one of the reasons it is postulated that those undergoing infertility treatments may be at higher risk for preeclampsia and HELLP due to reduced exposure and therefore less induced immunity to paternal antigens by this mechanism.

Maternal-fetal tolerance is a necessary immunologic adaption to allow pregnancy to occur. In most cases preeclampsia includes liver involvement, and in all cases HELLP has liver involvement. As such it stands that there may be some maladaptation of immunology that occurs to allow these two conditions to exist. The liver is an organ that is known to mediate immunological tolerance. Instead of reacting to the variety of antigens it is exposed, the liver responds with relative immunosuppression not activation. An example of this is portal circulation in which the digestive tract is continuously exposing the liver to bacterial antigens [5]. In immunocompetent patients this hardly causes any malady. This balance can be offset in patients with immunosuppressed states, such as those with cirrhosis, and is sometimes the culprit for infections in this population. Another good example of the liver's immunogenicity is seen in solid organ transplant. Organs that have been co-transplanted along with the liver see far less rates of rejection overall than those respective individual organs being transplanted themselves.

Preeclampsia

What symptoms should I expect to feel?
Most of the time, there are few to no symptoms associated with preeclampsia. The most common symptoms if felt include nausea, vomiting, and right upper quadrant

pain. Often hypertension will be diagnosed (blood pressure greater than or equal to 140 mmHg/90 mmHg). Additionally you may have protein leaking in the urine as well, known as proteinuria.

What are the risk factors for having or being predisposed to getting Preeclampsia?
Having previously been diagnosed with preeclampsia or having a family history of preeclampsia puts you at greatest risk for being diagnosed with this disorder. Other risk factors that exist are having a body mass index greater than 35, having high blood pressure going into pregnancy, and maternal age greater than or equal to 40. Also having any preexisting autoimmune disease can place you at a higher risk for developing preeclampsia.

Preeclampsia

With that background in mind, clinically, preeclampsia is a condition in pregnancy where de novo hypertension occurs in the second half of pregnancy. This is characterized by systolic blood pressure greater than or equal to 140 mmHg and a diastolic blood pressure greater than or equal to 90 mmHg [2]. It is important to note that this new diagnosis of HTN occurs in this condition after 20 weeks of gestation [1, 2]. It is further characterized by the presence of greater than 300 mg/day of protein in the urine or a spot urine/creatinine ratio of >30 mg/mmol [1]. Until recently, proteinuria alongside hypertension was a signature defining trait of this condition, but more recent studies have found that proteinuria is not necessary for this condition to exist. Alternately preeclampsia can have a more severe presentation with HTN and either renal failure, pancreatitis, pulmonary edema, or seizures, also known as eclampsia.

The incidence of preeclampsia is ten times more common than HELLP and so more likely to be encountered in practice [2, 4]. It occurs in 3–5% of all pregnancies and can extend beyond the gestational period of 20 weeks to up to 2 weeks postpartum [1, 2, 4]. Often this condition is comanaged alongside a high-risk obstetrician or maternal fetal medicine specialist. It has long been postulated that preeclampsia may be a predisposing or precursor condition to the development of HELLP.

There are several hypothesized risk factors for the development of preeclampsia. There does appear to be some penchant toward development of this if the mother already has HTN [2]. Similarly, if there is a prior history of preeclampsia or a family history of preeclampsia than there is a higher likelihood to develop preeclampsia (RR 7.19, CI 5.85–8.83) [6]. Additionally as preeclampsia and HELLP are both thought to emanate from the improper implantation of the trophoblast early in pregnancy which can lead to restricted perfusion of the placenta, it stands that autoimmune diseases may predispose to the development of this maladaptive implantation with background inflammation [6]. In preeclampsia it also appears that the systemic vascular resistance does not decrease as it does so in proper pregnancy, and there is an increased sensitivity to vasospasm. Other risk factors for preeclampsia include a BMI >35, preexisting insulin-dependent diabetes mellitus type II (DMII), nulliparity, and advanced maternal age greater than 40 [2, 6].

Clinically preeclampsia may be relatively asymptomatic upon presentation. If symptoms do surface, they are usually headaches, visual changes, right upper quadrant pain, and nausea or vomiting [7]. Unfortunately these are symptoms that are quite nonspecific and relatively germane to some stage of pregnancy. Ceruloplasmin may be a marker for the development of preeclampsia, but this has yet to be used clinically [8]. It is assumed that placental hypoxia associated with preeclampsia increases placental expression of ceruloplasmin [8].

Once preeclampsia is diagnosed, magnesium sulfate should be administered to help reduce the likelihood of seizures during delivery, and antihypertensives are used to manage elevated blood pressures [1]. There are conflicting data as to oral calcium supplementation potentially reducing the risk of preeclampsia [1, 9], and current guidelines do not support its use. The use of aspirin in women identified at high risk for developing preeclampsia is currently recommended at a dose of 81–162 mg [10]. It is theorized that aspirin helps through the inhibitory effects on cyclooxygenase on thromboxane (TXA2) and prostacyclin (PGI2) [10]. When commenced before 16 weeks, it is thought to help improve placental blood flow and reduce risk of placental thrombosis [10].

HELLP Syndrome

What is HELLP syndrome?
Hemolysis, elevated liver test, and low platelets make up the syndrome known as HELLP. It can occur in the third trimester of pregnancy to up to 2 weeks postpartum.

What symptoms should I expect to feel?
Most of the time, there are few to no symptoms associated with HELLP until the very end. The most common symptoms include nausea, vomiting, right upper quadrant pain, swelling in the legs, and headache, much of what is experienced in preeclampsia. Often high blood pressure will be diagnosed (blood pressure greater than or equal to 140 mmHg/90 mmHg), and you may have protein leaking in the urine as well, known as proteinuria.

HELLP

Dr. Louis Weinstein first described the syndrome of HELLP in 1982. He had studied case reports dating as far back as 1954 that seemed to describe hemolysis and elevated liver enzymes in a toxemia of pregnancy which he postulated was actually the first description of this disorder [11]. He himself had studied 29 obstetric patients with these constellation of symptoms of hemolysis, elevated liver enzymes, and low platelets. Truly remarkable was that up until his discovery and description, the

treatment for patients with these combination of symptoms was conservative watchful waiting. Weinstein's assertion that one be aggressive in the treatment of HELLP with expeditious delivery, even if by way of cesarean section, was a bold and novel declaration [11].

HELLP occurs in 0.2–0.8% of pregnancies and exclusively occurs in the third trimester to postpartum period [2, 5]. The maternal mortality associated with this disorder is 1.1–2.0%, and perinatal mortality is as high as 33% [2, 5]. There clearly is a marked fold difference in maternal to fetal mortality in this disorder. HELLP includes up to 80% of the cases of preeclampsia, and this is why it is so difficult to learn about HELLP without also knowing about preeclampsia [5] (Fig. 18.1, Table 18.1).

There are two widely accepted classification systems for describing and diagnosing HELLP. These are the Mississippi classification system and the Tennessee classification system [4]. In the Mississippi classification system, there are three classes based on severity of presentation, and these are dictated by platelet count (Table 18.2).

As expected most maternal deaths occur in Class I patients [12]. The clinical presentation of HELLP typically includes symptoms such as severe abdominal pain, vomiting, and the most dreaded complication of liver rupture. In reality hepatic hematoma is far more likely to occur than hepatic infarction [7] (Fig. 18.2). In those that develop hepatic hematomas, there is a 12% incidence of hepatic rupture [7]. This leads to a maternal mortality of 32% and a fetal mortality of up to 51% [7]. Capsular rupture occurs in 0.53–2.0% of women with preeclampsia and HELLP [7]. In this clinical scenario, maternal mortality is 17%, and fetal mortality is 38% [7]. The exact culprit for the intrahepatic hematoma is not clearly known. It has been hypothesized that fibrinoid thrombin within sinusoids from disseminated intravascular coagulation (DIC) that is associated with HELLP leads to periportal hematomas and necrosis (Fig. 18.3). Ultrasound is still first line to detect any hepatic abnormalities that may precede capsular rupture [7]. If any abnormalities are found, it is appropriate to proceed with magnetic resonance (MR) or multidetector CT imaging. In a severely ill patient with hemodynamic instability and HELLP, a multidetector CT

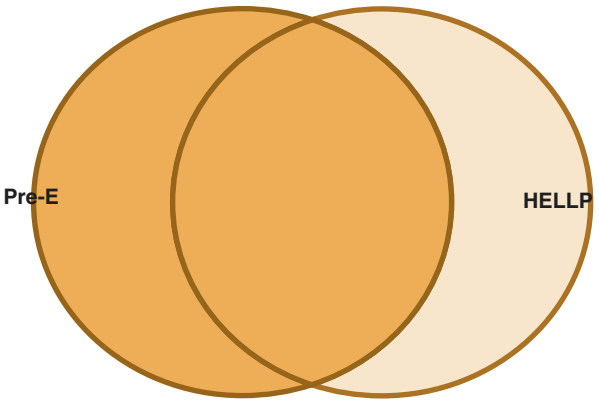

Fig. 18.1 The interrelatedness of preeclampsia and HELLP

Table 18.1 Clinical features and laboratory findings

	HELLP	Preeclampsia
Clinical features	Abdominal pain, vomiting, proteinuria, headache, peripheral edema	Abdominal pain, hypertension, proteinuria, headache, blurred vision, peripheral edema
Trimester	Third (less common second an postpartum)	Late second or third
Ascites	–	–
Thrombocytopenia	+	+
Bilirubin	<5 mg/dL (ULN 1.9 mg/dL)	<5 mg/dL (ULN 1.9 mg/dL)
Bile acid elevation	–	–
Hypoglycemia	–	–
Coagulopathy	DIC	–
Proteinuria	+/–	+
Aminotransferases	1–100×	1–100×
Uric acid elevation	+	+
Hemolysis	+	+/–
Renal dysfunction	+/–	+
Histopathology	Fibrin deposition, hemorrhage, hepatocellular necrosis	Fibrin deposition, hemorrhage, hepatocellular necrosis
Treatment	Delivery	Delivery

Courtesy of Dr. Sheila Eswaran
ULN upper limit of normal

Table 18.2 Mississippi classification system for HELLP

Type	Platelet count
Class I	<50,000/μL
Class II	50,000–100,000/μL
Class II	100,000–150,000/μL

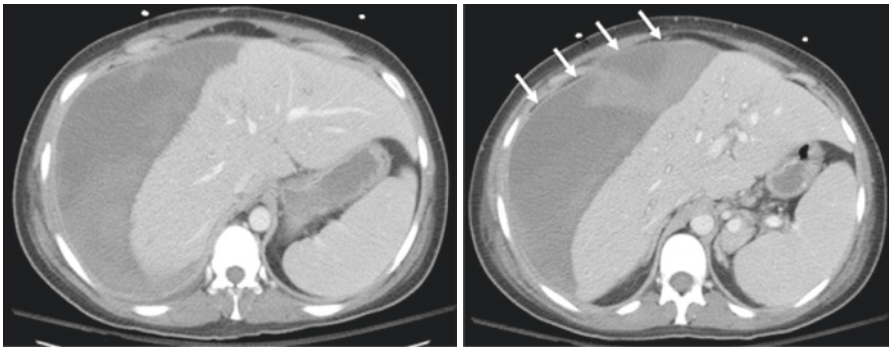

Fig. 18.2 Thirty-three-year-old female at 28 weeks 3 days gestation who presented with nausea and vomiting and then developed acute severe right upper quadrant pain. CT shows acute subcapsular hematoma exerting substantial mass effect on the liver parenchyma. (Courtesy of Dr. Daniel Myers)

imaging is recommended as first line [7]. If capsular rupture should occur, there exist both surgical and nonsurgical treatment options. Transcatheter arterial embolization can be used and has been shown to decrease maternal and fetal mortality from 17% to 0% and 38% to 30%, respectively [7]. The surgical options that exist consist of surgical packing, arterial ligation, partial liver resection, and orthotopic liver transplant.

Some of the risk factors that are known to exist for the development of HELLP include nulliparity, the instance of having a gestational hypertensive disorder in previous pregnancy, and having essential HTN in nulliparous women (not so if multiparous) [13]. There is no worldwide genetic cause for preeclampsia or HELLP as of yet discovered, and likely there will not be one single causative gene and more likely a multifactorial process that consists of both genetic and environmental influences [1, 5]. The pathophysiology of HELLP is thought to be one where there is an enhanced inflammatory state where maternal immune and endothelial cells react to syncytiotrophoblast cells. The syncytiotrophoblast membrane separates maternal and fetal blood, and it is known in preeclampsia and HELLP; there is an abnormal morphology to its brush border [1, 5, 14, 15]. In HELLP, placental protein 13 (PP13) is abnormally incorporated into the membrane. Additionally there is a shift toward soluble FMS-like tyrosine kinase 1 (sFLT1) protein which favors an overall more antiangiogenic environment [14, 15]. There is a drop in the placental growth factor (PlGF) levels in both preeclampsia and HELLP [14, 15]. This subtle shift in balance toward increased antiangiogenic factors is thought to induce maternal vascular endothelial dysfunction which causes arterial hypertension and increases the inflammatory response and ultimately leads to the downstream cascade of events seen in HELLP. In the later stages of HELLP, near term, there are defects that occur in the complement pathway that leads to thrombotic microangiopathy and hemolysis. With this knowledge of the shift in antiangiogenic factors, there has been development of assays to detect these factors as a potential biomarker to help predict the risk of preeclampsia or HELLP. The ratio of sFLT1/PlGF might be a better predictor of the development of preeclampsia than either biomarker alone. It has been found that a sFLT1/PIGF ratio of 38 or lower had a 99.3% negative predictive value (95% confidence interval [CI], 97.9–99.9) [15].

The damage to the liver that occurs in HELLP is specifically caused by soluble CD95L (sCD95L) [5]. This has been found in increased levels in maternal blood in HELLP and causes liver cell apoptosis [5]. Interestingly the severity of clinical presentation in HELLP does not correlate to histopathology. In the rare instances that a liver biopsy has been performed in HELLP, findings of periportal hemorrhage and fibrin deposition are found, but the degree of this does not correlate with the severity of clinical findings [3, 16] (Fig. 18.3).

Treatment for HELLP as Dr. Weinstein had proposed several years ago has not changed much over these past few years. Immediate delivery is recommended and expectant supportive management. If gestation is less than 34 weeks, then delivery is recommended within 48 h after administration of corticosteroids, to allow for fetal lung maturity [1].

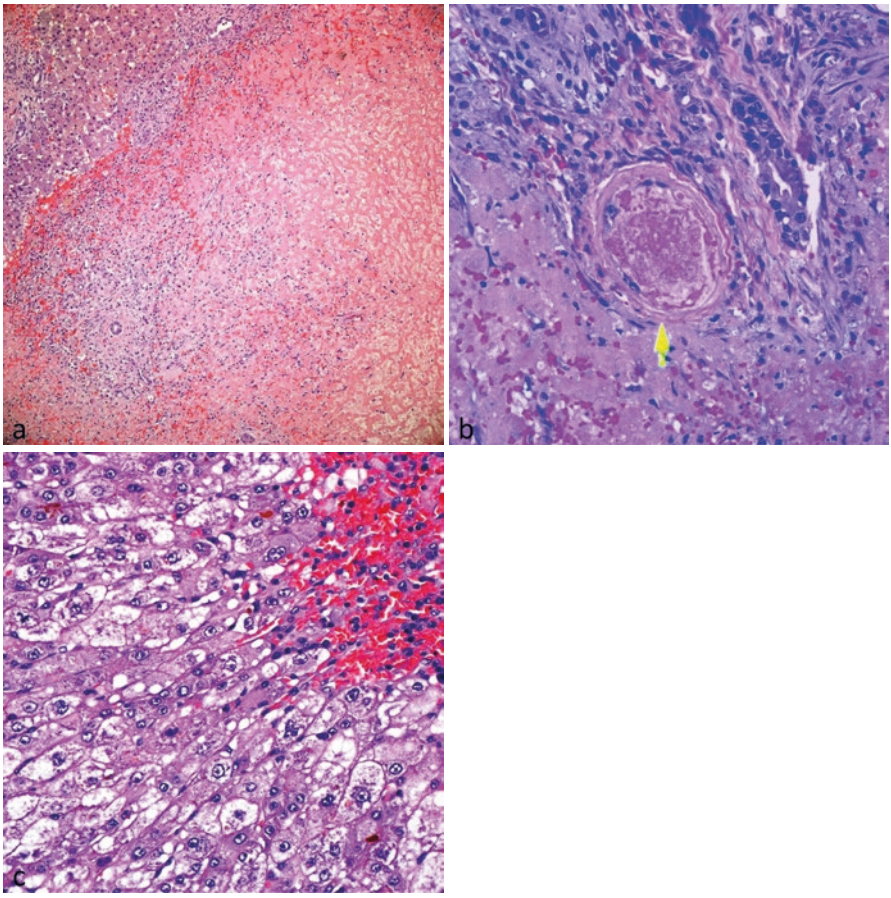

Fig. 18.3 (**a**) Histological findings from a HELLP patient, explanted liver, H&E: showing hepatic parenchyma with extensive necrosis. (**b**) Fibrin thrombus in a vessel adjacent to necrotic hepatic parenchyma. (**c**) Residual viable parenchyma with marked ballooning degeneration. (Courtesy of Dr. Jiang Wang)

Future Trends

While not much has changed with regard to treatments for preeclampsia and HELLP in the past few years, there is much that has been under study. Pravastatin has been shown in mice models to help prevent and treat preeclampsia [17–19]. Statins in general are HMG-CoA reductases that lower LDL but also have antioxidant, anti-thrombogenic, and anti-inflammatory properties. In murine models pravastatin was shown to decrease the increased sFLT1 levels in preeclampsia [19]. It was also shown to increase levels of nitric oxide synthetase, and in this way pravastatin may prove to be a valuable new treatment in both prevention and treatment [8, 17, 19]. There is a phase 1 trial in the United States that is underway and thus far has found

no serious adverse fetal or maternal effects with the use of pravastatin. There is a double-blind randomized placebo-controlled multicenter trial underway in the United Kingdom called StAmP or Statins to Ameliorate early-onset Preeclampsia. Additionally a few case reports have shown success with using salvage postpartum plasma exchange within 24 h in patients with Class I HELLP whose symptoms are persisting after delivery [12].

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Chapter 19
Pregnancy-Specific Liver Disorders: Acute Fatty Liver

Archita Desai and Deeksha Seth

Patient Questions

1. What is acute fatty liver of pregnancy?

   Acute fatty liver of pregnancy is a rare condition that can occur during the third trimester of pregnancy. Early recognition and prompt management are necessary as both the mother and fetus are at risk for complications.

2. What factors can put me at risk of this disease?

   Low BMI, enzyme deficiencies, multiple pregnancies, and coexisting liver diseases are some of the risk factors which can predispose a pregnant woman to AFLP.

3. What is the cause of this disease?

   While the exact cause of AFLP is unknown, it has been linked mainly to a deficiency in long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD). This enzyme plays a crucial role in fatty acid metabolism. In few of the cases, the deficiency of this enzyme is genetically linked. The deficiency of this enzyme leads to build up of intermediate products which are a cause of AFLP and its complications.

4. What is the usual clinical presentation?

   Patients initially present with malaise, headache, nausea, vomiting, abdominal pain, and anorexia. As the disease progresses, hypoglycemia, encephalopathy, jaundice, and ascites can occur with liver failure at the terminal stage.

