Medical Problems During Pregnancy

A Comprehensive Clinical Guide

Carolyn Bernstein
Tamara C. Takoudes
Editors

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Preface

This book is written by a unique group of authors who were inspired to write about pregnancy in a case-based series. There are many resources for clinicians when dealing with the pregnant patient, yet many providers still have concerns about treating pregnant patients.

Some of our concerns about pregnancy are trying to establish the normal changes from pathological changes, and it is often hard to discern. For example, a pregnant woman can present with a headache: Is it a simple headache or could it be a migraine or worse preeclampsia? Other examples are also very specific to each trimester: Is the TSH too low or is it just that she is 8 weeks pregnant? Is the hematocrit 34 % normal for 32 weeks of pregnancy? What medications can a pregnant woman take safely, and why is the FDA-classified medication D fine to take at 20 weeks. The list of questions continues.

This book hopes to address some concerns for practitioners treating pregnant patients. When a woman is pregnant, I ask myself the following questions: How would I treat this patient if she was not pregnant? What medications would I use? What trimester is the patient in? What trimester-specific concerns are for each medication? Is it better to treat the patient or leave the condition untreated?

One major difficulty with medications is that the FDA classification system is too simplified, and a class D medication at 8 weeks may be unsafe for the fetus but at 32 weeks not dangerous. Many pregnant women need surgery in pregnancy, and medications for anesthesia vary in safety greatly depending on the trimester. Many women have medical conditions that require medication despite some risks such as epilepsy, hypertension, cardiac arrhythmias, and renal disease. Most often the risk of untreated disease is much worse than the risks of treatment. This case-based book is addressing these exact concerns.

Often pregnant patients are denied necessary treatment because they are "pregnant," and this can be much worse than small risks or no risks of therapy. Pregnant women also receive confusing information from social media, the Internet (or Dr. Google as we fondly call it), friends, family, and even very educated people in the medical field such as their primary care providers or a pharmacist.

While this book cannot address all concerns, we hope that the case-based format is useful for you in treating the next pregnant patient. We also hope that the practical approach makes it easy to read and that you are less nervous next time you are treating a patient who comes in with issues pertaining to medicine and her pregnancy. Thank you for reading and hopefully the easy reading cases will be useful.

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Gastrointestinal Diseases During Pregnancy

Mona Akbari and Jacqueline L. Wolf

Abbreviations

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AAP	American Academy of Pediatrics
ADA	Adalimumab
AGA	American Gastroenterology Association
anti-TNF	Antitumor necrosis factors
AZA	Azathioprine
CD	Crohn's disease
CZP	Certolizumab pegol
ECCO	European Crohn's and Colitis Organization
EGD	Esophagogastroduodenoscopy
FDA	Food and Drug Administration
FODMAP	Fermentable oligo-, di-, and monosaccharrides and polyols
GERD	Gastroesophageal reflux disease
GLB	Golimumab
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IFX	Infliximab
IPAA	Ileal pouch/anal anastomosis
LES	Lower esophageal sphincter
NAT	Natalizumab
PPI	Proton pump inhibitor

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RPC	Restorative proctocolectomy
TCA	Tricyclic antidepressants
UC	Ulcerative colitis
VDZ	Vedolizumab

Gastroesophageal Reflux

Case 1

P.A. is a 27-year-old healthy primigravida who is currently 24 weeks pregnant with a single fetus. She has a history of gastroesophageal reflux disease (GERD) diagnosed several years ago. At that time she took daily omeprazole for symptoms that occurred approximately 3–5 times per week, 1–2 times per day. Her BMI was 26 (ideal BMI 18.5–24.9), and weight loss was recommended. Over the course of a year, she managed to lose weight with diet and exercise. Her symptoms improved, and, ultimately, she was able to discontinue omeprazole without difficulty. She never underwent endoscopic evaluation, as her symptoms were uncomplicated and resolved with proton pump inhibitor (PPI) therapy. Her mother is overweight with hypertension and her maternal grandfather has diabetes. She has one younger sibling whose only medical issue consists of seasonal allergies. She has no family history of gastrointestinal malignancies. She is a nonsmoker and denies current alcohol consumption.