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5. How can this disease be diagnosed early in pregnancy to avoid complications?
   Vigilance for symptoms by the care team, especially for those with risk factors for the disease, is important. Using Swansea criteria for screening in suspected cases can also aid in earlier diagnosis.
6. What is the mode of delivery and management?
   Immediate delivery of the fetus through cesarean section is the mainstay of management. Admission to the hospital before delivery with correction of metabolic derangements in the mother and fetus is necessary. Mothers who are critically ill will need intensive care monitoring and management with a small percentage needing support of organ function through dialysis and mechanical ventilation. In very rare cases, liver function does not recover requiring liver transplantation.
7. What are its complications on me and my child?
   Liver injury in the mother is usually reversible, improving after the delivery of the fetus, but can progress to liver failure in a small proportion of cases. In case of the infants, complications such as metabolic derangements, hypotonia, etc. can occur, and hence close follow-up is advised.
8. Will this happen to me in future pregnancies as well?
   Previous episode of AFLP is a risk factor for developing AFLP in future pregnancies, but the recurrence risk is 25% or less.

Introduction

Acute fatty liver of pregnancy (AFLP) is regarded as a rare obstetric emergency with life-threatening complications and poor outcomes for both the mother and the fetus [1]. It usually occurs in the third trimester with a median gestation age being 36 weeks of pregnancy [1–3]. The present chapter will review the epidemiology, pathogenesis, diagnosis, and management strategies as well as identify populations at greater risk for developing AFLP and strategies for preventing long-term maternal and fetal outcomes.

Epidemiology and Risk Factors

AFLP is rare with an incidence of 1 per 7000–16,000 deliveries [4, 5]. Risk factors which predispose to AFLP include low maternal body mass index (BMI <20 kg/m^2) (OR 1.4, 95% CI 0.6–2.9) [6], fetal long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) (OR 50.0, P = 0.001), short- or medium-chain acyl-CoA dehydrogenase (OR 12.3, P = 0.001) [6, 7], and multiple gestation or twin pregnancy (OR 14.3, 95% CI 6.4–28.6) [8]. Studies note that pregnancies with male infants are also at high risk of AFLP [1, 3, 4]. Furthermore, women with a prior episode of AFLP are also at a risk of developing AFLP in their future pregnancies

[9]. Those with coexisting liver diseases of pregnancy such as preeclampsia or hemolysis, elevated liver enzymes, and a low platelet count syndrome (HELLP syndrome) are thought to have a higher risk of AFLP with 20–40% overlap between the diagnoses [4, 10]. Diabetes type 2 has also been reported as a risk factor for the development of AFLP in a previous case report [11].

Pathophysiology

The exact pathophysiology of AFLP development is unclear, but it has been strongly linked to defects in fatty acid metabolism especially pertaining to long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency [7, 12, 13]. LCHAD (located on the C-terminal portion of the alpha-subunit of the mitochondrial trifunctional protein (MTP) on the inner mitochondrial membrane) catalyzes a step in the beta-oxidation of mitochondrial fatty acids [10]. The fatty acid metabolism is crucial for the growth and development of the fetus. Defects in free fatty acid metabolism during pregnancy produce intermediate products which accumulate and cause complications in both the mother and the fetus [14] (Fig. 19.1).

The carrier frequency of LCHAD deficiency has been reported to be 1 in 675 in the United States, and it is transmitted in an autosomal recessive pattern [15]. When

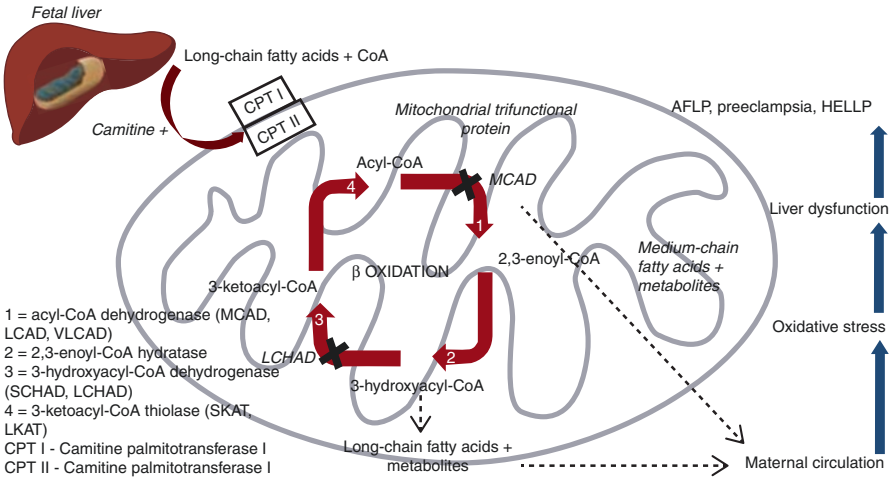

Fig. 19.1 Homozygous defects in the LCHAD and MCAD enzymes in the fetal and placental beta-oxidation of fatty acids lead to the accumulation of fatty acid chains that are transferred to a heterozygous mother producing the clinical symptoms of acute fatty liver of pregnancy [12–14]. Each step of the pathway is catalyzed by homologous enzymes such as LCHAD or MCAD enzyme that creates 2,3-enoyl-CoA. The black "x" depicts the effect of an LCHAD or MCAD enzyme deficiency that leads to the accumulation of fatty acid intermediates that gain entry into the maternal circulation and contribute to the development of acute fatty liver in the mother. (Source: Liu et al. [10])

the mother is heterozygous, there is a reduced capacity of beta-oxidation of fatty acids which is exacerbated during the later stages of pregnancy due to increased demand for fatty acid oxidation contributing to increased stress on the liver. This leads to an increase in the reactive oxygen species and inflammation leading to cellular necrosis, damage, and subsequent liver injury manifesting as AFLP [13, 14]. If the fetus is found to be homozygous for LCHAD deficiency, it is unable to perform the beta-oxidation of fatty acids due to which the level of the intermediate products rises and enters the maternal circulation producing detrimental effects on the maternal hepatocytes [7, 13].

The most common mutation associated with the development of AFLP has been found to be homozygous G1528C mutation (which results in the exchange of glutamic acid for glutamine at amino acid position 474 called the E474Q mutation) which is reported to be seen in around 65–90% of LCHAD patients, while the heterozygous and wild-type genotypes are not [10]. Although LCHAD mutation is strongly linked with AFLP, few cases have been reported where AFLP has occurred even without LCHAD deficiency mutation [10, 14–17]. Previous studies have also found associations of G1528C mutation with hemolysis, elevated liver enzymes, and a low platelet count and preeclampsia during pregnancy, which has overlap in phenotypic features with AFLP [14, 17, 18].

Some more enzyme deficiencies apart from LCHAD have also been found to be associated with AFLP, but they occur less commonly than the G1528C mutation such as carnitine palmitoyl transferase, medium-chain acyl-CoA dehydrogenase (MCAD), and short-chain acyl-CoA dehydrogenase (SCAD) enzyme deficiencies [7, 19–22].

Clinical Presentation

AFLP is usually a diagnosis of the third trimester, but few cases have been reported as early as 22 weeks and as late as 4 days post-delivery [1, 6]. Diagnosis is mainly based on the clinical presentation and the laboratory findings which also help in distinguishing it from other liver diseases of pregnancy. Early in the course of AFLP, a pregnant mother clinically presents with nonspecific signs and symptoms including malaise, headache, nausea, vomiting, abdominal pain, and anorexia [3, 6]. In the case of coexisting liver diseases of pregnancy such as preeclampsia or HELLP syndrome, they can also have signs of hypertension, which may or may not be accompanied by proteinuria [10]. Elevated aminotransferase level (aspartate aminotransferase or alanine aminotransferase), usually ranging from 5 to 10 times the upper limit of normal, but not exceeding 500 IU/L with bilirubin not exceeding 10 mg/dL, is a characteristic lab finding [10] (Table 19.1).

With delayed diagnosis and increased severity of AFLP, pregnant women can also demonstrate signs of jaundice, ascites, hypoglycemia, and encephalopathy and can progress to acute liver failure, disseminated intravascular coagulopathy, and multi-organ failure, while few of them can also progress to acute renal failure [4, 10]. AFLP has also been associated with central diabetes insipidus due to increased

Table 19.1 Features of AFLP (Differentiate from other liver diseases of pregnancy)

Acute fatty liver of pregnancy	
Clinical features	Abdominal pain vomiting, polydipsia/polyuria, encephalopathy
Trimester	Third (less common second and postpartum)
Ascites	+/−
Thrombocytopenia	+/−
Bilirubin	Usually <10 mg/dL (ULN 1.9 mg/dL)
Bile acid elevation	−
Hypoglycemia	+/−
Coagulopathy	+/−
Proteinuria	+/−
Aminotransferases	5–10×
Uric acid elevation	+
Hemolysis	−
Renal dysfunction	+
Histopathology	Microvesicular steatosis
Treatment	Delivery

Source: Adapted and modified from Liu et al. [10]

levels of the vasopressinase enzyme in the setting of impaired liver clearance resulting in decreased levels of vasopressin [23]. Rarely, acute pancreatitis can also be seen with AFLP and acute liver failure during pregnancy [24].

Differential Diagnosis

There is an overlap in clinical presentation among AFLP, HELLP syndrome, and severe preeclampsia, yet differentiating between these entities is critical to timely management. Development of acute liver or kidney failure, encephalopathy, coagulopathy, pancreatitis, pulmonary edema, and adult respiratory distress syndrome aids in the diagnosis of AFLP but occur late in the presentation [25–28]. Earlier in the course, the following points are generally used to differentiate AFLP from other liver diseases of pregnancy (Fig. 19.2):

- Proteinuria which is common with HELLP and preeclampsia but rare with AFLP.
- Ascites and hypoglycemia while absent in other liver diseases of pregnancy suggest, if present, AFLP diagnosis.
- The level of bilirubin in AFLP is usually less than 10 mg/dL as compared to that of other liver diseases of pregnancy.
- The bilirubin level does not rise above 5 mg/dL.
- Also a small rise in aminotransferase level is noted in AFLP compared to that of other liver diseases of pregnancy (5–10× AFLP vs 1–100× HELLP and preeclampsia).

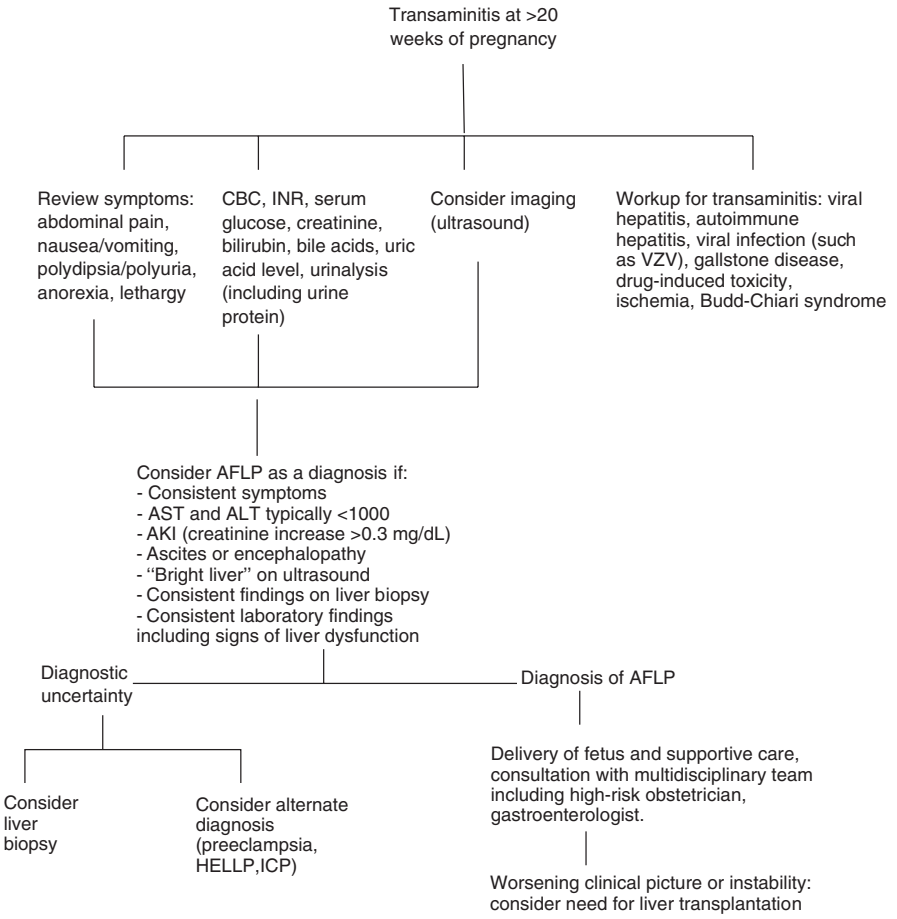

Fig. 19.2 Diagnostic algorithm for AFLP. Algorithm for diagnosis and management of AFLP, highlighting the features of AFLP and differentiation from other liver diseases of pregnancy. (Source: Liu et al. [10])

- Hemolysis is usually a feature of HELLP syndrome but is no present in AFLP.
- Renal failure can occur in AFLP but rare in the course of HELLP syndrome and preeclampsia [10].

Importantly, these diseases can coexist, and eclampsia and HELLP syndrome should be considered after making the diagnosis of AFLP and vice-versa.

The Swansea criteria have been developed and validated for the diagnosis of AFLP [3, 6] (Table 19.2). It is also used for screening the pregnant women for AFLP. It is found to be more accurate if the AFLP is severe, but the accuracy decreases if other pregnancy-associated liver diseases coexist making the diagnosis challenging [10, 29]. Diagnosis of AFLP is considered likely if 6 or more out of 15 criteria are met with a study noting 85% positive predictive value and a 100% negative predictive value in a small group of patients [10].

Table 19.2 Swansea criteria

S.no	Clinical features	Laboratory values	Imaging	Biopsy
1	Vomiting	Bilirubin >14 μmol/L	Bright liver on ultrasound	Microvesicular steatosis
2	Abdominal pain	Hypoglycemia <4 mmol/L		
3	Polydipsia/ polyuria	Elevated urea >340 μmol/L		
4	Encephalopathy	White blood cell count $>11 \times 10^6$ cells/L		
5	Ascites	ALT or AST >42 μmol/L		
6		Ammonia >47 μmol/L		
7		AKI or Creatinine >150 μmol/L		
8		Coagulopathy or PT >14 s or APPT >34 s		

Source: Tran et al. [3]

While considered by some as gold standard, liver biopsy is not typically used for diagnosing AFLP due to risk of complications of the procedure; stabilization and management of the mother and the fetus should not be delayed for liver biopsy if AFLP has already been confirmed clinically [1]. If the liver biopsy is performed, a transjugular approach in lieu of a percutaneous approach is preferred to minimize the risk of bleeding in patients with AFLP. The characteristic histological finding is microvesicular fatty infiltration of the hepatocytes involving the pericentral zone with sparing of the periportal hepatocytes confirmed on the Oil Red O stain which is done on frozen sections [10]. Majority of the cases have reported microvesicular fatty changes, while few cases have also demonstrated the presence of giant mitochondria and lymphocytic infiltration in the hepatocytes in patients with AFLP with some evidence of intrahepatic cholestasis [30]. The histological changes occurring during pregnancy in an AFLP patient have been found to reverse to normal after delivery without progression to cirrhosis [31].

Imaging usually does not aid in the diagnosis of AFLP and is nonspecific showing fatty infiltration or brightness [10, 32]. In a case series of five patients with AFLP, serial magnetic resonance imaging (MRI) showed increased detectable fat that was found to resolve within 2 weeks post-delivery [33].

Management

AFLP is an obstetric emergency and requires a multidisciplinary approach in order to reduce the risk of associated complications. In order to decrease the mortality and morbidity of the patients with AFLP, immediate delivery of the fetus is required irrespective of the gestational age of the patient, and the route of delivery depends on the severity of the disease and maternal and fetal decompensation [10]. Monitoring and correction of metabolic derangements are crucial in case of patients

presenting with thrombocytopenia, hypoglycemia, and altered metabolic panel since they are at a risk of multisystem failure. Both the fetus and the mother should be monitored closely in order to avoid complications. Invasive hemodynamic monitoring should be avoided due to the risk of bleeding. Due to the risk of encephalopathy, regular evaluation of maternal mental status can lead to early identification of a serious complication.

If the disease becomes severe, the patients are shifted to an intensive care unit (ICU) before and after delivery, and close attention is paid to their fluid status as previous cases have been reported to have developed pulmonary edema in the setting of low oncotic pressure [4]. Principles of critical management for acute liver failure are pillars of management of AFLP with frequent assessment of liver function and coagulation by exam and labs (i.e., plasma glucose, platelet count, prothrombin time, fibrinogen) to monitor for progression into DIC and acute liver failure [34, 35]. Similarly, regular monitoring of renal function with creatinine and blood-urea nitrogen for early identification of renal dysfunction is important. In cases of severe renal failure, patients may also require dialysis [10]. Combined plasma exchange with continuous hemodiafiltration has also been shown to be successful in treating terminally ill patients with AFLP [36]. Indications for plasma exchange include severe encephalopathy, liver or renal failure, or patients on mechanical ventilation who rapidly deteriorate and fail to respond to the above management [37–39].

AFLP has been seen to resolve post-delivery with the return of normal liver functions in 7–10 days [4]. In the case of multisystem failure, the patients may have a prolonged course in the hospital requiring supportive care and management [3]. Liver transplantation can be considered if the liver dysfunction persists with evidence of hepatic encephalopathy and lactic acidosis as suggested by previous studies [2, 10, 40]. Less than 0.1% liver transplants performed are due to AFLP but have shown excellent outcomes. Mostly these are performed within 1 week after delivery and have shown to be lifesaving in severe cases of AFLP [41–43]. Currently, there are no guidelines to identify women with AFLP and perform liver transplantation, and the decision to perform liver transplantation is made by worsening or persistence of symptoms or the evidence of hepatic encephalopathy and lactic acidosis [2, 10, 40, 41].

Complications

AFLP is associated with life-threatening conditions such as acute liver and renal failure, encephalopathy, disseminated intravascular coagulation, and gastrointestinal bleeding usually immediately postpartum [44–46]. Few cases have also reported having a hematoma and hepatic rupture with AFLP which are usually seen with preeclampsia or HELLP syndrome in pregnancy [47, 48]. Since women with AFLP are at increased risk for the above complications, they often require admission to ICU for frequent monitoring for coagulopathy, correction of glucose levels due to hypoglycemia, dialysis, and mechanical ventilation in case of acute respiratory distress syndrome (ARDS).

Maternal Outcomes

Earlier diagnosis of AFLP, immediate delivery, and advances in critical care have been successful in decreasing the maternal mortality rate from 75% to less than 10% over the past few years [4, 6, 10, 29, 49]. History of termination of pregnancy (OR 1.958, 95% CI 1.13–3.385), total bilirubin (OR 1.009, 95% CI 1.003–1.014), and serum creatinine (OR 1.010, 95% CI 1.003–1.017) have been identified as potential and independent risk factors for poor maternal outcomes post-delivery [50]. Post-delivery, reversal of histological changes (few cases have reported the persistence of fatty infiltration for up to 5 weeks), normalization of the liver function, and resolution of renal injury within a week are expected [10]. On the other hand, cases of AFLP with pancreatitis can take up to 3 months for resolution [29, 51].

Few studies have demonstrated none to minimal adverse events post-delivery indicating a relatively benign course thereafter [31]. The risk of recurrence is around 25% (fetus is homozygous or compound heterozygous for LCHAD deficiency) in women with prior episode of AFLP during pregnancy, but not many studies support this fact, and recurrence is not definite [9, 52–54]. Hence, expecting mothers should be informed of the risk of AFLP and should be followed up closely during subsequent pregnancies for an earlier diagnosis and prompt management.

Fetal Outcomes

Fetal mortality has been reported to be as high as 50% until 1985 [55]. Advances in critical care have contributed to improved fetal prognosis, but fetal mortality still remains high as compared to the maternal mortality which is attributed to maternal acidosis and prematurity [56]. Concerns regarding fetal outcomes remain high because of LCHAD deficiency, the effects of which can be mild to profound, and hence, close follow-up of the fetus after birth is suggested. Complications such as retinopathy, metabolic derangement, hypotonia, and muscle pain have been identified in a few cases in long-term [57]. Children with no fatty oxidation defect are free from adverse outcomes [57]. Fetal and/or newborn screening has been suggested for fatty acid oxidation deficiency which can help in detecting the disease earlier preventing unforeseen outcomes [17].

Conclusion

Although AFLP is rare, several important studies have enhanced our understanding of AFLP which has led to the decrease in mortality and morbidity due to early recognition, prompt delivery, and management, crucial to the well-being of both the mother and the fetus. The severity of this disease lays importance on the need for

early diagnosis and immediate delivery and management in order to avoid life-threatening complications.

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Chapter 20
Intrahepatic Cholestasis of Pregnancy

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Introduction

The management of liver disease in a pregnant woman can be a challenge. The assessment begins with determining if the patient has preexisting or coincidental liver disease not related to pregnancy versus liver disease related to pregnancy. Consideration of both the expectant mother and fetus is important in the approach to treatment. Intrahepatic cholestasis of pregnancy (ICP), one of several liver diseases specific to the liver, was originally described in the late 1800s and has been described as jaundice in pregnancy, pruritus gravidarum, obstetric hepatosis, hepatosis gestationalis, and obstetric cholestasis [1–4]. ICP is defined as pruritus beginning during pregnancy associated with elevated liver biochemistries in the absence of other liver diseases and resolves with delivery.

- **Clinical question**: "I was diagnosed with intrahepatic cholestasis of pregnancy. Why did I get this?"
  Answer: ICP is the most common pregnancy-associated liver disease. No one knows exactly why most women develop this complication; however, there are several risk factors. A very small percentage of women with ICP have genetic defects in canalicular transporters. But as this is a small minority of those affected, routine genetic testing is not recommended.

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Epidemiology

The prevalence of ICP is variable with location and ethnicity; however, it typically ranges from 0.3% to 28% [3, 5]. It is the most common liver disease in pregnancy [6, 7]. Factors such as advanced maternal age, prior personal history of ICP, and family history of ICP are associated with higher rates of ICP [8–10]. Women planning for conception or who are pregnant should be queried regarding a personal or family history of ICP or pruritus with oral contraception. In pregnancy with multiples, the risk of ICP increases to as high as 22% [11, 12]. There is thought to be a genetic predisposition in the setting of variant hepatobiliary transport proteins, impaired turnover of reproductive hormones, and environmental factors [10]. There is also a higher risk of developing ICP in patients who conceive via in vitro fertilization [8, 13, 14]. Most epidemiologic factors cannot be modified, but associated conditions should be considered. Patients with gallstone disease, nonalcoholic fatty liver disease, and hepatitis C also have higher rates of ICP [8, 15].

There is a significantly higher incidence of ICP in women who are hepatitis C positive. This association was first described in 1999 and was later confirmed by multiple institutions [10, 15–17]. Ropponen et al. performed a retrospective analysis of the Finnish Hospital Discharge Register spanning 1972–2000 and a cohort of 21,008 patients. Of the 10,504 who had ICP, the rate ratio between cases and controls for hepatitis C was 3.5 ($p < 0.001$), indicating a significantly higher rate of HCV in ICP patients than in control patients [15]. Patients with ICP and HCV can also have a higher viral load than patients without ICP [18].

For women of reproductive age with known HCV infection, antiviral therapy is recommended before conception, whenever practical and feasible, to reduce the risk of HCV transmission to future offspring [19]. This may also impact the development of ICP. Based on AASLD guidelines, HCV testing in pregnancy is now recommended to maximize opportunities for education, linkage to treatment after delivery, and appropriate testing for the exposed infant. In addition, testing for HCV in those women diagnosed with ICP should be considered.

- **Clinical question**: "I told my obstetrician I was itching. She thinks I have ICP. Why does she think this and how can we confirm?"
  Answer: Although itching in pregnancy is common, itching from ICP is unique, like most pruritus from liver-associated cholestasis, as it often involves the palms and soles. This presentation increases the suspicion that ICP may be the answer. The diagnosis is easily confirmed by blood tests for bile acids which can also help predict the chance that the infant may be at risk for complications.

Clinical Presentation

ICP typically develops late in the second trimester or in the third trimester with pruritus, most predominantly in the palms and soles, although may occur anywhere (Table 20.1). Pruritus can be severe enough to wake patients from sleep and often

Table 20.1 Clinical features and laboratory findings

Intrahepatic cholestasis of pregnancy	
Clinical features	Pruritus
Trimester	Second to third
Ascites	–
Thrombocytopenia	–
Bilirubin	<5 mg/dL (ULN 1.9 mg/dL)
Bile acid elevation	30–100×
Hypoglycemia	–
Coagulopathy	–
Proteinuria	–
Aminotransferases	1–5×
Uric acid elevation	–
Hemolysis	–
Renal dysfunction	–
Histopathology	Hepatocellular bile and canalicular bile plugs
Treatment	Pruritus management (UDCA first line), delivery at 37 weeks

UDCA ursodeoxycholic acid, *ULN* upper limit of normal

worsens in severity as pregnancy progresses. There is no associated rash, beyond secondary skin changes due to itching. These skin changes can range in severity from simple excoriation to prurigo. Pruritus can precede or follow the first laboratory evidence of cholestasis with elevations in aminotransferases and bile acids [20]. Some patients may have onset prior to 28 weeks, with earlier onset associated with higher rates of preterm labor [21]. Clinically apparent jaundice is uncommon, occurring in less than 25% of ICP patients, always after the onset pruritus. Jaundice, especially prior to itching, should also warrant a thorough search for alternative explanations.

Additional symptoms such as right upper quadrant pain, nausea, loss of appetite, and steatorrhea secondary to fat malabsorption resulting may also occur. Patients may develop systemic symptoms of cholestasis, including dark urine, pale stools, and jaundice; however, this is rare and should prompt investigation into other potential etiologies of symptoms [22, 23].

Biochemical Findings

Lab abnormalities are remarkable for elevated aminotransferases, typically less than two times the upper limit of normal. Rarely, they may rise to levels greater than 1000 μ/L. The rise in aminotransferases can occur 1–2 weeks prior to the rise in serum bile acid [20]. Elevation in serum bile acid levels, typically greater than 10 μmol, is diagnostic of ICP. Low chenodeoxycholic acid levels and high cholic acid levels are also present in ICP. Dramatic elevations in bile acid concentration higher than 40 μmol are strongly associated with fetal distress and fetal

complications, while levels higher than 100 μmol are associated with higher risk of fetal demise [22, 24–26]. After the diagnosis of ICP, bile acids should be monitored weekly.

Mild predominantly conjugated hyperbilirubinemia may also be present (no higher than 6 mg/dL), but this is in a small proportion of patients with ICP [9]. Alkaline phosphatase may be elevated as well; however, as this is produced by the placenta and is frequently elevated in healthy pregnancies, it is a nonspecific marker of ICP [27]. Gamma-glutamyl transpeptidase (GGT) is typically normal but can be modestly elevated in up to 30% of cases of ICP.

Coagulation factors remain largely normal, with the only potential derangement being prolongation of prothrombin time, related to vitamin K deficiency in the setting of fat malabsorption and steatorrhea, or the use of bile acid sequestrates such as cholestyramine [23].

Diagnosis, Differential DDx, and Pathology

Pruritus can affect 23% of pregnancies; however, only a small fraction of this is due to ICP [28]. Diagnosis requires the presence of pruritus with elevated total serum bile acids, elevated aminotransferases and the absence of other etiologies. Pregnant patients with abnormal liver tests should undergo a standard workup as any non-pregnant individual. This includes recognition of different patterns of elevated LFTS and serologic and radiographic evaluation. Pruritus is the predominant feature of ICP, and its presence in addition to an elevation in total bile acids helps distinguish it from other pregnancy-related derangements in liver tests (Table 20.2).

Because pruritus can precede laboratory derangements, it is recommended to repeat laboratory evaluation weekly if initial values are within normal range. Right upper quadrant ultrasound should be done to rule out other etiologies such as cholelithiasis. Ultrasound findings are normal in ICP, without any evidence of biliary ductal dilation and unremarkable appearance of hepatic parenchyma.

ICP is a clinical diagnosis. Liver biopsy is not typically necessary; however, if done, biopsy findings show perivenular canalicular cholestasis with bile plugs

Table 20.2 Differential diagnosis for abnormal liver tests in a pregnant person

Differential diagnosis
Preexisting or coincidental liver disease during pregnancy
Viral hepatitis
Other chronic liver diseases
Cholelithiasis/cholecystitis/choledolcholithiasis
Liver disease specific to pregnancy
Intrahepatic cholestasis of pregnancy
Preeclampsia/eclampsia
Acute fatty liver of pregnancy
HELLP

within canaliculi and hepatocytes, most predominantly in Zone 3. Portal tracts remain intact, and notably, there is an absence of inflammation [29].

Atypical symptoms suggestive of liver failure, such as ascites, encephalopathy, and asterixis, should prompt investigation into other potential etiologies of elevated aminotransferases and pruritus.

- **Clinical question**: "I read that intrahepatic cholestasis of pregnancy runs in families. Should my siblings get tested?"
  Answer: Although there is a genetic component of ICP and there is an increased risk in first-degree relatives, there are only a small number of defined mutations which lead to ICP. Surveillance for family members is not recommended.

Pathophysiology

The pathophysiology of ICP is not completely understood, but the process of developing ICP is likely multifactorial. There is a genetic component, hormonal influence, and environmental factors.

Genetic ICP appears to occur in clusters of families, with increased risk in first-degree relatives. The adenosine triphosphate-binding cassette, subtype B, member 4 (ABCB4) gene encodes the multidrug resistance 3 (MDR3) protein, which is a canalicular phospholipid translocator. This protein is responsible for bile clearance along the hepatocyte canalicular membrane, and mutations are known to result in a spectrum of phenotypes that include progressive familial intrahepatic cholestasis (PFIC) type 3 and cholelithiasis. Mutations in the ABCB4 gene are found in 16% of patients with ICP [30]. Abnormalities in additional canalicular transporter genes, such as FIC1 encoded by the ATP8B1 gene; BSEP by ABCB11; MRP2 by ABCC2; and FXR by NR1H4 [30–32], and their regulators have also been identified. Given the small number of defined mutations with ICP, genetic testing is currently recommended only in those with early onset and recurrent ICP or in families with other individuals affected by cholestasis independent of pregnancy.

Hormones In vitro studies have determined 17-beta estradiol glucuronide, an estrogen metabolite, inhibits bile excretion into the canaliculi, leading to cholestasis [33, 34]. Therefore, it stands to reason cholestasis of pregnancy occurs when concentrations of estrogen are at peak levels in the second half of pregnancy. In addition, ICP is more common in twin pregnancies and can occur during ovarian hyperstimulation during in vitro fertilization. ICP resolves after delivery of the placenta, which is a major source of estrogen production across the second and third trimesters [35].

Progesterone may also influence the pathogenesis of ICP. Total progesterone does not rise in comparison with normal pregnancies, but progesterone metabolites may impair hepatic transport systems utilized for biliary excretion [36, 37].

The cholestasis effect of hormones can also occur with the use of combination oral contraceptive pills in some women with ICP.

Environmental Seasons, geography, and vitamin levels may be environmental factors that lead to variability in the expression of the disease. The incidence of ICP is higher in the winter months than in the summer months, suggesting that exogenous factors may play a role in disease manifestation [7, 38, 39]. Deficiency of factors such as dietary selenium and environmental vitamin D, both of which are associated with lower levels in the winter months, have also been shown to be associated with higher rates of ICP, theorized to be related to altered oxidative hepatic metabolism [38].

It occurs in higher rates in Scandinavian and South American populations. European predominance ranges from 10 to 150 per 10,000 pregnancies [6]. The highest rates have been detected in Chile (16%), most particularly in women who were Araucanian Indian (28%). Interestingly, the rates of ICP in Chile have declined, suggesting that environmental and dietary factors may also play a role [6, 38].

- **Clinical question**: "My doctor told me that my child is at risk because I have intrahepatic cholestasis of pregnancy. What can I do to keep my baby safe?"
  Answer: Poor fetal outcome has been associated with ICP; however, the use of UDCA, close monitoring, and timing delivery between 36 and 37 weeks have been shown to significantly reduce complications.

Fetal Outcomes

While maternal outcomes are excellent, bile acids cross the placenta and can accumulate in the fetus and amniotic fluid, which carries significant risk for the fetus. Premature birth occurs in 20–60% of pregnancies affected by ICP [6, 11, 40, 41]. The rate of early delivery is due to both induction of labor and spontaneous labor. Bile acids increase expression of myometrial oxytocin receptors, which may explain the increase in spontaneous preterm labor. The 22–33% prevalence of fetal distress during delivery [2, 42] is attributed to bile acid entering the lungs during labor. Meconium staining of amniotic fluid, which is a sign of fetal distress, may also occur in 16–58% cases of ICP [2, 43]. Intrauterine fetal demise is the most concerning complication of ICP and occurs in 1–2% of cases of ICP, all after 37 weeks [11, 39, 42, 44–47]. Pathophysiology of fetal death is poorly understood but may be related to the sudden development of a fetal arrhythmia or vasospasm of the placental chorionic surface vessels induced by high levels of bile acids [48, 49]. Concomitant pregnancy complications (e.g., gestational diabetes, preeclampsia) may also play a role.

Management

Management of ICP focuses on treatment of maternal pruritus and reduction of perinatal morbidity and mortality. Patients that have clinical symptoms but normal serum bile acids and aminotransferase level may be treated empirically with

ursodiol, or laboratory evaluation of liver enzymes and bile acids may be repeated weekly. If diagnostic for ICP, the mother should be started on therapy, and monitoring should be continued to ensure that bile acid levels do not rise above 40.

- **Clinical question**: "I am so itchy! What can I do to relieve my symptoms?"
  Answer: There are several medications available to help relieve your itching. The most common treatment is ursodeoxycholic acid, a medication that is dosed twice a day. It has very few side effects and no fetal toxicity, so it is safe for both mother and fetus.

Treatment of Pruritus The first-line therapy for ICP is ursodeoxycholic acid (UDCA) at 10–15 mg/kg/day or 600 mg twice a day. It is well tolerated and has no fetal toxicity. It improves cholestasis in the mother by increasing bile salt export pumps, acting as a cytoprotective agent against the hepatotoxic effects of the bile acids.

In addition, UDCA improves placental bile acid transport, thereby reducing bile acid accumulation in amniotic fluid and in cord blood which leads to decrease in fetal complications [9, 22, 46, 47, 50]. There have been several meta-analysis evaluating UDCA for ICP [51–53]. However, quality of evidence is limited due to variation in reporting and outcome definitions in the various studies. For example, trials measured pruritus differently, and data on bile acid concentrations could not be pooled in some studies. Overall, UDCA is associated with significant improvement in maternal outcomes, with reduction in severity of pruritus and aminotransferase levels, and may improve fetal outcomes. There is an ongoing randomized controlled trial in the United Kingdom comparing UDCA with placebo [54].

Rifampin, S-adenosyl-L-methionine (SAMe), cholestyramine, or antihistamines may be considered for ICP [55]. Rifampin (300–900 mg) is the recommended second-line agent as it enhances bile acid transport and can lower bile acid levels in one-third of UDCA nonresponders [56, 57].

SAMe, a glutathione precursor, has shown to reverse estrogen-induced bile flow impairment in rat models and influences the composition and fluidity of hepatocyte plasma membrane in humans. A randomized clinical trial to evaluate intravenous high-dose SAMe (800 mg/day) for 20 days concluded that symptoms of pruritus, serum transaminases, conjugated bilirubin, and total bile acids fell significantly in respect to initial levels compared to lower dose SAMe (200 mg/day) and no treatment [58]. Later studies [59] have not supported this finding, and several controlled studies concluded SAMe is less effective than UDCA [55, 60].

Cholestyramine (8–16 g/day) is a nonabsorbable agent that binds bile acids and prevents their absorption from the terminal ileum through the enterohepatic circulation. Early studies in nonpregnancy-related cholestatic diseases showed 80–85% of patients completely or partially respond to cholestyramine treatment [61]. However, its effect on pruritus with ICP is limited and inferior to UDCA [62]. In addition, cholestyramine is often unpalatable, must be dosed apart from meals and medications, and is associated with fat-soluble vitamin deficiency including vitamin K, which is important with regard to hemorrhagic obstructive complications.

Antihistamines, such as hydroxyzine 25 mg every 6–8 h, improve pruritus. These agents are safe during pregnancy and may help with sleep disturbances related to symptoms.

Dexamethasone has some effect in reducing bile acids by suppressing fetal production of estrogen but is not effective in the treatment if ICP pruritus or associated with improvement in perinatal outcomes [63]. It may be used to promote fetal lung maturity before delivery [64].

Plasmapheresis for ICP has been reported in the literature for cases of severe recurrent symptoms [65, 66]. Pruritus may be debilitating in severely affected individuals, and plasmapheresis may provide substantial and instantaneous relief. This therapy is limited by the expense as well as the potential for rare but serious adverse effects.

Fetal Assessment Antepartum fetal monitoring such as biophysical profile and nonstress test for evaluation of chronic placental insufficiency on the fetus is recommended [46, 47], but evidence to support this approach is lacking. Because the mechanism of intrauterine fetal demise is thought to be a sudden event rather than the result of a chronic placental vascular process, fetal demise can occur in the presence of reassuring fetal testing.

Delivery Early delivery at or before 37 weeks gestation is recommended because intrauterine death is more common in the last month of pregnancy with rare deaths occurring before 37 weeks [67].

Some factors that may be considered for delivery prior to 37 weeks of gestation are severe maternal pruritus not relieved with pharmacotherapy, jaundice, prior history of premature fetal demise due to ICP, and a high total serum bile acid concentration ≥100 mmol (galantz 2014). Delivery prior to 36 weeks is associated with potential morbidity of prematurity. It is important to counsel patients that no definitive evidence suggests maternal and fetal benefits of ending the pregnancy before 36 weeks. Antenatal corticosteroids are administered for fetal lung maturity if delivery is planned before 36 weeks gestation.

Mode of delivery (i.e., cesarean section versus vaginal delivery) is not associated with change in outcome in ICP. Therefore, it should not be a deciding factor of the patient and the obstetrician in determining how to deliver. Continuous fetal monitoring during labor is indicated, given increased frequency of fetal death and nonfatal asphyxia events [68, 69]. Labor induction does not necessarily lead to an increased risk of cesarean delivery compared with expectant management [70]. Typically, the function of the liver is preserved, and no vitamin K or coagulation factors need to be tested or administered. There is no increased risk for postpartum hemorrhage when ICP is managed with UDCA [23]. In rare severe refractory cases, the prothrombin time can be checked and vitamin K administered if it is prolonged.