For the past 2 weeks, she has experienced symptoms of increasing regurgitation and an acid taste in her mouth that is reminiscent of her gastroesophageal reflux disease (GERD) symptoms years ago. These symptoms occur two to three times per week, typically after meals and occasionally at night. She has not taken any medications for her symptoms, as she is reluctant to take medications during her pregnancy. Her only medication at this time is a prenatal vitamin. Her prepregnancy BMI was 24. She has gained a total of 12 pounds. Because she had problems with similar symptoms when she was heavy and not pregnant, she wonders if her weight gain during this pregnancy has precipitated these symptoms. Her pregnancy thus far has been uncomplicated.

Discussion

GERD is a disease characterized by abnormal reflux of gastric contents into the esophagus. GERD symptoms are common during pregnancy. Approximately 45-80 % of women will experience GERD symptoms at some point in their pregnancies [1, 2]. In women with a diagnosis of GERD prior to pregnancy, symptoms can worsen as their pregnancy progresses. The clinical features of GERD are similar in pregnancy as in the nonpregnant general population. Symptoms include burning,

acid taste, regurgitation, and provocation after meals and when lying supine. Symptoms occur more commonly in the pregnant woman than in the nonpregnant woman, and the prevalence of GERD appears to increase throughout the course of pregnancy [1–3].

The pathogenesis of GERD during pregnancy is likely multifactorial and related to a series of functional and structural changes. Possible factors that contribute to GERD symptoms during pregnancy include reduced lower esophageal sphincter (LES) pressure and impaired LES contractility in response to pharmacologic stimuli. Alterations in esophageal motility are another potential mechanism, whereas increased abdominal pressure from the enlarged gravid uterus is less likely to explain symptoms [4]. There is evidence to suggest that the functioning and responsiveness of the LES are altered, even early in pregnancy. While in the first trimester the basal LES pressure remains within normal limits, the LES is less responsive to hormonal, pharmacological, and physiological stimuli such as pentagastrin, methacholine, and protein meals [5]. Increased circulating levels of estrogen and progesterone and potentially loss of the intra-abdominal LES segment result in a decrease in basal LES pressure as pregnancy progresses [4, 6]. Esophageal motility and 24-h pH monitoring demonstrate that in the second and third trimesters, the LES pressure falls [7] and nadirs at 36 weeks [8]. The LES pressure appears to return to prepregnancy values by 4 weeks postpartum [7, 8].

The prevalence of GERD increases throughout pregnancy. Approximately 12.5–22 % of women in their first trimester report heartburn, and by the third trimester, up to 35.3–72 % of women may report heartburn [3, 9, 10]. Symptoms of acid taste in the mouth and regurgitation become more prevalent as pregnancy progresses. By the third trimester, approximately 50–80 % of women will report GERD symptoms [2, 3, 9, 11]. The severity of symptoms also progresses throughout pregnancy. GERD symptoms prior to pregnancy are a risk factor for pregnancy-related GERD [2, 10]. Other potential predictors of heartburn in pregnancy include multigravidity, high prepregnancy body mass index, and pregnancy weight gain [10]. Symptoms often abate after delivery; however, there is some limited evidence that pregnancy-related GERD may be a risk factor for developing frequent heartburn 1 year after delivery [2].

Case 1 Continued

She returns for a clinic visit and is now 30 weeks pregnant. She has tried avoiding fatty foods and eating late at night, factors that aggravated her GERD symptoms before her pregnancy. These modifications helped initially for her symptoms, but now she feels her symptoms are occurring more frequently. She has had appropriate weight gain during her pregnancy and continues to take only a prenatal vitamin daily. She denies tobacco and alcohol consumption. Her pregnancy remains uncomplicated. She has not tried any over-the-counter medications, but wonders what medications she can safely take during pregnancy.

Discussion

The risks and benefits of medical management should be weighed in pregnant women. Typically a step-up approach (Fig. 1) is adopted for the management of pregnancy-related GERD, and the first-line recommendation for all patients should include lifestyle modifications. Lifestyle modifications include eating smaller meals and avoiding late night eating. Though the data to support the avoidance of caffeine and/or spicy foods is limited, patients should avoid any foods that trigger symptoms. In a nonpregnant individual, mint can relax the LES and therefore should be avoided, even though there are no data during pregnancy if mint also triggers reflux. For patients with nighttime symptoms, elevating the head of the bed with a wedge or blocks can reduce symptoms.