- **Clinical question**: “I had intrahepatic cholestasis of pregnancy with my last child. Can I use oral contraceptives now? If I decide to get pregnant again, will I get ICP again?”

Answer: Patients with ICP may take oral contraceptives after delivery. Certain types may be preferable depending on which hormones are present in the OCP. ICP can recur in 60–70% of subsequent pregnancies.

Postpartum Resolution of pruritus usually occurs within days of delivery. Follow-up total bile acids and transaminases are performed to confirm resolution of biochemical abnormalities. Because there is an association of ICP with HCV, gallstones, and primary biliary cholangitis, persistent abnormal chemistries should trigger evaluation of other explanations [10, 15]. ICP recurs in 60–70% of subsequent pregnancies [6, 35]. Progestin-only is preferred over combination estrogen-progestin contraception due to the risk of hormone-associated cholestasis [71–74]. However, neither are contraindicated. Breastfeeding is not contraindicated in pregnancy complicated by cholestasis.

Conclusion

Although ICP is the most common liver disease related to pregnancy, it also has the most favorable maternal and fetal outcome. Typically, symptoms of pruritus can be managed. Fetal distress is uncommon and fetal demise, the most concerning complication, is rare. Research is ongoing to evaluate additional gene mutations that lead to ICP. Targeting specific transporters and receptors with drug therapy may improve both maternal and fetal outcomes. In addition, a better understanding of environmental factors in high prevalence groups will augment the armamentarium for the management of ICP.

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Chapter 21
Inflammatory Bowel Disease and Pregnancy

Nedhi Patel and Andres Yarur

Introduction

Inflammatory bowel diseases (IBD) are a spectrum of immune-related conditions that include ulcerative colitis and Crohn's disease. The overall incidence of ulcerative colitis from age 15 to 64 is 10.4 in 100,000 people, while the incidence of Crohn's disease is 5.6 in 100,000 people. The peak onset of ulcerative colitis and Crohn's disease is between 25–35 and 15–24 years of age, respectively [1]. Thus, a high number of patients live with the disease through their fertile years.

There are many factors that affect a female IBD patient's decision to become pregnant. This includes fear of poor pregnancy outcomes, uncertainty of medication side effects (including teratogenicity), concerns of disease effect on baby, effects of the pregnancy on IBD, and fear of infertility [2]. It has been shown that patients with IBD have a higher rate of "voluntary childlessness" (18% for Crohn's disease and 14% for ulcerative colitis) when compared to the general population (6%) [3].

Will Having Inflammatory Bowel Disease Affect My Ability to Get Pregnant?

Suggested Response to the Patient

Fertility and fecundability are important concerns for both men and women. Infertility is defined as an inability to conceive after 12 consecutive months of regular intercourse; fecundability is the probability to achieving a pregnancy in one

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menstrual cycle. Both men and women with quiescent IBD have the same infertility rate as the general population [4, 5]. In patients with ulcerative colitis who had a colectomy followed by an ileal pouch-anal anastomosis, the risk of infertility is significantly higher when compared to those who have not. Therefore, when a colectomy is needed in patients who wish to bear children, the recommendation is to perform an end ileostomy with a rectal pouch. A proctectomy and pouch creation can be performed at a later time. Due to their effects on sperm function, it is recommended that men trying to father a child stop taking methotrexate and sulfasalazine. In the general population, women are referred for assisted reproductive therapy (ART) after 1 year of attempting pregnancy without success. In women with IBD, the recommendation is to refer to ART if no conception occurs after 6 months [6, 7].

Brief Review of the Literature

Women with IBD that have not undergone colectomy have a similar fertility rate when compared to those without IBD. Female patients with an ileal pouch-anal anastomosis (IPAA) have a twofold to threefold increased risk of infertility compared to patients controlled with medical management in lieu of surgery [8–10]. The reason for this higher risk of infertility with IPAA is thought to be due to damage of fimbria, hydrosalpinx, tubal damage, and/or tubal adhesions due to pelvic surgery. On the contrary, patients with a subtotal colectomy preserve their fertility [11, 12].

There is a lack of strong data associating medications used in the treatment of IBD and decreased fertility in women. However, there have been studies that show men taking sulfasalazine have decreased fertility due to a decreased (but reversible) sperm count and motility [13]. Methotrexate has been shown to cause oligospermia that resolves around 6 months after stopping the drug; therefore, methotrexate is not recommended in men trying to father a child [14].

Assisted reproductive therapy includes in vitro fertilization and transfer of frozen-thawed embryos. One large Danish nationwide study analyzed the success of ART in women with IBD versus no IBD. In patients with UC, 20.00% of the embryo transfers were successful, and 16.97% of transfers were successful in patients with CD. This is in comparison with a 23.78% success rate in the age-matched general population [15].

If I Get Pregnant, What Will the Outcomes Be?

Suggested Response to the Patient

Overall, pregnant women who have IBD may have an increased risk of preterm birth and babies with low birth weight. However, in patients with controlled disease, the outcomes are the same as in females without IBD. Therefore, it is important for

females with IBD to conceive when their disease is in remission and to continue their IBD medications during pregnancy in order to decrease the risk of any adverse outcomes of pregnancy.

Brief Review of Literature

When compared with healthy controls, some studies have shown that women with IBD are more likely to deliver prematurely and have infants with low birth weight [16]. There is also a higher risk of requiring a cesarean section [17].

One study showed that patients with IBD with or without active disease have an increased odds of having a preterm delivery, small for gestational age infant, and stillbirth [18]. The same study also reported an increased risk of congenital anomalies; however, multiple other larger studies did not corroborate this increased risk [18–20].

Disease control of IBD prior to conception is the single biggest modifiable factor that can impact pregnancy outcomes. Having active disease at the time of conception increases the risk of spontaneous abortion and preterm birth [21, 22]. Furthermore, the risk of low birth weight is doubled in patients with a nulcerative colitis exacerbation and triples in patients with a Crohn's disease exacerbation [23]. Data shows that when disease activity is accounted for, the risks of preterm birth and low birth weight are the same in controlled IBD and non-IBD patients [24, 25].

Will Pregnancy Worsen My Inflammatory Bowel Disease?

Suggested Response to the Patient

Most patients with IBD will not have a flare of their underlying ulcerative colitis or Crohn's disease if they are under control at time of conception and patients continue their treatment.

Brief Review of Literature

The effect of pregnancy on IBD is not well understood. In one study that looked at patients who conceived in remission, there was a 20% chance of a disease exacerbation if the patient had Crohn's disease versus a 33% chance of disease exacerbation if the patient had ulcerative colitis [26].

Coordination of pro- and anti-inflammatory cytokines is required for successful pregnancy. Many of these cytokines are made from the placenta. TNF is a pro-inflammatory cytokine that is made by the placenta. On the contrary, interleukin-10 (IL-10) is an anti-inflammatory cytokine. The obstetrics literature shows that high levels of TNF are associated with preeclampsia and gestational diabetes. IL-10 lev-

els have been shown to be decreased in patients with preeclampsia. The modulation of these cytokines during pregnancy likely plays a role in successful pregnancy in the IBD population as well [27–30].

Is My Medication Safe to Take During Pregnancy and While Breastfeeding?

Aminosalicylates

Suggested Response to the Patient

Aminosalicylates (ASAs) are generally safe in pregnancy. There are multiple preparations of ASAs. Asacol™, a certain formulation of mesalamine, contains a substance that in high doses can induce malformations. Sulfasalazine does cause a reversible decrease in sperm count in men and should be stopped on those men patients trying to conceive. Pregnant patients on sulfasalazine should be on folic acid supplementation.

Brief Review of the Literature

ASAs are medications that contain 5-aminosalicylic acid (5-ASA) such as mesalamine and sulfasalazine. Overall, mesalamine is a safe medication. However, an old formulation of Asacol™ contained a very small amount of dibutyl phthalate (DBP) that in high doses has been associated with external and skeletal malformations as well as adverse effects on the male reproductive system in animal studies [31]. Sulfasalazine inhibits the enzyme dihydrofolate reductase; therefore, patients taking sulfasalazine require high-dose folate supplementation with 2 mg of folate a day. This should be done while in consultation with their obstetrician [32]. Folate supplementation reduces the risk of cleft palate and cardiovascular teratogenicity. Given these risks, the recommendation is to avoid sulfasalazine during pregnancy [31]. ASA medications are safe when breastfeeding, as there is only a negligible amount of drug excreted into the breast milk [33].

Antibiotics

Suggested Response to the Patient

Two common antibiotics used in IBD are ciprofloxacin and metronidazole. Ciprofloxacin should be avoided during pregnancy and breastfeeding. Metronidazole is safe to use during pregnancy for a short period of time.

Brief Review of the Literature

Antibiotics are still used in IBD, especially when treating pouchitis and perianal Crohn's disease. Ciprofloxacin should not be used during pregnancy due to the risk of musculoskeletal abnormalities that have been observed in animal studies [34].

Metronidazole is relatively safe in pregnancy. A meta-analysis of around 900 pregnant women treated with metronidazole at different stages of pregnancy found no increased incidence of congenital malformations [35]. The long-term effects of metronidazole are not well known; therefore, the shortest course of this medication is recommended. Metronidazole can be detected in breast milk; however, it does not appear to have an immediate effect on the neonate [36].

Corticosteroids

Suggested Response to the Patient

Corticosteroids come in many different formulations including oral, intravenous, and topical forms. Steroids may cause an increased risk of cleft lip and cleft palate early in pregnancy. Ideally, these medications should be avoided early in pregnancy. However, in cases of an acute flare of IBD, corticosteroids may be necessary in order to get the disease under control which in turn could potentially lead to better pregnancy outcomes. The decision to use corticosteroids during pregnancy should include a discussion between the patient, gastroenterologist, and obstetrician.

Brief Review of the Literature

Most formulations of corticosteroids can cross the placental barrier, but they are quickly metabolized into less active metabolites [37]. Most studies show no increased risk of teratogenicity. This includes a large population-based study of about 51,900 pregnancies in which the women were exposed to steroids in the first trimester. There was no increased risk of orofacial malformations [38–40]. On the contrary, some other studies have shown an association of corticosteroids with cleft lip and palate [41–43]. There are very rare case reports of adrenal suppression in the neonate when the mother is treated with steroids late in pregnancy [40].

Thiopurines

Suggested Response to the Patient

The metabolism of thiopurines varies among the population. If the patient is on a stable dose of mercaptopurine or azathioprine, the recommendation is to continue the current dose. The consensus is that breastfeeding is low risk in women taking

thiopurines. When lactating, mothers should avoid breastfeeding within 4 hours after taking the thiopurine, and do so after "pumping and dumping" breastmilk.

Brief Review of the Literature

In mothers taking a thiopurine, the active metabolite (6-thioguanine) has been measured in the cord blood of the fetus—the cord blood had an average of 50% of the maternal levels [44]. A meta-analysis done in 2013 compared IBD patients taking a thiopurine and IBD patients not on a thiopurine; there was no reported increased risk for adverse outcomes [45]. Some studies have shown an increased risk of congenital malformations, perinatal mortality, and preterm birth in patients exposed to azathioprine/mercaptopurine during pregnancy; on the other hand, other studies have shown no increase rate of preterm birth, low birth weight, congenital anomalies, and neonatal adverse outcomes [46–48]. While studies have shown heterogeneous results, it is thought that many of these do not account for disease activity during pregnancy, thus leading to worse outcomes on some reports. Therefore, it is the current recommendation to continue thiopurines in women trying to conceive. One potential scenario where thiopurines could be discontinued is on those patients on combination therapy with a biologic and in remission, when de-escalating therapy would be reasonable.

Breastfeeding while on thiopurines also has mixed data. A small study of eight females taking mercaptopurine showed that the excretion of the drug in breast milk is very low, and mercaptopurine is only present within the first 4 hours after ingestion of the medication [49]. Another small study with 11 patients in Austria shows that children whose mothers were taking azathioprine did not have an increase rate of infection compared to children whose mothers were not taking azathioprine [50].

Methotrexate

Suggested Response to the Patient

Methotrexate is a known teratogen. It is contraindicated in pregnancy and should be stopped 6 months prior to conception. Similarly, breastfeeding is not recommended while taking methotrexate.

Brief Review of the Literature

Methotrexate, especially in the first trimester, is known to cause miscarriage, growth retardation, anencephaly, limb effects, and skeletal abnormalities [51, 52]. Even in the later stages of pregnancy, methotrexate is associated with growth retardation and

functional abnormalities [52]. Methotrexate has a long half-life and takes about 6 weeks to reach steady state in the body. In women, there is a recommended 6-month "washout" period to allow for drug metabolism prior to attempting pregnancy. In men, though there is no outcome data, the risk is high enough that the suggested washout period is at least 3 months.

Methotrexate is excreted in the breast milk at levels less than 10% of the maternal plasma concentration; however, the long half-life allows accumulation in the neonate's tissue [53]. Therefore, breastfeeding when on methotrexate is not recommended [54].

Infliximab and Adalimumab

Suggested Response to the Patient

Infliximab and adalimumab are both antibodies against tumor necrosis factor (TNF). Both of these medications are approved for the treatment of ulcerative colitis and Crohn's disease. Continuing the medication during pregnancy and during breastfeeding is recommended. Due to the possibility of drug being present in the offspring at birth until up to 6 months of life, live vaccines are contraindicated during this period of time. The live vaccines to avoid include Bacillus Calmette-Guérin (BCG), rotavirus, measles-mumps-rubella (MMR), and varicella zoster.

Brief Review of the Literature

Infliximab is a chimeric mouse and human antibody, whereas adalimumab is a fully human antibody. Infliximab and adalimumab are both IgG1 antibodies and both cross the placenta, especially in the second and third trimesters [55]. In animal studies, offspring that received anti-TNF therapy throughout pregnancy did not have abnormalities in the immune system [56, 57].

Infliximab and adalimumab have both been found in newborns at higher levels than in the circulating blood of the mother. These serum drug levels in the newborn may remain detectable for up to 6 months after birth [58, 59]. Another report found that when the medication was stopped before 30 weeks of pregnancy, the levels in the newborn were undetectable, while levels in the mother were not; therefore, some providers may recommend holding biologics after 28 weeks of gestation to minimize fetal exposure [60]. A small prospective study showed that discontinuation of the anti-TNF during the second trimester was not associated with increased risk of maternal flare of IBD [61]. One observational study compared outcomes in three different groups: direct exposure to infliximab or adalimumab (within 3 months prior to conception and/or until the second trimester), indirect exposure (infliximab or adalimumab prior to pregnancy), and those who were naïve to anti-TNF. The study showed that there was no difference in outcomes in the different groups [62].

However, these are noninterventional studies, and the interruption of biologic therapy should be evaluated in a case-to-case basis.

The Pregnancy in IBD and Neonatal Outcomes (PIANO) registry is a prospective study evaluating outcomes of neonates and mothers exposed to biologic therapy. In a preliminary report, there was no increased risk for congenital abnormalities due to anti-TNF exposure. It was noted, however, that the offspring of mothers taking combination therapy of infliximab or adalimumab plus azathioprine or mercaptopurine had an increased risk of infection at age 9–12 months compared to mothers on monotherapy [63].

It is important to report that most studies have shown no association of increased pregnancy complications with anti-TNF therapy; however, one review of reports submitted to the FDA found a high rate of congenital malformations in offspring exposed to infliximab or etanercept (another anti-TNF used for rheumatologic conditions) [64]. However, a population-based study published 2 years after the initial study did not support the findings that were initially reported [65].

There is a notable case report in which a baby exposed to infliximab in utero received the BCG vaccine at 3 months of age; the child then developed disseminated BCG that lead to death [66]. Therefore, live vaccines are contraindicated in neonates whose mother was taking an anti-TNF agent until at least 6 months of age.

The amount of anti-TNF excreted into breast milk is very small in comparison with the levels in the maternal circulation. According to the findings from the PIANO registry, breastfed infants exposed to an anti-TNF have similar milestone achievement as compared to unexposed breastfed infants [67]. Breastfeeding while taking anti-TNF is recommended given the low risk of effects of the anti-TNF and the benefit of breastfeeding.

Certolizumab Pegol

Suggested Response to the Patient

Certolizumab is in the same class of medication as infliximab and adalimumab (an anti-TNF). While there is not as much data on certolizumab as compared to infliximab and adalimumab, the studies show no increase risk of adverse outcomes. Because of certolizumab's structure, it does not cross the placenta and breastfeeding is also considered safe.

Brief Review of the Literature

Certolizumab is a humanized monoclonal antibody and, as infliximab and adalimumab, has activity against TNF. This drug differs from adalimumab and infliximab because it does not have an Fc region. This theoretically prevents its

transportation across the placenta. A small study of ten human pregnancies exposed to certolizumab showed very low levels of drug in the cord blood [68]. In the PIANO registry, the use of certolizumab throughout pregnancy was not associated with an increased risk of malformations or infections [63]. This medication is likely safe to use in pregnancy, though again, the data are limited in regards to pregnancy outcome as well as breastfeeding while taking this medication.

Vedolizumab

Suggested Response to the Patient

Based on the limited data available, vedolizumab has not been shown to cause adverse effects on pregnancy. There is insufficient safety data to completely deem it safe, and the risk and benefits of continuing the medications need to be discussed with the patient. In our practice, we continue the drug as the potential risk of developing a disease exacerbation likely outweights the risk.

Brief Review of the Literature

Vedolizumab is an IgG1 monoclonal antibody to alpha-4 beta-7 integrin that is used in the treatment for ulcerative colitis and Crohn's disease; this is a more "gut-specific" agent. Safety data for vedolizumab is limited to only case reports and small case series. According to the PIANO registry, serum levels of vedolizumab in infants at birth are about half that of the mother [69]. Also, based on the prolonged clearance of vedolizumab by infants, there is a consideration of delaying live vaccines to after 12 months of life rather than 6 months for an anti-TNF medication [70]. However, it has been shown that the immunologic response of the infant who has been vaccinated is not related to the fetal drug level at the time of vaccine, so this recommendation should be further studied [71, 72]. Given the small sample size, it is not possible to draw conclusions on the safety of vedolizumab and pregnancy [73, 74].

Natalizumab

Suggested Response to the Patient

Natalizumab has been available as therapy for Crohn's disease, but its use is currently limited due to its safety profile and the availability of other safer medications. There is no increased rate of adverse outcomes in animal models, but there is limited data on this medication in human pregnancy. It is likely

acceptable to continue if other, safer, options are not feasible. Breastfeeding cannot be recommended given the lack of data.

Brief Review of the Literature

Natalizumab is a humanized monoclonal IgG4 antibody to alpha-4 integrin that is used in the treatment of patients with Crohn's disease [75]. Natalizumab increases risk of development of progressive multifocal leukoencephalopathy; therefore, its use has been reserved for patients with Crohn's disease that is refractory to other agents. More recently, the availability of a "gut-selective" anti-integrin agent (vedolizumab) has limited the use of natalizumab even further. In animal models, natalizumab did not increase the rate of spontaneous abortion or have an increased rate of teratogenicity [76]. One study of 29 children whose mothers were on natalizumab found that 28 of the children had no major malformations; one child had a minor malformation [77]. Breastfeeding is not recommended given the lack of safety data.

Ustekinumab

Suggested Response to the Patient

Ustekinumab is a medication that has been used to treat psoriatic arthritis for years; it is now approved for Crohn's disease. There are some reports of patients receiving ustekinumab with healthy pregnancies; however, there is still a lack of safety data to establish its safety during pregnancy. As with vedolizumab, the risk and benefits need to be discussed with the patient. Breastfeeding is also not recommended given the lack of data.

Brief Review of the Literature

Ustekinumab is a monoclonal antibody that has been used to treat psoriatic arthritis. It blocks the p40 subunit shared by interleukin-12 and interleukin-23. Recent randomized controlled trials have shown a benefit in Crohn's disease; as of September 2016, the FDA has approved ustekinumab for the treatment of moderate to severe Crohn's disease [78]. Given the relatively recent approval for the use in Crohn's disease, there is no strong data to suggest that ustekinumab is safe in pregnancy and/or in breastfeeding. In the dermatology literature, there are case reports of successful pregnancy while inadvertently on ustekinumab [79]. There was 1 series of 26 patients exposed to ustekinumab who had a spontaneous abortion rate that was similar to the general population [80]. Breastfeeding is not recommended while taking ustekinumab given the lack of experience in this setting.

Cyclosporine and Tacrolimus

Suggested Response to the Patient

Cyclosporine and tacrolimus are calcineurin inhibitors that are widely used in the prevention of organ transplant rejection, and they are used in select IBD cases. There is mixed data on the safety of these medications while pregnant; therefore, this medication should only be used as a salvage therapy for patients with severe ulcerative colitis.

Brief Review of the Literature

The calcineurin inhibitors can have a role in the treatment of IBD, specifically in acute severe ulcerative colitis. For cyclosporine, a meta-analysis including 410 pregnant patients did not have an increased risk of congenital malformations [81]. However, another systematic review of mostly transplant patients taking cyclosporine showed increased rates of pregnancy complications including preterm birth and low birth weight. This finding may have been due to maternal illness; however, the association could not be made with cyclosporine and adverse outcomes alone [82]. Limited studies in posttransplant patients taking tacrolimus have not shown worse outcomes [83]. Calcineurin inhibitors could be considered in specific cases as salvage therapy. Patients on cyclosporin should not breastfeed. Even though breastfeeding could potentially be safe while on tacrolimus, there is limited data, and we recommend against it (Table 21.1).

Conclusion

Given the age of onset of IBD, discussion of fertility and pregnancy outcomes between patients and gastroenterologists is vital. It is essential to discuss with any woman of childbearing age the effect of her IBD on pregnancy and appropriate education regarding the recommendation to control the disease prior to attempting pregnancy. The majority of pregnancies in patients with IBD have good outcomes. The highest success rate in pregnancy can be achieved with thorough preconception counseling, medication adherence counseling, and adequate monitoring of the disease and pregnancy.

While many of the drugs have some data in pregnancy, it is important to discuss the lack of data for the more novel agents and the risk and benefits of becoming pregnant on them. A multidisciplinary approach is needed, including the involvement of maternal-fetal obstetricians, gastroenterologists with a focus on IBD, colorectal surgeons, and pharmacists in order to have a successful pregnancy.

Table 21.1 Medications used in inflammatory bowel diseases and their safety in pregnancy and breastfeeding

Drug class	Recommendations for pregnancy	Recommendations for breastfeeding
Aminosalicylates	Low risk. Preparations with dibutyl phthalate are likely low risk but should be switched if possible	Excretion of aminosalicylate metabolites is very low. Breastfeeding is low risk
Adalimumab and infliximab	Minimal transfer to the fetus in the first trimester; high transfer to the fetus in the third trimester. Increased risk of neonatal infections when combined with thiopurines. Live vaccines contraindicated in the first 6 months of life	May be detected in breast milk in insignificant amounts; nursing is low risk
Azathioprine and 6-mercaptopurine	Low risk to continue medication if the patient has been on a stable dose. Consider checking the fetus for neonatal anemia	Insignificant amounts of drug in breast milk if measured 4 hours after ingestion. "Pump and dump" recommended
Certolizumab pegol	Minimal transfer to the fetus throughout pregnancy. Safe to continue	Likely safe to use while breastfeeding
Ciprofloxacin	Risk for arthropathies. Avoid during pregnancy as lower risk medications are available	Limited data, likely safe. But, long-term effects are unknown therefore would avoid breastfeeding
Corticosteroids	Possible association with cleft lip and palate when used early in pregnancy. Rare reports of neonatal adrenal suppression when used late in pregnancy	Low levels in breast milk, likely safe to breastfeed
Cyclosporine and tacrolimus	No increased teratogenicity, but the data is mixed. Should only be used as salvage therapy if other therapies have failed	Drug can be detected in breast milk; therefore, breastfeeding should be avoided
Methotrexate	Absolute contraindication. Should be discontinued at least 3 months prior to conception	Excreted into breast milk and should not be used while breastfeeding
Metronidazole	No increased risk when used for a short period of time	Can be detected in breast milk, and long-term exposure risks are not clear. Breastfeeding not recommended
Natalizumab	Very limited data in pregnancy, probably safe if other options are not available	Lack of safety data
Ustekinumab	Very limited data. Likely safe as there are case reports showing successful pregnancy	Lack of safety data
Vedolizumab	Limited data on its use during pregnancy. Can be used on a case-by-case basis	Lack of safety data

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Chapter 22
Gallstone and Biliary Disease

Gillian L. Fell and David Brooks

Patient Questions and Brief Answers

Questions 1: I was referred to you because I was found to have gallstones on imaging obtained for another reason. Do I need surgery to remove my gallbladder?

Answer 1: The answer to this question depends on the patient's previous symptoms. Typically, a patient asking this question has never had complicated gallstone disease, such as cholecystitis, choledocholithiasis, gallstone pancreatitis, or cholangitis. However, it is very important to take a good history, because some of these patients may have experienced biliary colic in the past but have never come to clinical attention. Important questions to ask include whether the patient has ever experienced right upper quadrant or epigastric abdominal pain related to the intake of fatty or greasy foods. Additionally, patients may report referred pain to the right scapular region. Typically the onset of the pain is within 30–60 min of eating and lasts approximately 1–3 h before resolving spontaneously. In patients who have had this type of pain characteristic of biliary colic, we recommend elective cholecystectomy in suitable operative candidates. For patients who have never experienced symptoms referable to their gallstones, we do not recommend operative intervention, as there is a chance that symptomatic gallstone disease will never develop.

Questions 2: What are the risks of having my gallbladder removed?

Answer 2: The surgical consent process always includes a discussion of the risks and benefits of surgery, and patients frequently desire an understanding of the risks of surgery. Major risks specific to laparoscopic cholecystectomy include (1) bile leak from dislodgement of the surgical clips from the cystic duct remnant; (2) injury to the common bile duct that would require a second operative intervention with the potential need to reroute the gastrointestinal tract in the form of a Roux-en-Y hepat-

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icojejunostomy; (3) bleeding or hematoma formation from inadequate hemostasis at the end of the case or from dislodgement of the surgical clips from the cystic artery remnant; (4) a retained gallstone in either the cystic duct remnant or common bile duct that would require a postoperative ERCP or operative common bile duct exploration. If there is any concern for choledocholithiasis at the time of cholecystectomy, an intraoperative cholangiogram can be performed to assess for this; and (5) injury to the bowel, either from inserting the laparoscopic trocars or in dissecting the infundibulum to obtain a critical view of the cystic duct and cystic artery. The transverse colon and the duodenum can be very near the area of dissection and vulnerable to injury. While conversion to an open cholecystectomy is always a possibility, we do not see this as a risk of the surgery but rather an operative maneuver undertaken should conditions be too unsafe to proceed in a laparoscopic fashion. While this possibility should always be discussed with patients, many surgeons do not typically include it as a risk on the consent form.

Question 3: I am pregnant and developed symptoms of gallstones. Should I have my gallbladder removed? If so, when is the safest time to do so for me and my baby?

Answer 3: The answers to these questions depend very much on both the nature of the patient's gallstone disease and how close she is to delivering her child. In pregnant patients with a single episode of biliary colic, surgical intervention would not be recommended, as there is a chance that additional episodes may never occur. For patients in the first or second trimester who develop recurrent biliary colic, an elective cholecystectomy during pregnancy is typically offered. For patients in the late third trimester of pregnancy who develop recurrent biliary colic, the typical recommendation is to undergo elective cholecystectomy approximately 6–8 weeks after delivery. For pregnant patients with complicated gallstone disease including cholecystitis, Mirizzi syndrome, choledocholithiasis, gallstone pancreatitis, or cholangitis, expeditious cholecystectomy is recommended. In these cases, the risk of maternal and fetal complications is greater than that of cholecystectomy. For pregnant patients with choledocholithiasis or gallstone pancreatitis, preoperative ERCP to clear the common bile duct is recommended, with lead protection for the fetus during fluoroscopy.

Gallstone Disease in Women

Women are more likely to develop gallstone disease than men, with double the risk of developing cholesterol gallstones over the course of a lifetime. The majority of that increased risk occurs between menarche and menopause, with a female-to-male ratio of approximately 4:1 during reproductive years [1].

Why Women Are at Increased Risk of Gallstone Disease

Cholesterol gallstones form when the concentration of cholesterol in bile is elevated to a degree that supersaturates the ability of bile salts to solubilize. In this setting, the excess cholesterol precipitates into gallstones. This can occur in the setting of increased hepatic uptake or synthesis of cholesterol, increased release of hepatic cholesterol into bile, and biliary stasis or obstruction in which bile is not effectively excreted from the gallbladder. The female sex hormones estrogen and progesterone play key roles in increasing the content of cholesterol in bile and in promoting cholesterol gallstone formation.

Estrogen receptors are expressed in hepatocytes and when stimulated by estrogen promote upregulation of hepatocyte cholesterol synthesis [2, 3]. Estrogen receptor signaling in hepatocytes also results in increased secretion of cholesterol into bile [3]. Progesterone contributes to increasing biliary cholesterol through inhibition of the enzyme acyl-coenzyme A-cholesterol acyl-transferase [4]. This results in decreased production of cholesterol esters, making more free cholesterol available for release into bile. Progesterone also decreases gallbladder contractility and blunts the contractile response to cholecystokinin signaling [5]. Overall the combination of increased biliary cholesterol with gallbladder stasis creates an environment that favors gallstone formation.

While women do carry a higher risk of developing gallstone disease compared to men, the typical presentation, symptom patterns, diagnostic workup, and management between men and women do not differ. However, during pregnancy, women are particularly susceptible to developing gallstone disease. The diagnosis and management of gallstone disease in the pregnant patient require several special considerations, which will be the main focus of this chapter.

Gallstone Disease During Pregnancy

During pregnancy, women are at increased risk of developing gallstone disease than in the nonpregnant state. The estrogen- and progesterone-rich hormonal milieu during pregnancy is believed to account for this increased risk [6]. Risk factors for the development of gallstone disease during pregnancy include prepregnancy obesity, elevated leptin levels, and multiparity [7, 8]. Gallbladder sludge or gallstones occur in approximately 5–10% of women at some time during pregnancy or in the postpartum period. Ko et al. prospectively surveilled 3254 pregnant patients for gallbladder disease by right upper quadrant ultrasound and found that 5.1% developed sludge or gallstones by the second trimester, 7.9% by the third trimester, and 10.2% by 6 weeks postpartum [7]. Studies in smaller cohorts have reported an incidence of

biliary sludge or gallstones during pregnancy as high as 30% [6, 9, 10]. Biliary sludge and gallstones that develop during pregnancy often resolve postpartum. In studies that have followed women beyond delivery, a 61–96% rate of sludge resolution and a 20–28% rate of gallstone resolution have been reported [7, 9].

Despite the relatively common occurrence of gallstones during pregnancy, only a small subset of pregnant women experience symptomatic gallstone disease, with an estimated incidence of 0.05–0.8% [7, 11, 12]. Complicated gallstone disease (cholecystitis, choledocholithiasis, gallstone pancreatitis) occurs more rarely, with an incidence of 0.01–0.06% [13, 14]. In one of the largest population-based studies that included over 1 million pregnancies and nearly 2000 cases of symptomatic gallstone disease, 12.7% of symptomatic patients underwent cholecystectomy during pregnancy. An additional 19% of the symptomatic patients underwent cholecystectomy in the postpartum period [12].

Presentation of Symptomatic Gallstone Disease in Pregnant Patients

Gallstones can be an asymptomatic incidental finding during routine prenatal ultrasounds. While the presence of gallstones should be noted in case symptoms develop, nothing further needs be done for asymptomatic patients. Among patients who develop symptomatic gallstones, there is a range of presenting symptoms along the spectrum of gallstone disease.

In the majority of patients who develop symptomatic gallstones, the initial manifestation is biliary colic. These patients typically present with right upper quadrant abdominal pain that occurs approximately 30–60 min after ingesting a meal, lasts for several hours, and resolves gradually on its own. These episodes of pain often occur following a particularly fatty meal.

Patients with gallstones may more rarely present initially with acute cholecystitis. In these cases, patients typically report postprandial right upper quadrant or epigastric abdominal pain that fails to resolve in the usual time course for biliary colic. Patients with acute cholecystitis may also have fevers, chills, anorexia, nausea, or vomiting. While anorexia, nausea, and vomiting can occur in pregnant patients for nonpathologic reasons, the presence of these symptoms in the setting of localized right upper abdominal pain or fevers should prompt suspicion and further diagnostic workup for gallstone disease.

Least frequently initial presentations of symptomatic gallstones include choledocholithiasis, cholangitis, and gallstone pancreatitis. Choledocholithiasis and cholangitis result from gallstone obstruction of the common bile duct, while gallstone pancreatitis results from gallstone obstruction at the ampulla of Vater. These entities require expeditious recognition and treatment, as they have the potential to carry a high morbidity and mortality. These patients can present similarly to patients with acute cholecystitis. Choledocholithiasis and cholangitis may be distinguished clini-

cally from acute cholecystitis if the patient is jaundiced, whereas acute gallstone pancreatitis often results in pain that is more centrally located in the epigastrium or mid-back. Biochemically, choledocholithiasis and cholangitis characteristically result in a direct hyperbilirubinemia, while gallstone pancreatitis results in elevated serum lipase and amylase. These laboratory abnormalities are not seen in isolated acute cholecystitis. However, derangements in laboratory parameters can be difficult to detect in pregnant patients due to normal changes of certain laboratory reference ranges over the course of pregnancy (discussed below).

Differential Diagnosis of Right Upper Quadrant Abdominal Pain in Pregnant Patients

In all patients who present with right upper quadrant abdominal pain, there is a differential diagnosis that includes nonbiliary diseases such as hepatitis, hepatoma, hepatic cyst or abscess, pyelonephritis, peptic ulcer disease, and nonbiliary pancreatitis [15]. There are particular elements of a differential diagnosis for right upper quadrant pain unique to pregnant patients that must always be considered (Table 22.1).

Preeclampsia/HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelets) The characteristic abdominal pain and the elevation in liver function laboratories can obscure the differentiation of these from symptomatic gallstone disease. However, characteristic findings in preeclampsia include hypertension and proteinuria. Thrombocytopenia is a diagnostic criterion for HELLP that is not observed in gallstone disease. Thus, normal blood pressure, lack of urine protein, and normal platelet levels rule out preeclampsia and HELLP.

Acute Fatty Liver of Pregnancy This is a serious condition usually occurring in the third trimester of pregnancy in which patients present with jaundice and constitutional symptoms including fever, anorexia, nausea, and vomiting. Typically, transaminases are elevated more than would be expected for gallstone disease. Rapid recognition of this condition is important because it comes with a high risk of maternal and fetal mortality. While supportive care can be attempted, the definitive therapy of this condition is delivery.

Intrahepatic Cholestasis of Pregnancy This typically presents as severe pruritus and right upper abdominal pain late in pregnancy during the third trimester. Other common symptoms include dark urine, acholic stool, anorexia, and fatigue. Jaundice can be observed but is less common. Diagnostically it is differentiated from symptomatic gallstone disease by the absence of gallstones on ultrasound, and the most common biochemical abnormality is elevated serum bile acids. It resolves spontaneously after delivery [16].

Table 22.1 Common characteristics to differentiate elements of the differential diagnosis of right upper quadrant abdominal pain in pregnant women

	History/physical	Laboratories	Imaging
Biliary colic	Postprandial pain that resolves	Normal	Ultrasound with gallstones
Cholecystitis	Pain that does not resolve +/− Fever, anorexia, nausea, vomiting	Leukocytosis	Ultrasound with gallstones, gallbladder wall thickening, pericholecystic fluid
Choledocholithiasis	Pain that does not resolve +/− Jaundice, fevers, anorexia, nausea, emesis	Direct hyperbilirubinemia +/− Leukocytosis, transaminitis	Ultrasound with gallstones, dilated common bile duct MRCP with stone in common bile duct
Gallstone pancreatitis	Pain in epigastrium or mid-back	Elevated lipase/amylase	Ultrasound with gallstones, dilated common bile duct MRCP with stone in proximal duct near ampulla
Preeclampsia	Pain persists Hypertension Later pregnancy	Proteinuria	Normal
HELLP	Pain persists Later pregnancy +/− Jaundice	Thrombocytopenia Anemia Elevated liver function enzymes	Normal
Acute fatty liver of pregnancy	Pain persists Late third trimester Fevers +/− Anorexia, nausea, vomiting	Transaminitis	Normal
Intrahepatic cholestasis of pregnancy	Pain persists Third trimester Pruritus +/− Dark urine, acholic stool, jaundice, fatigue	Elevated serum bile salts	Normal
Appendicitis	Pain can be in mid- to lower abdomen as well +/− Fevers	Leukocytosis	Ultrasound with dilated appendix, appendiceal wall thickening, +/− fecolith MRI if ultrasound is nondiagnostic
Intrauterine pathologies	Typically lower abdominal pain, contractions +/− Vaginal bleeding, fevers	+/− Leukocytosis	Ultrasound can diagnose uterine rupture or placental abruption

Appendicitis While appendicitis should be on the differential diagnosis of any patient with right upper quadrant pain, it warrants a higher priority on the differential diagnosis of a pregnant patient with right upper quadrant pain. This is particularly true for patients during late pregnancy. As the fundal height increases, the position of the appendix is typically shifted cephalad, into the right upper abdomen. Thus, appendicitis during mid- to late pregnancy can very often present as right upper abdominal pain rather than the classic symptom of right lower quadrant abdominal pain seen in nonpregnant patients.

Primary Intrauterine Pathologies While right upper quadrant abdominal pain is an atypical presentation of entities such as placental abruption, intrauterine infection, and uterine rupture, these must be kept in mind as they are important and potentially lethal complications of pregnancy that are associated with abdominal pain. These important pathologies requiring rapid recognition and intervention can easily be missed in patients with atypical presentations. In most situations there are key features to distinguish a primary intrauterine pathology from gallstone disease. Placental abruption typically includes abnormal vaginal bleeding, uterine contractions, fetal distress, and symptoms of disseminated intravascular coagulopathy. Uterine rupture typically occurs during labor and is associated with uterine tenderness and fetal distress. Intrauterine infections often include leukocytosis and fevers, uterine tenderness, maternal and fetal tachycardia, and abnormal uterine contractions.

Diagnostic Workup in the Pregnant Patient with Suspected Gallstone Disease

Laboratory Values

Physiologic changes in normal laboratory values during pregnancy can confound the interpretation of laboratories obtained in the setting of symptomatic or complicated gallstone disease. Often, changes in laboratory parameters occur continuously over the course of pregnancy, further complicating efforts to glean meaningful information [17]. One recent meta-analysis of 70 studies provided reference ranges for laboratory values during pregnancy [18]. Several of the normal changes in laboratory values during pregnancy are germane and important to account for in assessing the pregnant patient suspected of symptomatic gallstone disease.