For symptoms not responding to lifestyle changes, the risks and benefits of drug therapy should be discussed (Tables 1 and 2). For the pregnant patient with mild to moderate GERD symptoms, initial therapy can begin with either an antacid or a histamine$_2$ (H_2)-receptor antagonist. Some expert opinion suggests that the initial

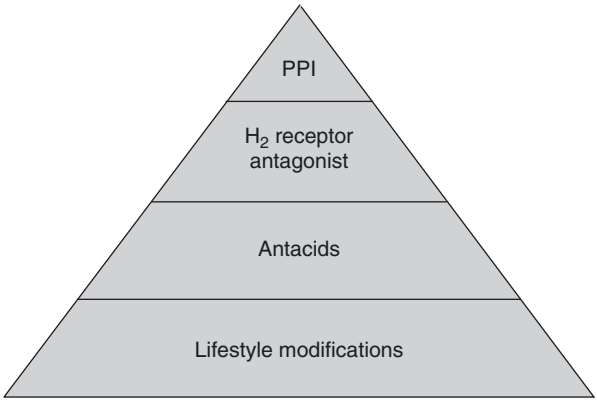

Fig. 1 Management of GERD during pregnancy, step-up approach. *PPI* proton pump inhibitor, *H_2-receptor antagonist* histamine$_2$-receptor antagonist

Table 1 US Food and Drug Administration (FDA) categories[a]

FDA category	Definition
Category A	Controlled studies show no risk to the fetus
Category B	Animal studies show no risk to the fetus; however, there are no adequate and well-controlled studies in pregnant women, *or* animal studies show risk but adequate and well-controlled human studies have failed to demonstrate risk
Category C	Animal studies show risk but there are no adequate and well-controlled studies in pregnant women *or* no adequate studies in animal or pregnant women
Category D	Fetal risk based on data from investigational, marketing experience, studies in human, but potential benefits may warrant use despite potential risks
Category X	Animal or human studies show fetal abnormalities; risks outweigh benefits

[a]FDA ratings of drugs in pregnancy and lactation will be changed as of June 30, 2015

Table 2 Safety of medication use during pregnancy

Drug	FDA classification	Comments
Antacids		
Calcium based	None	Low risk, preferred first line after lifestyle modification
Magnesium based	None	Low risk, preferred first line after lifestyle modification. Has tocolytic properties; avoid in the last several weeks of pregnancy
Aluminum based	None	Likely low risk in low doses, calcium- and magnesium-based antacids preferred
Histamine$_2$-receptor antagonist		
Cimetidine	B	Low risk
Ranitidine	B	Low risk
Famotidine	B	Limited safety data
Nizatidine	B	Limited safety data
Proton pump inhibitors		
Omeprazole	C	Animal study suggests fetal toxicity; epidemiologic studies in human suggest low risk
Lansoprazole	B	Likely low risk based on epidemiologic studies. Avoid during 1–4 weeks prior to conception given possible risk of birth defects
Pantoprazole	B	Likely low risk based on epidemiologic studies
Esomeprazole	B	Likely low risk based on epidemiologic studies
Sucralfate	B	Poorly absorbed, likely low risk
Metoclopramide	B	Likely low risk, avoid long-term use given neurologic side effects

medical therapy for pregnant women with mild GERD symptoms be calcium- and magnesium-based antacids [12].

Calcium-, magnesium-, and aluminum-based antacids are thought to be low risk in pregnancy [4, 13]. Low-dose (<1g/day) and high-dose (≥1 g/day) calcium supplementation during pregnancy appear to be associated with a reduced risk of hypertension and preeclampsia [14]. Oral magnesium supplementation has been shown to reduce the risk of high blood pressure compared to placebo, with conflicting results [15, 16]. Magnesium has tocolytic properties and its use is not advised during the last several weeks of pregnancy. Aluminum-containing antacids in large and chronic doses carry several potential concerns, such as constipation, malabsorption, skeletal impairment, and potential fetal neurotoxicity. For these reasons, high-dose aluminum antacids should be avoided and calcium-/magnesium-based antacids are preferred [4, 12]. Antacids containing sodium bicarbonate, which have the potential of causing metabolic alkalosis and fluid overload, should be avoided during pregnancy [4, 17].