White blood cell count increases steadily over the course of pregnancy, such that by the third trimester, values as high as 17,000/mm^3 are within normal limits. The neutrophil fraction of white blood cells also increases, rendering it difficult to detect a true left shift. Among the liver function enzymes, the transaminases tend to decrease slightly during pregnancy; however, alkaline phosphatase increases to as high as 229 U/L in the third trimester. Direct and indirect bilirubin levels tend to

Table 22.2 Normal pregnancy reference ranges of laboratories most useful in the diagnosis of gallstone disease

	Prepregnancy	First trimester	Second trimester	Third trimester
WBC ($\times 10^3/mm^3$)	3.5–9.1	5.7–13.6	5.6–14.8	5.6–16.9
AST (U/L)	12–38	3–23	3–33	4–32
ALT (U/L)	7–41	3–30	2–33	2–25
AP (U/L)	33–96	17–88	25–126	38–229
TBili (mg/dL)	0.1–0.5	0.1–0.5	0.1–0.4	0.1–0.5
DBili (mg/dL)	0.1–0.4	0–0.1	0–0.1	0–0.1
Amylase (U/L)	20–96	24–83	16–73	15–81
Lipase (U/L)	0–60	0–104	0–140	5–148

WBC white blood cell count, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *AP* alkaline phosphatase, *TBili* total bilirubin, *DBili* direct bilirubin

decrease over the course of pregnancy, rendering it easy to overlook a mild hyperbilirubinemia during late pregnancy. Lipase levels increase modestly during pregnancy to just over 100 U/L by the third trimester. Amylase values do not change appreciably over the course of pregnancy. These laboratory changes over the course of pregnancy are shown in Table 22.2.

Imaging

Ultrasound Ultrasound is the gold standard for diagnosing gallstone-related disease in both pregnant and nonpregnant patients. It is a radiation-free modality that is safe for both the mother and the fetus. It is 95–98% accurate in the detection of gallstones and is the test of choice for the detection of classic sequelae of cholecystitis, including gallbladder wall thickening, pericholecystic fluid, and sonographic Murphy's sign [19]. Ultrasound can also be used for fetal or intrauterine assessment and, in select patients with a highly experienced ultrasonographer, can detect other intra-abdominal pathologies including appendicitis and hepatic masses of fluid collections. Finally, ultrasound can detect common bile duct dilation that may be helpful in the diagnosis of choledocholithiasis.

HIDA In cases in which acute cholecystitis is suspected but the ultrasound is nondiagnostic, HIDA scans are used to detect cystic duct obstruction. Radiolabelled technetium-99m is administered, and its excretion through the biliary system is monitored. Inability of the gallbladder to fill with the tracer is consistent with cystic duct obstruction and cholecystitis. Technetium-99m does not cross the placenta, and the radiation delivered to the fetus is approximately 0.15 rad, which is well below the level considered harmful [20]. The American College of Obstetricians and Gynecologists (ACOG) has stated that radionuclide scans that utilize technetium-99m can safely be used during pregnancy when used appropriately to make a diagnosis [21]. It is important to note that a certain amount of radionuclide tracers, including technetium-99m, is secreted into the milk of lactating women. ACOG recommends

consultation with lactation specialists and nuclear medicine experts to determine an appropriate time for disposing of breastmilk after a radionuclide scan [21].

Overall, HIDA scans are not the first test of choice in the diagnosis of cholecystitis, and the diagnosis can most often be made utilizing other modalities that do not require radiation exposure. HIDA scans can typically be avoided; however in rare cases, it may be necessary. Typically, this is in the setting of diagnostic uncertainty despite a thorough history and physical exam, an ideal ultrasound assessment, and accounting for laboratory abnormalities.

Magnetic Resonance Cholangiopancreatography Magnetic resonance imaging (MRI) modalities, including magnetic resonance cholangiopancreatography, are considered safe for use during pregnancy. However, there is some uncertainty regarding the effect of magnetic resonance during the first trimester when organ development is most rapid. In general, MRI and MRCP are considered acceptable when other diagnostic modalities are insufficient or would otherwise require ionizing radiation exposure [22, 23]. As in nonpregnant patients, MRCP is most useful to detect the etiology of biliary ductal dilation when there is uncertainty about the presence of an obstructing gallstone in the common bile duct. One study that assessed the role of MRCP in 18 pregnant patients demonstrated its ability to differentiate a common bile duct stone, Mirizzi syndrome, and choledochal cyst to guide appropriate intervention via ERCP or surgery. This study also demonstrated the ability of MRCP to exclude obstructive etiologies of biliary ductal dilation in a subset of the study participants and avoid unnecessary intervention [22].

Endoscopic Retrograde Cholangiopancreatography During Pregnancy

Endoscopic retrograde cholangiopancreatography (ERCP) is utilized to diagnose and treat obstructing gallstones in the common bile duct and pancreatic duct. This procedure is typically performed by a gastroenterologist and involves an upper endoscopy with cannulation of the ampulla of Vater into the biliary ductal system. Once cannulated, the ductal system can be swept to clear stones, sphincterotomies can be performed to facilitate passage of stones, and stents can be placed to maintain biliary ductal patency. During the procedure fluoroscopy is utilized to confirm appropriate cannulation of the biliary ductal system and perform cholangiography to navigate and understand the anatomy of the ductal system. ERCP has supplanted surgical common bile duct exploration as the predominant method for clearing the ductal system of gallstones.

ERCP is considered safe for pregnant patients, although some concern over the risks of the procedure, particularly the radiation dose during fluoroscopy, has prompted the development of modifications to optimize safety in pregnant patients [24]. In general, purely diagnostic ERCPs are avoided in pregnant patients. Use of MRCP or endoscopic ultrasound to confirm diagnoses is preferred [24, 25]. The endoscopist should be highly experienced, and a multidisciplinary team including

an obstetrician, an anesthesiologist with obstetric experience, a radiologist with radiation safety expertise, and a surgeon should be involved in each case. Some studies have suggested that ERCP during the first trimester should be avoided due to increased risk of preterm delivery and low birth weight [25, 26]. There is uncertainty, however, regarding whether these risks are due to first trimester development of complicated gallstone disease or due to the ERCP itself. Thus, the general recommendation is to perform ERCP at any time indicated with appropriate precautions and modifications in place [25, 27]. In terms of procedural modifications during pregnancy, nonpregnant patients are typically positioned prone to facilitate cannulation of the common bile duct, but pregnant patients are positioned supine or in the left lateral decubitus position to avoid undue pressure on the gravid uterus and compromise to aortic and inferior vena cava blood flow.

One of the most important considerations for ERCP during pregnancy is use of appropriate shielding and techniques to minimize the radiation dose to the fetus without compromising the safety or efficacy of the study. It is recommended to drape the lower abdomen and pelvis with lead aprons anteriorly and posteriorly to optimally protect the fetus from radiation exposure [24, 26]. More recent studies have investigated the safety and efficacy of a radiation-free ERCP that utilizes endoscopic ultrasound to identify the stone burden within the common bile duct. This relies purely on direct vision of guidewire cannulation of the ampulla of Vater and does not utilize fluoroscopy to confirm guidewire position or guide sweeps of the common bile duct. One feasibility study of nonradiation ERCP in 31 patients reported successful fluoroscopy-free cannulation of the common bile duct and successful stone removal in 26 of the 31 patients (84%) [28]. Another prospective randomized trial comparing fluoroscopy-free ERCP and conventional ERCP in 111 patients demonstrated a 96.4% successful common bile duct cannulation rate and 85.5% stone clearance rate in the fluoroscopy-free ERCP group compared to 100% success rate in both parameters for the conventional ERCP group [29]. This group noted that stone clearance by fluoroscopy-free ERCP was improved when only 1–2 stones were present. Overall, conventional ERCP can be performed safely during pregnancy with appropriate modifications, and the current fluoroscopy-free modalities of ERCP have not demonstrated equal efficacy compared to conventional ERCP.

Management of the Pregnant Patient with Symptomatic Gallstone Disease

Operative Versus Nonoperative Intervention

Table 22.3 outlines the recommended course of care along the spectrum of gallstone disease in the pregnant patient. For pregnant patients who present with a single episode of biliary colic, it is typical practice to manage nonoperatively. For patients with recurrent biliary colic early to mid-pregnancy, it is recommended to offer a cholecystectomy during pregnancy. For patients who develop recurrent biliary colic during late pregnancy, it is appropriate to monitor the patient nonoperatively and

Table 22.3 Management of the spectrum of gallstone disease during pregnancy

	Procedure	Surgery
Asymptomatic gallstones	None	None
Biliary colic	None	None if first episode Elective laparoscopic CCY if recurrent
Cholecystitis	None	Laparoscopic CCY urgently
Choledocholithiasis	ERCP	Laparoscopic CCY after ERCP (same admission)
Cholangitis	ERCP	Laparoscopic CCY (same admission after resolution of symptoms)
Gallstone pancreatitis	ERCP if supportive care fails	Laparoscopic CCY (same admission after resolution of pancreatitis)

plan for an elective cholecystectomy in the postpartum period. Six to eight weeks postpartum is generally an appropriate time for an elective cholecystectomy. While biliary colic itself is not dangerous for the mother or the fetus, an important reason to consider intervention is the risk of developing complicated gallstone disease, which carries a more significant morbidity risk than cholecystectomy. Nonoperative management of recurrent biliary colic during pregnancy is also associated with more hospitalizations [30–32]. Cholecystectomy performed during pregnancy is regarded as safe, associated with low rates of preterm labor and minimal maternal and fetal morbidity [33–37].

In the past, nonoperative management with antibiotics and IV hydration was recommended for pregnant women with cholecystitis due to the high risk of fetal loss with operative intervention [38]. As operative techniques have been optimized, perioperative medication options have become safe during pregnancy, and the recurrence rate of complicated gallstone disease recognized as significant, early operative intervention has gained favor [14, 37]. In one meta-analysis aimed at defining best practices in treating complicated gallstone disease during pregnancy, nonoperative versus operative management of cholecystitis resulted in no difference in preterm labor and fetal mortality rates [11], with the benefit of avoiding the risk of recurrent or progressive complicated gallstone disease. One scenario in which nonoperative management with antibiotics and supportive care tends to be favored is in very-near-term patients who present with cholecystitis. Pregnant patients who present with choledocholithiasis ERCP followed by cholecystectomy with appropriate modifications, precautions, and multidisciplinary team involvement, as previously described, are recommended. Gallstone pancreatitis is typically managed.

Operative Considerations for Cholecystectomy in the Pregnant Patient

Once the decision is made to perform a cholecystectomy for a pregnant patient with symptomatic or complicated gallstone disease, there are several important perioperative considerations that must be addressed. Positioning on the operating table

with left side slightly downward relieves compression of the inferior vena cava by the gravid uterus.

The laparoscopic approach is generally preferred over the open approach, with fewer maternal and fetal complications associated with laparoscopic cholecystectomy [39, 40]. If the laparoscopic approach is unfeasible, however, or becomes unsafe intraoperatively, the open approach can be performed safely, and conversion to an open approach can be considered if necessary.

Change in uterine fundus height over the course of pregnancy is an important consideration when planning trocar placement and entry into the abdomen. The Hasson technique is often recommended for laparoscopic abdominal entry in pregnant patients. Entering under direct vision allows for better appreciation of and adjustment to anatomic shifts associated with pregnancy. However, regarding the Veress needle and optical trocar techniques, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) states that these are acceptable modes of abdominal entry in surgeons highly experienced in these techniques when fundus height is taken into account [41]. For surgeons who typically utilize a left upper quadrant abdominal Veress needle technique, there is typically no need to adjust the point of entry along the left subcostal margin. For surgeons who typically enter the abdomen around the umbilicus, it may be necessary to shift the point of entry superiorly above the umbilicus in mid- to late second and third trimester patients. The two right upper abdominal trocars and the subxiphoid trocar typically do not require adjustment from their usual locations. As in nonpregnant patients, it is often beneficial to place the subxiphoid trocar as cephalad as possible to optimize the intra-abdominal work space.

Intraoperative cholangiogram is a technique that can be performed to delineate biliary anatomy and assess for obstructing common bile duct gallstones intraoperatively. This technique utilizes fluoroscopy to visualize the biliary system following an injection of contrast dye into the cystic duct. It can be an important tool in the prevention of injuries to the common bile duct for cases in which biliary anatomy is unclear intraoperatively. Similar to ERCP, intraoperative cholangiography can be performed safely, as long as the lower abdomen and pelvis are protected appropriately with lead shielding [34].

In terms of perioperative fetal monitoring, consensus guidelines recommend fetal heart monitoring preoperatively and postoperatively for fetuses that could be considered independently viable, usually at and after 22 weeks gestation [41]. This perioperative fetal monitoring can occur in the preoperative area and in the postanesthesia care unit.

Summary

Gallstone disease affects women more than men, and pregnancy is a time of particular increased risk of gallstone disease. There are several important considerations in assessing and managing pregnant women with gallstone disease.

- Incidentally identified, asymptomatic gallstones require no further management.
- A single episode of biliary colic can be managed nonoperatively with observation.
- Recurrent biliary colic in early to mid-pregnancy should be managed with an elective cholecystectomy. Recurrent biliary colic that develops in the late third trimester can typically be managed nonoperatively through delivery with elective cholecystectomy 6–8 weeks postpartum.
- Expeditious cholecystectomy is recommended for the majority of pregnant women with complicated gallstone disease including cholecystitis, choledocholithiasis, and gallstone pancreatitis. Patients with choledocholithiasis and gallstone pancreatitis should undergo preoperative ERCP with precautions taken to protect the fetus from radiation exposure and appropriate involvement of a multidisciplinary team. Nonoperative management can be pursued to avoid surgery in very-near-term patients. In this situation, interval cholecystectomy is recommended 6–8 weeks postpartum.
- In general, the laparoscopic approach is favored over the open approach to cholecystectomy. However, if cholecystectomy is indicated and the laparoscopic approach is contraindicated or unsafe, the open approach can be performed safely.
- Changes in fundus height over the course of pregnancy must be considered when determining appropriate abdominal entry strategy and trocar placement.
- Intraoperative cholangiography can be safely performed if necessary, with appropriate measures taken to protect the fetus from radiation exposure.

Future Trends

Rendering diagnostic studies and surgical intervention as safe as possible for the pregnant mother and fetus is of paramount importance and is a primary focus of current efforts. It has become increasingly rare to require a HIDA scan as experience with ultrasound technique and ultrasound capabilities expand. Radiation-free ERCP modalities and expanded use of endoscopic ultrasound should emerge in the clinical setting as work to optimize their effectiveness progresses. Work aimed at risk-stratifying women at particular risk of developing gallstone disease has identified several important risk factors, and future efforts to develop integrated strategies for risk minimization through lifestyle modifications and pharmacologic therapy may help minimize the incidence of symptomatic and complicated gallstone disease.

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Chapter 23
Safety of Procedures During Pregnancy

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Introduction

There is limited information available on the safety and efficacy of gastrointestinal endoscopy in pregnant patients, with a majority of practice recommendations based on clinical reviews and case studies. During pregnancy it is critical to consider the potential harm to the fetus secondary to teratogenesis, hypoxia, trauma, or premature labor, and therefore all gastrointestinal endoscopic procedures performed during pregnancy should be undertaken by expert endoscopists. Informed consent should include not only risks to the mother but also risks to the fetus. To maximize efficacy and safety while minimizing maternal and fetal risks, a few important steps must be taken.

If the indication for the procedure and intervention is weak, then it should be delayed until after pregnancy. If it cannot wait, it is important to recognize whether the second or third trimester is safest to perform each individual procedure, as the first trimester should be avoided. A therapeutic ERCP may be necessary in certain scenarios, but with the use of minimal radiation to decrease risk to the fetus.

Once an intervention is expected, a multidisciplinary team consisting of obstetricians, anesthesiologists, gastroenterologists, and possibly surgeons should coordinate the management of a pregnant patient (Table 23.1). Preprocedural as well as intraprocedural risk reduction strategies help in achieving a good outcome (Fig. 23.1). An obstetric consultation is critical for appropriate level of monitoring, before, during, and after procedures, and to assure maternal and fetal safety in cases of early labor. The obstetrician will monitor fetal and maternal vital signs to assess any distress that necessitates the discontinuation of the procedure or the delivery of

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Table 23.1 Circumstances where multidisciplinary team is mandatory for endoscopic procedures

1. High-risk pregnancies
2. During the first trimester due to increased teratogenic risk
3. During late third trimester due to impending labor or risk of premature delivery
4. During ERCPs and other high-risk invasive, prolonged procedures
5. Patients with severe GI bleed
6. Patients with choledocholithiasis complicated by ascending cholangitis

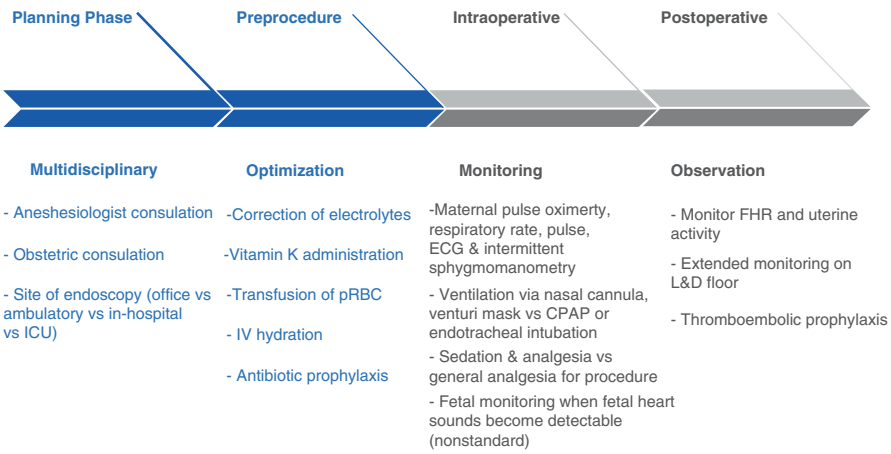

Fig. 23.1 Risk reduction strategies

the baby. Anesthetic medications are the greatest concern to fetal safety, and therefore it is critical that an anesthesiologist be involved in the preoperative management as well as the continuous intraprocedural monitoring of the patient.

Section "Medication Safety During Pregnancy" is dedicated to all the medications that mother and baby may encounter throughout gastrointestinal procedures as well as the best way to mitigate risks to their safety. Section "Procedural Safety During Pregnancy" aims to provide concise recommendations based on the quality of evidence available regarding specific endoscopic interventions and possible therapies that may be needed during pregnancy. Section "Radiation Safety During Pregnancy" will focus on radiation and procedural safety, with a focus on therapeutic ERCP and alternatives.

Medication Safety During Pregnancy

What medications am I going to get during my procedure and are they safe for my baby?

To provide you with a safe and comfortable procedure, you will receive anesthetic medications that reduce anxiety and minimize pain. These drugs are the greatest

concern to fetal safety. Therefore, your anesthesiologist will only use medications with the best safety profile in pregnant women based on recommendations of the Food and Drug Administration. Teratogenic drugs (i.e., causing fetal growth restriction, developmental delays, or birth defects) will be avoided if possible. Only the minimal effective dose of necessary medications will be administered. Unless emergent, procedures will be scheduled in the second and third trimester to decrease any risks.

Some of the medications you may encounter during your procedures include antibiotics to decrease the risk of infections (e.g., PEG tube placement). Your physician will only administer antibiotics with a proven safety profile during pregnancy (e.g., penicillin). Prior to a colonoscopy or flexible sigmoidoscopy, you will drink a colon-cleansing agent to evacuate your bowels so your endoscopist can perform a thorough evaluation of your colon. The solutions prescribed have verified safety during pregnancy.

Finally, your endoscopist, obstetrician, and anesthesiologist will come together to choose the best and most appropriate medications at each step of your procedure. This multidisciplinary approach provides comfort and safety for you and your baby.

Current Evidence and Recommendations

Sedation and Analgesia During Pregnancy

Clinical studies [1–5] and clinical reviews [6–8] suggest that anesthetic medications pose the greatest direct and indirect risk to fetal well-being during endoscopic procedures. The direct risk is highest in the first trimester [9–11] when the fetus is most vulnerable during organ development and growth. Drugs indirectly cause fetal distress through maternal side effects like hypoxia [12], hypotension, or cardiac arrhythmias [13]. Maternal hypoxia can be further compounded during EGD or ERCP by vagally mediated bronchospasms [12, 14–16] or pulmonary aspiration of gastric contents [17]. Safety of sedation can be improved by maternal assessment before endoscopy. Diuretics and antihypertensives may need to be held, and blood products or intravenous fluid hydration is often necessary to maintain maternal blood pressure during the procedure. A continuous electrocardiogram, pulse oximeter, heart and respiratory rate monitors, and intermittent sphygmomanometers during procedures improve anesthetic safety during endoscopy. All patients undergoing procedural sedation also require capnographic monitoring, which provides early, rapid detection of adverse respiratory or airway issues.

The level of sedation required depends on the procedure and potential therapeutic interventions. A greater level of sedation is required in therapeutic EGDs for variceal sclerotherapy, banding, or stricture dilation. Therapeutic ERCPs involving a sphincterotomy or stent placement require the most profound levels of sedation. Placement of a percutaneous endoscopic gastrostomy tube also requires deeper sedation. The minimal effective dose of sedation and analgesia is recommended as decreased MAC (minimum alveolar concentration) during pregnancy results in a

greater depth of anesthesia at lower doses of medication, increasing the risk of hypotension and hypoxia which decreases uteroplacental perfusion [18]. When the goal of anesthetic administration exceeds anxiolysis or mild to moderate sedation, the expertise of both anesthesiologist and obstetricians is required. Together, they can determine the most appropriate drugs for deep sedation (e.g., onetime use of a category D medication), as well as mitigate any subsequent complications requiring early intervention or delivery.

Teratogenicity of Anesthetic Drugs

Placental transfer of anesthetic drugs and the potential for drug-induced teratogenicity pose a great threat to fetal safety. Safety in animal models is used to assess risk in pregnant women, who are generally excluded from drug trials. However, variations in species susceptibility contribute to our inability to appropriately assess true efficacy and safety in humans who may not have the same response as animals. Estimates of drug teratogenicity are primarily obtained from retrospective, nonrandomized studies. No anesthetic drug, local or inhaled, has proven to be teratogenic in humans, except for benzodiazepines which demonstrate risk of congenital anomalies [19]. Other manifestations of teratogenicity range from structural abnormalities and growth restrictions to long-term functional deficiencies, such as behavioral or learning difficulties [20].

The US Food and Drug Administration drug classification for pregnancy divides medications into five categories based on their safety profile and associated fetal risks. Risk is calculated from the quality and number of both experimental and clinical studies on laboratory animals and humans (Table 23.2).

Sedatives and Analgesics

The main challenge of sedative and analgesic drugs during pregnancy is their potential to decrease placental perfusion. To mitigate some of this risk, these drugs are divided into those given by endoscopists and those administered by anesthesiologists. Endoscopists commonly administer meperidine, lidocaine, fentanyl, midazolam, and diazepam for conscious sedation. Anesthesiologists commonly administer propofol and ketamine for moderate sedation.

The most commonly used narcotic, meperidine, is the preferred opiate analgesic drug for endoscopy in pregnant women [21–23]. Two large studies demonstrated safety of meperidine use in the first trimester. The Collaborative Perinatal Project, which followed over 50,000 pregnant women across 12 US health centers [21], showed 6 of the 268 cases in which meperidine was administered was diagnosed postpartum with inguinal hernias. A surveillance study of Michigan Medicaid recipients followed over 200,000 pregnancies from 1985 to 1992 [22–24] and demonstrated no risk of teratogenicity when meperidine was administered during the first

Table 23.2 FDA pregnancy categories

A	B	C	D	X
Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy	Animal reproduction studies have failed to demonstrate a risk to the fetus	Animal reproduction studies have shown an adverse effect on the fetus	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans	Studies in animals or humans have demonstrated fetal abnormalities, and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience
There is no evidence of risk in later trimesters	There are no adequate and well-controlled studies in pregnant women	There are no adequate and well-controlled studies in humans Potential benefits may warrant use of the drug in pregnant women despite potential risks	Potential benefits may warrant use of the drug in pregnant women despite potential risks	The risks involved in use of the drug in pregnant women clearly outweigh potential benefits
Category A drugs are safe in pregnancy, but not utilized for gastrointestinal procedures	*For endoscopic procedures, category B drugs are the mainstay*	*There is occasional need for category C drugs during endoscopic procedures*	*Category D drugs are avoided as their risk outweighs the benefits*	*Category X drugs are contraindicated and never used for gastrointestinal procedures*

∗Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling (Federal Register/Vol. 73, No. 104/Thursday, May 29, 2008)
∗Cappell MS, Nature Reviews/Gastroenterology and Hepatology. Nov 2011 [8]

trimester. Major congenital defects were reported in 3 of the 62 exposed infants, a rate similar to the unexposed group.

Meperidine changes from a category B to category D if given at term and in high doses close to parturition. This change is due to the associated risk of neonatal respiratory depression with this medication [25, 26]. Transient fetal heart rate abnormalities, such as decreased cardiac variability, were also observed with meperidine administration [27]. However, heart rate changes are not associated with poor prognosis in the absence of other fetal changes [28, 29]. Although it crosses the placenta shortly after administration to the mother, studies show it to be safe at doses of 50–75 mg and in procedures with short duration. Toxic side effects, like maternal respiratory depression and seizures, are due to an accumulation of the

active metabolite, normeperidine. This risk increases under prolonged administration (>36 h) and when the dose exceeds 75 mg [22].

Lidocaine, a category B drug [18], is a topical anesthetic applied to the oropharynx to decrease the gag reflex and alleviate discomfort before EGD or EUS/ERCP. Although it crosses the placenta, lidocaine has a long history of reported safety in pregnant patients, even at 6.6 times the recommended human dose [18]. No fetal malformations were reported in the largest study of 293 cases with first term exposure [30]. Despite low teratogenic potential, use prior to endoscopy in pregnant patients is unnecessary. If administered, endoscopists may ask patients to spit after lidocaine administration to minimize systemic absorption. In addition, no fetal malformations were associated with intravenous lidocaine administered to pregnant patients with ventricular arrhythmias [31]. If intravenous lidocaine is necessary during endoscopy, it will be administered by an anesthesiologist.

Fentanyl, a potent narcotic agonist, may be used as an alternative to meperidine for endoscopies because of its more rapid onset of action and faster recovery time [32]. Although it crosses the placenta, fentanyl has not shown to be teratogenic in humans. Fentanyl was shown to be embryocidal in rat studies [18, 33]. In these studies, rats were either exposed to fentanyl for prolonged durations or the dosage exceeded the safest maximal human equivalent dose. Despite this, there are a few single case reports of respiratory depression, muscle rigidity, and opioid withdrawal in neonates [34–36]. It is classified as category C, with no evidence of harm demonstrated at low doses <125 mg. Fentanyl administered at a high dose for prolonged periods receives a category D rating [15, 19]. In summary, low doses may safely be administered to pregnant patients undergoing endoscopy.

Benzodiazepines are category D drugs. Several studies have demonstrated an association between diazepam use during the first trimester and fetal mental retardation, congenital malformations, cleft palate, neural defects, as well as cardiac defects [37–43]. Early use of diazepam during pregnancy should be restricted during endoscopy [22]. If needed, midazolam is the preferred benzodiazepine for endoscopic procedures. Compared to diazepam, it has a faster onset of action and shorter recovery time. Although there are no published reports on first or second trimester fetal exposure to midazolam, it has not been associated with cleft palates or congenital abnormalities [18].

Propofol, generally administered by an anesthesiologist, is a category B drug and the preferred agent for sedation in endoscopy. Fast acting with a narrow therapeutic index, propofol has the potential for respiratory depression or respiratory arrest without close monitoring [32]. Limited use during the first and second trimesters is recommended due to insufficient studies on exposure risks. It rapidly transfers across the placenta at term [44–46], resulting in a reversible neuro-depression and depressed Apgar scores in newborns [47]. Numerous other studies have reported no neonatal toxicity when administered later during pregnancy [18, 44].

When propofol sedation is insufficient, ketamine may be given by the anesthesiologists for deeper sedation. Although ketamine rapidly crosses the placenta [48], it has not been associated with fetal teratogenicity [49] nor seen to be unsafe across various animal studies [23, 50]. Administration during delivery can precipitate pro-

found, transitory neonatal respiratory depression and decreased Apgar scores [51, 52]. Ketamine, although considered a category B drug, should be avoided during the first trimester and used with caution at other times during pregnancy, as fetal safety is not reported.

Naloxone and flumazenil are the two most commonly used reversal agents studied in pregnancy. Naloxone is a category B [18], rapidly acting, narcotic antagonist that crosses the placenta [22, 23]. Its use is limited to situations where maternal respiratory depression or systemic hypotension is observed. Its use should be limited post procedure to only unresponsive patients as one neonatal death has been attributed to naloxone exposure in utero [53]. It is contraindicated in pregnant patients who are narcotic dependent as it can increase risk of seizures and withdrawal.

Flumazenil is a category C benzodiazepine antagonist with an unknown risk to the exposed fetus [18]. In one animal study, neurobehavioral changes were noted in male rats exposed to flumazenil in utero [54]. In pregnant rats and rabbits, no teratogenicity was seen at 60 times the maximal human dose, but it was embryocidal at 200 times the acceptable dose [18]. Small doses and infrequent use are recommended due to risk of maternal seizures especially in mothers chronically habituated to benzodiazepines [55].

Common sedative and analgesics used in gastrointestinal interventions can be found in Table 23.3.

Bowel Prep Agents

The safety of bowel preparation agents for colonoscopy in pregnant patients is presented in published case reports and retrospective studies. Sodium phosphate solution (SPS) and polyethylene glycol with or without an electrolyte lavage solution (PEG-ELS) are two category C drugs most frequently used as colon-cleansing agents.

Patients prefer consuming sodium phosphate because only a small volume is needed to evacuate the bowels. SPS is an osmotic laxative with a rapid onset of action, similar to magnesium citrate (category B) [56]. Both frequently cause fluid and electrolyte abnormalities, including hypocalcemia, hypokalemia, hypernatremia, and hyperphosphatemia [57]. In one case report, repeated use of phosphate enemas by the mother was associated with demineralization and bone growth failure in her newborn [58]. The consensus is to limit the use of SPS during pregnancy to avoid systemic complications associated with dehydration and severe electrolyte imbalances.

PEG-ELS is an isotonic cathartic that is associated with a low risk of complications in the general population. Risk to the fetus is unknown as it has not been extensively studied in pregnant patients [56] and no animal reproductive studies have been conducted [18]. Its safety was demonstrated in 1 report of 225 pregnant patients treated for constipation [59]. Using surveys at their institution, Vinod et al. compared the preferences of gastroenterologist and obstetricians in choosing a bowel preparation for pregnant patients undergoing colonoscopies or sigmoidoscopies [60]. While PEG solution was most frequently chosen by the gastroenterologist as a pre-colonoscopy preparation, both specialists favored the use of fleet enemas

Table 23.3 Common sedatives and analgesics used in gastrointestinal interventions

Drug class	FDA category	Drug	Administered by	Crosses placenta	Evidence and recommendations
Opiate analgesic	B	Meperidine	Endoscopist	Yes	Safe at 50–75 mg doses
	D—at term				Increases maternal risk for respiratory depression and seizures with high doses >75 mg and prolonged administration >36 h
Narcotic agonist	C	Fentanyl	Endoscopist		Safe in low doses <125 mg Embryocidal in rats but not teratogenic in humans
Narcotic antagonist	C	Naloxone	.	Yes	Contraindicated in patients who are narcotic dependent for risk of withdrawal 1 neonatal death reported Use limited to 3 situations: Maternal respiratory depression Systemic hypotension Unresponsive post procedure
Benzodiazepine	D	Diazepam	Endoscopist		Associated with fetal mental retardation, congenital malformations, cleft palate, neuro defect, and cardiac defects Early use in pregnancy discouraged
Benzodiazepine	D	Midazolam	Endoscopist		Limited data but thus far not associated with cleft palates or congenital abnormalities Preferred after meperidine
Benzodiazepine antagonist	B	Flumazenil	.		Risk unknown Recommend small doses and infrequent use due to risk of maternal seizures; neurobehavioral changes were noted in male rats only in one animal study
Sedative	B	Propofol	Anesthesia		Limit use in first trimester Fast acting with narrow therapeutic window; requires close monitoring for risk of respiratory depression and death

Table 23.3 (continued)

Drug class	FDA category	Drug	Administered by	Crosses placenta	Evidence and recommendations
Sedative	B	Ketamine	Anesthesia		Limited data in humans Not shown to be unsafe in animals
Topical anesthetic	B	Lidocaine	Endoscopist		Study showing no fetal risk with sample size of 293 Safe for use; ask patient to spit instead of swallow for precaution

prior to a flexible sigmoidoscopy. Consensus guidelines recommend PEG-ELS use for both colonoscopy preparation and constipation during pregnancy.

Other cathartic medications such castor oil, category X, is contraindicated due to risk of uterine rupture and should be avoided [61]. Mineral oil should be avoided as it can interfere with maternal fat-soluble vitamin absorption and cause neonatal coagulopathy and hemorrhage [62]. An alternative to enteral medications is a tap water enema which is acceptable in preparation for sigmoidoscopy during pregnancy [56]. Although tap water enemas are the safest option during the first trimester, obstetricians were less likely to prescribe them throughout the pregnancy due to risks of uterine contraction, induction of labor [60], and possible uterine rupture [61].

Antibiotics

Recommendations on antibiotic use during pregnancy reference past investigations as current regulations intentionally exclude pregnant women from drug studies. The safety of newer antibiotics is limited to animal models or results from observational studies with expected confounders. Despite these challenges, several antibiotic classes have been used in various stages of human pregnancy without evidence of fetal harm (Table 23.4).

As in the general population, one common indication for pre-procedure antibiotic prophylaxis is in patients with a high-risk cardiac lesion. The American Heart Association recommends prophylactic IV ampicillin (category B) in patients with a medium to high risk of endocarditis, who are getting endoscopic sclerotherapy, stricture dilation, or an ERCP for biliary obstruction [56]. According to the Collaborative Perinatal Project, no associated risk for major or minor congenital malformations was reported in the 3,546 pregnant mothers who received ampicillin during their first trimester or the 7,171 cases of ampicillin exposure at any other time during pregnancy [21]. Similarly, a surveillance study of over 10,000 newborns with first trimester, in utero exposure to ampicillin, reported no increase in the incidence of congenital abnormalities [23]. Based on these reports, it is unlikely that ampicillin is teratogenic.

Table 23.4 Antibiotic safety in pregnancy

Safe	Penicillins Cephalosporins Clindamycin Erythromycin (except estolate)
Avoid in first trimester	Metronidazole
Avoid in third trimester	Sulfonamides Nitrofurantoin
Avoid in pregnancy	Quinolones Streptomycin Tetracyclines

Source: Shergill et al. [102]

In penicillin allergic patient's gentamicin, a category C medication may be used as prophylaxis before ERCP when needed [56]. Although it is not teratogenic, it is similar to other aminoglycosides, with the associated risk of nephrotoxicity, hypertension, and rarely fetal ototoxicity [23]. Risks to the fetus are unknown during long-term administration. In one large case-controlled study, no significant toxicity was observed. Despite limited data, it should not be withheld to treat biliary sepsis in pregnant patients [56] but should be avoided for routine prophylaxis.

PEG tube placement may be necessary in the pregnant patient and is most commonly done because of severe hyperemesis gravidarum. Pre-procedural antibiotic administration with IV cefazolin is often recommended [63–65]. Cephalosporins, such as cefazolin, are safe for use in pregnancy and have not been directly associated with an increased risk of congenital malformations in newborns exposed in utero [23]. Reproductive studies in rabbits and mice have not demonstrated teratogenicity [23]. The ASGE guidelines further recommend pre-procedural screening for MRSA in areas where it is endemic, to appropriately decontaminate before the feeding tube is placed [65].

Drugs Used in Gastrointestinal Procedures

Simethicone and Glucagon

Simethicone (category C) is a nonabsorbable, silicone product that can be irrigated into the gastrointestinal lumen during endoscopic procedures to dissipate bubbles or bilious secretions [7, 56]. In a surveillance study of Michigan Medicaid patients from 1985 to 1992, 14 of 248 pregnant patients receiving simethicone during the first trimester had major birth defects as compared to 11 in the control group [23]. Although this study revealed insignificant results, the current recommendation is to avoid the use of simethicone during pregnancy and to use water perfusion followed by endoscopic aspiration instead [7].

Glucagon, a category B drug, is an antispasmodic and is safe for use during ERCP to decrease duodenal motility [27]. Although data is limited on fetal risk, cannulation of the bile duct during a therapeutic ERCP can help prevent life-threatening cholangitis, ensuring maternal and fetal safety [7]. In reproductive studies, pregnant rats receiving 40 times the maximal human dose of glucagon did not show any evidence of fetal harm [23]. Glucagon can also be used to treat colonic spasms during colonoscopy. In pregnant patients, glucagon can relax a spastic colon without inducing uterine smooth muscle relaxation [66]. However, it is strongly recommended that the colonoscopy be terminated in place of repeat glucagon injections, if colonic spasms persist [7].

Epinephrine and Botox

Due to its alpha-adrenergic qualities, epinephrine (category C) is used to achieve hemostasis in an upper gastrointestinal bleed. Literature is limited on epinephrine use in pregnant patients undergoing gastrointestinal interventions. In some animal models, profound decreases in placental perfusion have been reported at high doses, while others do not demonstrate teratogenicity [18, 37]. In the Collaborative Perinatal Project, the 189 infants with epinephrine exposure during pregnancy (route unknown) had a higher incidence of congenital inguinal hernias than the control group [21, 56]. In contrary, a surveillance study found that 35 pregnant patients exposed to epinephrine between 1985 and 1992 resulted in no major birth defects [23]. Only one case report showed a fatal intracranial hemorrhage of an infant in which the mother was given high-dose epinephrine during childbirth for hypotension [67]. Epinephrine use in an emergent, therapeutic endoscopy is acceptable when benefits outweigh the risks to mother and fetus. Systemic side effects can be minimized if care is taken to inject only around the bleeding site and not directly into the bloodstream [56].

In cases of severe maternal malnutrition associated with achalasia, treatment with botulinum toxin (category C) may serve as a temporary alternative during pregnancy [68]. Endoscopic treatment with intrasphincteric injection of botulinum toxin A results in blocking of the calcium-dependent release of acetylcholine from presynaptic nerve endings leading to lower esophageal sphincter relaxation and immediate relief reported in 80% of nonpregnant patients after one dose [68].