H_2 receptor antagonists inhibit gastric secretion stimulated by histamine and can be used in management of GERD symptoms concomitant with antacids. In prospective

and retrospective studies, H_2 receptor antagonist use during pregnancy was not associated with increased congenital malformations [18–20] or preterm delivery and low birth weight [19, 20]. For more severe symptoms or patients nonresponsive to therapy outlined above, a proton pump inhibitor (PPI) can be initiated. The US Food and Drug Administration (FDA) classifies all PPIs, except for omeprazole, as category B medications. Omeprazole, the first PPI approved on the market, at doses 5–56 times the human dose in animal studies resulted in embryo toxicity [21] and is therefore classified as category C.

In an earlier study, PPI use in the first trimester was associated with hypospadia [22]. However, this study was based on a small number of exposures (12 women exposed to lansoprazole, omeprazole, or esomeprazole). Moreover, there was no increased risk of hypospadia in a follow-up population-based study that included nearly 3,000 women exposed to PPI (including omeprazole) at conception or during pregnancy [23]. In a subgroup analysis restricted only to omeprazole use, the risk of hypospadia in the PPI exposed was similar to that in the unexposed group. In a meta-analysis of seven studies including data from 134,940 patients (1,530 exposed to PPIs), there was no difference in the risk of congenital malformations with first-trimester use of a PPI [24]. In many of these studies, the most common [25, 26], or often only [18, 27, 28], PPI exposure was omeprazole. In secondary analysis there was no difference in spontaneous abortions and preterm delivery. Analysis limited to omeprazole, alone, showed similar results. In two large epidemiologic studies published since this meta-analysis, exposure to PPIs in the first, second, and third trimester was not associated with congenital malformations [29, 30]. Similarly, a subgroup analysis of omeprazole use during pregnancy failed to show an increased risk of congenital malformations [29].

There is limited evidence from one epidemiologic study that PPI exposure at 1–4 weeks before conception was associated with birth heart and urinary tract defects [29]. Approximately 28 % of births exposed to PPI 1–4 weeks before conception were also exposed to other medications, such as corticosteroids, beta-blockers, and ACE inhibitors, 58 % were from mothers above the age of 30, and 23 % were from mothers reporting smoking during pregnancy. Subgroup analysis demonstrated that the risk of birth defects was significant only for lansoprazole, and not omeprazole, pantoprazole, or esomeprazole. Twenty-nine defects were reported in 541 births exposed to lansoprazole. In additional analysis looking at groups of birth defects, the odds of heart and urinary tract defects seemed to be associated with PPI exposure at 1–4 weeks before conception. The overall number of exposed cases was small with 30 cases of heart defects and 12 cases of urinary tract defects reported in 1,969 live births exposed to PPIs 1–4 weeks before conception. Further studies are needed to further explore this possible association. There are no guidelines on the use of PPI for patients contemplating pregnancy, although patients trying to become pregnant should be counseled on this possible risk [31]. If tolerated and not medically necessary, cessation of PPI therapy should be attempted in all women.

Other agents that can be considered for management of GERD symptoms include sucralfate and metoclopramide. Sucralfate, a surface agent and mucosal protectant, is poorly absorbed systemically with few side effects other than constipation and

generally is regarded to be safe in pregnancy [32]. Metoclopramide, a prokinetic agent primarily used for treatment of delayed gastric emptying and nausea, may decrease GERD and has not been shown to be associated with increased adverse pregnancy outcomes [33, 34]. Metoclopramide could be considered for patients not responding to PPI therapy [31]. Its long-term use should be avoided given serious risks of neurologic complications, such as dystonia and akathisia.