Use of botulinum toxin (category C) injection in the management of achalasia during pregnancy has only been reported in one case study [69]. The decision was made to use intrasphincteric botulinum toxin in a 23-year-old pregnant female with achalasia refractory to medical therapy, who continued to lose weight, placing her and her fetus at risk of severe malnutrition. Treatment was successful, resulting in maternal weight gain and healthy at term birth, with no complications reported [69]. However, there is insufficient data on fetal safety and long-term adverse effects with intrasphincteric botulinum toxin injections [70–72]. Therefore, treatment of achalasia during pregnancy should include the options discussed further in Sect. 2.

Tattoo: Methylene Blue and India Ink

Tattooing lesions found during endoscopic procedures can help detect the location for future monitoring or resection. India ink (permanent dye) and methylene blue (temporary marker) are two dyes traditionally used in tattooing. Neither dye has been studied in pregnant patients undergoing gastrointestinal procedures [18, 23]. A few studies report adverse outcomes when methylene blue was used during amniocentesis to detect ruptured membranes [73, 74]. Thus, until further evidence of reported safety during pregnancy, avoidance of dyes is recommended.

Procedural Safety During Pregnancy

Do I need to have this procedure now and what does it entail? What extra precautions are taken to ensure my and my baby's safety?
In general, endoscopic procedures allow your physician to examine the lining of your gastrointestinal tract, including the esophagus, stomach, small intestine, and colon. Your doctor will use a thin, flexible tube called an endoscope, which has its own lens and light source, and will view the images on a video monitor to look for inflammation, bleeding ulcers, or tumors. Most of the procedures are performed with sedation so you will be asleep during the procedure, although in special circumstances you may be awake.

Although procedures are generally preferred during the postpartum period, sometimes they are required while you are pregnant. Timing of any procedure is crucial for you and your baby's safety and therefore should be avoided during the first trimester when your baby is doing the most organ development and growth. Risks are decreased in the second and third trimester, with second trimester being most optimal. During the procedure your anesthesiologist will only use medications that have the best safety profile in pregnancy. Additionally, the least invasive and safest endoscopic interventions will be used, and radiation will be minimized or not used at all.

Current Evidence and Recommendations

Diagnostic and Therapeutic Endoscopy

The most common indication for upper endoscopy in pregnancy is gastrointestinal hemorrhage, dysphagia, and refractory nausea and emesis with varying diagnostic yield based on etiology. During pregnancy, increased progesterone and estrogen levels are responsible for a 50% decreased lower esophageal sphincter pressure which along with decreased gastric emptying may cause symptoms of gastroesophageal reflux disease (GERD) [75]. As pregnancy progresses, the frequency and

intensity of GERD symptoms may increase because of changes in GI motility and the physical effects of the gravid uterus. Despite this, EGD is rarely helpful or indicated for nausea or vomiting during pregnancy or hyperemesis gravidarum. Interestingly, Farghali et al. showed that 95% of pregnant patients with hyperemesis gravidarum who underwent EGD had normal findings except for *Helicobacter pylori* infections [76]. This suggests the potential benefit of routine testing of pregnant patients with hyperemesis for *Helicobacter pylori* via noninvasive means and foregoing an upper endoscopy.

In patients who have major upper GI bleeding or severe, refractory nausea and vomiting with abdominal pain, EGD may be indicated. A retrospective study of 83 consecutive pregnant patients who underwent EGD at 8 university teaching hospitals over 14 years showed no significant endoscopic complications [2]. Excluding 6 voluntary abortions and 3 unknown pregnancy outcomes, 70 (95%) of 74 patients delivered healthy babies (pregnant control rate = 94%, national control rate = 98.4%, not significant). The four poor outcomes (three stillbirths and one involuntary abortion) occurred in high-risk pregnancies and were unrelated to EGD temporally or etiologically.

A larger nationwide analysis looking at 1210 hospitalized pregnant women with nonvariceal upper GI bleeding between 1998 and 2007 found that pregnant women were less likely to require a blood transfusion (4.3% vs 15.3%; $P < 0.0001$) and were less likely to present with hypovolemic shock compared with nonpregnant women (7.6% vs 13.8%; $P < 0.0001$) [77]. In comparing outcomes between pregnant patients who did and did not undergo endoscopy, there was no difference in fetal loss, fetal distress/complications, or premature delivery. Furthermore only 8.9% of the procedures led to a therapeutic intervention for pregnant women, and there were no in-hospital deaths among this cohort of patients. This study deemed that it was appropriate to defer endoscopy in most pregnant patients who had a self-limited nonvariceal upper gastrointestinal bleed and were hemodynamically stable.

Other studies have looked specifically at variceal bleeding in pregnant patients as this indication carries a higher incidence of mortality. It is important to note that the typical cause of portal hypertension in pregnant patients is different than the general population due to increased water retention and high cardiac output during pregnancy. Women with non-cirrhotic portal hypertension are more likely to have bleeding during their second trimester with a varying incidence rate that has been reported as high as 34% with a subsequent incidence of abortion of 29% and perinatal death 33% [78]. The safety of beta blockers as either primary or secondary prophylaxis for variceal bleeding in the pregnant population is controversial, being FDA category C, as it may result in premature labor, fetal growth restriction, neonatal apnea, bradycardia, and hypoglycemia [79]. Therefore, for these patients, endoscopic intervention becomes a primary mode of treatment.

Although rarely reported, prophylactic or urgent endoscopic injection sclerotherapy (EIS) and endoscopic band ligation (EBL) are considered appropriate therapy for patients with variceal bleeding during pregnancy. The use of sclerosing agents, such as polidocanol, absolute alcohol, or sodium tetradecyl sulfate, have been reported in only a few cases involving pregnant patients, none of which

assessed the effects of sclerosing agents on the fetus [80]. To the contrary, several case reports have shown EBL to be effective in both prophylaxis as well as treatment of active variceal bleeding during pregnancy, with no additional risk to the fetus [79]. EIS should then be reserved only as a secondary option due to its unknown risks on fetal outcomes. Due to the need for radiation and prolonged fluoroscopy, transjugular intrahepatic portosystemic shunt (TIPS) placement is only recommended as a last resort when all other options have failed [79].

Endoscopic evaluation and treatment may be necessary in pregnant patients presenting with achalasia with resulting poor nutritional status. Achalasia treatment during pregnancy should be designed to reduce lower esophageal sphincter pressure and to relieve esophageal obstruction without having any adverse effects on the fetus. Medical therapies such as calcium channel blockers and nitrates may be tried with caution as they have been designated as category C medications. Vogel et al. recently published a retrospective study of 43 pregnant women with achalasia and concluded that pneumatic dilation should be attempted initially in the pregnant woman when complications threaten maternal or fetal health [81]. Over the past decade, there has been one case report of successful treatment of severe achalasia during pregnancy with botulinum toxin injection into the LES [70]. Intentional administrations of botulinum toxin during pregnancy have also been reported by some authors for selected cases of movement disorders without adverse risks to the mother or fetus if dosage was kept below 300 IU [72]. Despite these reassuring reports, there is no formal recommendation currently regarding botulinum toxin treatment for achalasia in pregnancy.

Enteroscopy

There are no studies on the safety of deep enteroscopy in pregnancy and therefore no information on maternal or fetal safety of this procedure. It should be noted that this procedure should not be performed in pregnant patients unless necessary. Enteroscopy requires greater doses and frequency of anesthetic medications which can lead to maternal complications and risk fetal safety.

Video Capsule Endoscopy (VCE)

Based on manufacturer recommendations, the use of video capsule endoscopy during pregnancy is contraindicated. Capsule retention is a potential complication in pregnant patients due to slow intestinal transit time in conjunction with a gravid uterus which may displace or compress the small bowel. Despite these warnings, one case report revealed that VCE was useful in a pregnant woman for uncovering a jejunal carcinoid tumor when upper and lower endoscopies failed to identify a source of gastrointestinal bleeding [82]. The current guidelines deem capsule endoscopy as experimental during pregnancy, although it may be considered when strongly indicated.

Sigmoidoscopy and Colonoscopy

Lower endoscopy should be avoided in pregnancy, but if indicated, it should be performed in the second trimester. There is evidence that supports flexible sigmoidoscopy as being safer than colonoscopy during pregnancy. Endoscopists should always use cautionary maneuvers while performing colonoscopy in a pregnant patient. For example, in late pregnancy, patients should not be placed in the decubitus or prone positions, and external abdominal pressure towards the gravid uterus should be avoided. Vascular compression can further be prevented before and after the procedure by placing a wedge or pillow under the patient's right hip and creating a pelvic tilt.

Cappell reported in a multiyear, retrospective study of 46 pregnant patients undergoing sigmoidoscopy that 93% of the patients delivered healthy babies [1]. Sigmoidoscopy was more frequently diagnostic for hematochezia than for other indication, and the most common findings were reactivated or newly diagnosed inflammatory bowel disease, bleeding internal hemorrhoids, and other colitides. More importantly, therapeutic changes because of sigmoidoscopic findings occurred in 24 patients, including changing or starting drugs for inflammatory bowel disease in 15 patients, steroid enemas for nonspecific proctitis in 2 patients, avoiding surgery in 2 patients, and treatment of hemorrhoids in 2 patients. This study concluded that sigmoidoscopy is not contraindicated in pregnancy and it may be beneficial in pregnant patients with significant lower gastrointestinal bleeding. For evaluation of a change in bowel habits, abdominal pain, family history of colon cancer, or routine screening or surveillance, sigmoidoscopy is not recommended during pregnancy but should be deferred until >6 weeks postpartum.

In the largest study of colonoscopy performed on 20 pregnant patients, Cappell reported episodes of mild and transient hypotension in 2 patients [83]. Study patients had one involuntary abortion and one infant born with congenital defects, while all other infants were born relatively healthy. Colonoscopy was diagnostic in 10 of 19 cases, was therapeutic in 1 case, and led to changes in medical management in 7 patients. Therefore, colonoscopy may be considered in the pregnant patient with life-threatening emergencies or when flexible sigmoidoscopy is unable to lead to adequate diagnostic or therapeutic results.

Pregnant IBD women have an increased risk of undergoing lower gastrointestinal endoscopy when compared with healthy pregnant patients. IBD activity during pregnancy has been proven to be harmful for the pregnancy and the fetus. As a result, endoscopic evaluation is often warranted to strategize treatment regimens. A recent study of 42 pregnant patients with clinically active IBD revealed that endoscopic results enabled the safe discontinuation of medications [84]. In addition, the results led to treatment initiation or alteration in 75% of women with no direct maternal adverse events noted in any case. Interestingly, spontaneous abortion occurred more often in the controls (10 [23.8%] vs 2 [4.8%], $P = 0.03$) as did lower median birthweight [3017 g vs 3495 g, $P = 0.01$].

Another urgent indication for lower endoscopic intervention during pregnancy is for sigmoid volvulus treatment. Although a rare occurrence, it is the most common

cause of bowel obstruction during pregnancy, accounting for up to 44% of reported obstruction cases [85]. Pregnancy increases the incidence of sigmoid volvulus through displacement, compression, and partial obstruction of the sigmoid colon due to the gravid uterus. The physiological changes during pregnancy may hinder the timely diagnosis of this condition which leads to high morbidity and mortality during pregnancy. If there is no evidence of bowel necrosis or perforation, then sigmoidoscopic detorsion and rectal tube insertion is recommended. Some described the use of a flexible gastroscope which can be more easily tolerated without sedation [85]. In recurrent cases of sigmoid volvulus, endoscopic detorsion can be repeated until the second trimester when sigmoidectomy is recommended [86].

PEG

Long-term nasogastric feeding is limited by patient intolerance and nasal septal necrosis. During pregnancy, PEG tube placement is feasible for optimal enteral nutrition in the critical care setting. Less invasive alternative techniques, such as a nasoenteric feeding tube or peripherally inserted catheter for parenteral nutrition, should be considered, and PEG tube placement may be offered when other methods are unsuccessful or declined by the patient. A major risk of PEG during pregnancy is puncture of the uterus or fetus during transabdominal needle insertion. This risk may be minimized by demarcating the upper border of the uterus and inserting the PEG needle ≥5 cm cephalad. Data thus far have shown there were no major complications with PEG tube placement in the 11 reported cases [87]. In these cases, enteral nutritional support was provided for an average of 14 weeks prior to discontinuation. After PEG placement, careful attention should be given to tension placed on the external bumper. Adjustments of the bumper by 2–3 cm will be necessary as the pregnancy progresses to avoid pressure necrosis of the surrounding skin.

Radiation Safety During Pregnancy

Will I be getting radiation during the procedure and if so how do you keep me and my baby safe?

If your procedure requires radiation, specific precautions will be taken to minimize you and your baby's exposure. The use of lead aprons will protect you and your baby from direct radiation. The use of radiation will itself be limited by minimizing the number of pictures that are taken during your procedure. A common endoscopic procedure requiring radiation is endoscopy to evaluate and remove gallstones that block the flow of bile out of the liver. If this condition is left untreated, it can lead to serious infections and other complications for both you and your baby.

There are a few alternatives to this procedure such as endoscopic ultrasound (an ultrasound device that is attached to the tip of the endoscope and does not use any radiation) or MRI which is a noninvasive picture of your abdomen. MRI may not be

an option for you because it requires prone positioning. Laying on your back for extended periods of time may lead to decreased blood flow to your uterus. Although these procedures allow for visualization of the affected area, neither can directly remove nor treat impacted gallstones. Finally, depending on your specific situation, any combination of these modalities can be used to diagnose and treat a potential emergency while keeping you and your baby's safety a priority.

Current Evidence and Recommendations

ERCP and EUS

Pregnancy predisposes a woman to increased gallstone formation and its associated complications. Acute biliary tract disorders, estimated to complicate approximately 3–12% of all pregnancies, are the most frequent indications for non-obstetric surgery during pregnancy [88]. Current recommendations advise nonoperative treatment whenever possible and to delay intervention until after pregnancy or the second trimester. Endoscopic retrograde cholangiopancreatography (ERCP) during pregnancy was first reported in 1990, and since then, numerous reports have shown that if precautionary measures are taken, therapeutic ERCP can be safely performed.

Tang et al. published one of the largest retrospective single center studies with 68 ERCP's performed on 65 pregnant women over a 6-year period [88]. Patients did not encounter any perforations, sedation-related adverse events, post sphincterotomy bleeding, cholangitis, or procedure-related maternal or fetal deaths. ERCP led to a diagnosis of choledocholithiasis in 51.5% of all patients with 91% of procedures including a biliary sphincterotomy. Post-ERCP pancreatitis was diagnosed in 11 patients (16%) which is higher than the general population (2–9%), with almost all cases being mild and without systemic complications. Most importantly they noted post-ERCP pancreatitis did not adversely affect pregnancy-related outcomes. They concluded that hepatobiliary diseases during the first trimester were associated with the lowest percentage of term pregnancy (73.3%), the highest risks of preterm delivery (20.0%), and the low birth weight (21.4%), although the procedure itself did not impact these risks.

During ERCP, radiation exposure to the fetus may increase the risk of intrauterine fetal death, malformations, disturbance of growth and development, mutations, and cancer. Lead shielding should be used to minimize radiation exposure to the uterus. When the radiation source is underneath the patient, the lead apron shield must be placed underneath the patient and not draped over the abdomen. External shielding may not completely eliminate fetal exposure because of internally scattered radiation, and for this reason, all efforts should be made to avoid performing ERCP during the first trimester. Studies have shown that fetal radiation exposure should not exceed 0.001 Sv (0.1 rem) during the first trimester with the maximum permitted dose during the entire pregnancy being 0.005 Sv (0.5 rem) [89]. In the

largest study measuring the fetal radiation exposure dose during ERCP, the mean (SD) fluoroscopy time was 14 (13) seconds. The fetal radiation exposure was 40 mad (SD, 46) which is substantially below the level considered to be a risk for teratogenesis [90].

Other methods to avoid radiation have included the use of ERCP without fluoroscopy including a two-step procedure with biliary sphincterotomy and stenting with definitive ERCP and stone extraction after delivery. In one study, deep CBD cannulation was performed with a double lumen sphincterotome, and bile was aspirated to confirm CBD position [91]. After the biliary orifice was identified, a complete biliary sphincterotomy was performed, and a 7-French double pigtail stent was placed which was later removed after delivery with repeat ERCP. Although these techniques may be less risky for the pregnant woman and fetus, ERCP should be avoided for weak indications. Magnetic resonance cholangiopancreatography (MRCP) may provide diagnostic information for various hepatobiliary conditions, but there is a paucity of data on the safety of MRI in the first trimester of pregnancy. Some authors have raised concerns of thermal injury to the fetus in first trimester, but the Safety Committee of the Society for MRI concluded that MRI is indicated in pregnant women if other non-ionizing forms of diagnostic imaging studies are inadequate [92].

Endoscopic ultrasonography (EUS) is yet another safer option which is highly sensitive and specific for CBD stones. When used prior to ERCP, it may reduce unnecessary interventions in patients who have a low probability of choledocholithiasis. The largest study included endoscopic ultrasonography performed in six pregnant patients for suspected CBD stones [93]. EUS found CBD stones in two patients and biliary sludge in the other four which was confirmed on subsequent ERCP. Furthermore, the authors add that in certain scenarios choledochoscopy (Spyglass) can be used to confirm a clear CBD rather than fluoroscopy, further decreasing radiation need. There were no reported maternal complications in any patient that underwent EUS or Spyglass. The authors determine that although EUS ± Spyglass may prolong the evaluation by several minutes it often clarifies when ERCP intervention is truly warranted.

Future Directions

Recent advancements in patient monitoring may diminish anesthesia doses for endoscopy amid pregnancy and consequently diminish fetotoxicity. Computerized electroencephalogram monitors that utilize the bispectral (BIS) list, NarcoSense, CARDEAN-guided intraoperative opioid administrator, facial electromyography, and Narcotrend, are engineered to quantify and characterize the depth of anesthesia [94–97]. Advancements to fetal monitoring in surgeries during the third trimester may, likewise, enhance fetal safety [98] during gastrointestinal procedures, especially therapeutic ERCP.

Innovations will likely authorize use of modalities that are not yet promoted during pregnancy due to the paucity of data. Unsedated, nasal endoscopy provides advantages that are alluring in pregnancy, such as limiting the use of teratogenic sedative medications and avoiding direct endoscopic injury to the uterus [99]. Specialized advancements to video capsule endoscopy which provide active propulsion or steering [100, 101] may prevent retention and render it a suitable option during pregnancy. MRCP may be an appealing alternative to ERCP during pregnancy, as it decreases radiation teratogenicity and doesn't require sedation. Molecular genetic testing of stool or serum may postpone the need for a colonoscopy during pregnancy if there is concern for rectal bleeding and colon cancer [102]. Additionally, techniques to assess polyp histology before polypectomy, such as narrowband imaging or chromoendoscopy [103], might help to defer polypectomy of polyps encountered at colonoscopy during pregnancy. Friedel et al. proposed innovations such as mini-endoscopes, endoscopic glues for hemostasis, and novel mechanical hemostatic devices, such as endoscopic suturing that may facilitate diagnosis and treatment in pregnancy [104].

In conclusion the need for large prospective studies, with follow-up of fetal outcome, is ultimately needed to determine fetal safety in gastrointestinal procedures performed during pregnancy. Furthermore, until gold standards are outlined, the publication of best practice recommendations based on evidence-to-date may provide gastroenterologists greater confidence when faced with common gastrointestinal issues during pregnancy.

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