Case 1 Continued

She is now 35 weeks pregnant. Her symptoms continued despite lifestyle modifications and use of calcium-based antacids and ranitidine 150 mg twice a day. She stopped these medications and it was suggested that she start a trial of pantoprazole 40 mg daily. Her symptoms have improved, although occasionally she will experience breakthrough reflux. She does admit to not taking pantoprazole daily, because she remains concerned about taking medications during her pregnancy. She denies signs or symptoms of burning or pain during swallowing, difficulty swallowing foods or food getting stuck, nausea, vomiting, and black or bloody stools. She has mild, infrequent generalized abdominal and back discomfort that developed during the course of her pregnancy. She continues to have appropriate weight gain during her pregnancy. Her labs have all been within normal limits. She wonders if she will require any further work-up now or after her pregnancy.

Discussion

The diagnosis of GERD can be made based on symptoms and more invasive testing during pregnancy is typically not necessary.

Barium radiographs, which expose the fetus to radiation, are not necessary for the diagnosis of GERD and therefore may be avoided during pregnancy. Esophageal manometry and pH studies are safe but are rarely necessary during pregnancy. For the general population, progressive symptoms or symptoms not responding to therapy can be evaluated with esophagogastroduodenoscopy (EGD). Signs and symptoms of dysphagia, odynophagia, and significant or continued gastrointestinal bleeding are considered to be indications for endoscopy during pregnancy by the American Society for Gastrointestinal Endoscopy (ASGE) [35]. Other experts have suggested that a moderate indication for EGD is recurrent nausea and emesis in patients past 16–18 weeks with a concern for peptic ulcer disease that have had inadequate response to PPI therapy [36]. Weak indications for EGD include self-limited nausea, emesis, or abdominal pain and GERD symptoms (aside from dysphagia) not responsive to empiric PPI therapy [36]. In this patient, who has no alarm features and symptoms and has been partially responsive to therapy, an EGD is not necessary. Symptoms should be monitored, daily PPI use recommended, and therapy increased with the addition of an H2 blocker at bedtime if needed.

The data on the safety and efficacy of EGD during pregnancy is sparse and limited to case series. The potential risks include maternal hypoxia, hypotension, and inferior vena cava compression during maternal positioning, as well as medication exposure to the fetus. The risks and benefits should be discussed in a multidisciplinary fashion. Maternal blood pressure and oxygen should be carefully monitored. As recommended by the American Society of Anesthesiologists and American College of Obstetrics and Gynecologists, when the fetus is previable, the fetal heart rate should be assessed before and after non-obstetric surgery, and when viable, at a minimum, fetal heart rate and contraction monitoring should be performed before and after procedure [37].

Judicious sedation is recommended. Propofol is category B by the FDA for use during pregnancy, while fentanyl and meperidine are category C and benzodiazepines are category D. The safety of propofol early in pregnancy is not known, but is considered relatively safe in pregnancy when given by a trained anesthesia provider. Meperidine and its active metabolites have been demonstrated to cross the placenta [38, 39]. Studies of teratogenicity from meperidine in animal models and humans are lacking. However, it is generally felt to be relatively safe for use during pregnancy. Fentanyl crosses the placenta as well [40], but is short acting and has faster procedural recovery time. Benzodiazepines are category D and diazepam has been associated with congenital abnormalities, including cleft lip and palate, with conflicting results [41–44]. Reports of infant floppy syndrome and neonatal withdrawal symptoms have been described in late third-trimester use of benzodiazepines [45]. If used, midazolam is the preferred benzodiazepines and should be given at its lowest effective dose.

In regard to the use of sedation during lactation, many sedatives are excreted in breast milk. Midazolam is excreted in breast milk and levels of midazolam and its metabolite appear to be undetectable after 4 h. Therefore, nursing should be withheld for at least 4 h after its exposure [35]. Fentanyl and propofol are excreted in breast milk, though at very low doses. Within 24 h of administration, 0.027 % of the propofol dose and 0.033 % of the fentanyl dose were detected in breast milk [46]. Fentanyl and propofol are considered to be compatible with breastfeeding [35]. Meperidine can be detected in breast milk up to 24 h after administration, and because of potential neurobehavioral effects on the infant, fentanyl is preferred when possible [35].

Functional Bowel Disorders

Case 2

S.T. is a 33-year-old gravida 2 para 1 woman who is currently 15 weeks pregnant. She has a history of asthma that is well controlled with rare use of albuterol inhaler as needed. During her first pregnancy, she reported constipation during her second and third trimesters. This was managed with increased fiber intake and occasional

Metamucil. After her first pregnancy, her symptoms of hard stools generally resolved, though occasionally she found herself straining depending on her diet. Currently, she reports straining and hard stools, almost daily. She finds these symptoms to be more bothersome and frequent than what she experienced in her first pregnancy. She denies any vomiting, abdominal pain, or blood in her stools. She has been gaining weight appropriately. She has never had a colonoscopy. She has a paternal grandfather who had colon cancer in his seventies, but no other family members with colorectal cancer. She takes prenatal vitamins and occasionally Benadryl at night as a sleep aid. She feels that her symptoms interfere with her daily activity and would like to discuss this further.

Discussion

Functional bowel disorders such as irritable bowel syndrome (IBS) and functional constipation consist of gastrointestinal symptoms for which investigation does not reveal an organic cause. Alterations in the brain-gut axis as well as dysbiosis of the gut microbiome and its metabolic byproducts are thought to contribute to the underlying physiology of functional bowel disorders. Functional bowel symptoms can be common during pregnancy, with up to two thirds of women reporting one or more functional bowel symptoms during their first trimester of pregnancy. In a survey-based study of women in their first trimester, 46 % reported constipation, 49 % reported bloating, 44 % had irritable bowel syndrome, and 5 % reported diarrhea [47].

Constipation, often defined as hard stools, straining, incomplete evacuation, or infrequency of defecation, is a common gastrointestinal complaint during pregnancy. The prevalence of constipation during pregnancy has been reported with variable results. Approximately 45 % of women in their first trimester self-report symptoms of constipation [47, 48], and 51 % of patients self-report constipation at some point during their pregnancy [49]. Using a more narrow definition of constipation (fewer than three bowel movements per week and straining in more than 25 % of defecations), one study reported that only 5–9 % of women are affected by constipation throughout their pregnancy. The prevalence of constipation defined by the Rome criteria (Table 1), which includes symptoms of incomplete evacuation, hard stools, and use of manual maneuvers for defecation, during the first, second, and third trimester ranges from 24 to 30 %, 19 to 26 %, and 16 to 22 %, respectively [48, 49]. Similarly, in the postpartum period, the prevalence of constipation as defined by the Rome criteria is 24 % [48, 49]. Some studies suggest that the prevalence of constipation declines by the third trimester [49, 50] and in the postpartum period [50]. Sex hormones and decreased colonic transit time from elevated progesterone and reduced motilin levels may contribute to constipation. Other risk factors include decreased activity and vitamin supplementation (iron and calcium). Women with a history of treatment for constipation prior to pregnancy are more likely to report constipation during their pregnancy [49].

Despite its potentially high prevalence, bowel dysfunction and its recommended treatment are not always addressed during clinic visits, possibly reflective of underreporting or patient/provider perceptions that constipation symptoms are part of pregnancy. However, quality of life studies suggest that pregnant women reporting one or more functional bowel complaints have lower mean overall quality of life scores. Similarly, body image, health worry, activity interference, and food avoidance scores were lower for women who complained of functional bowel disorders during their pregnancy [47].

The most common symptoms of constipation during pregnancy are straining and hard stools. Occasionally women will report incomplete evacuation [49]. Anorectal obstruction and manual maneuvers to produce a stool appear to be the least commonly reported symptoms. Patients may report symptoms relating to constipation that do not conform to strict Rome criteria (Table 3). Often patients report constipation despite daily bowel movements, but further questioning will reveal symptoms such as straining, hard stools, unproductive urges, and incomplete evacuation. While the majority of pregnant women with constipation will have simple constipation without alarming underlying etiologies, history and physical examination are important in the evaluation of constipation. A number of medications, including prenatal multivitamins with iron, iron supplements, antihistamines, calcium channel blockers, and antidepressants, can be associated with constipation. A thorough review of medications, both prescription and over the counter, should be performed. Endoscopic evaluation is rarely necessary unless there are alarm signs such as gastrointestinal bleeding, uncontrolled diarrhea, new anemia not due to pregnancy, or possibly weight loss. In this patient, who has no alarm signs, endoscopic evaluation is not necessary. Limiting antihistamine use could be recommended as it can contribute to constipation.

Case 2 Continued

She returns for a follow-up visit 4 weeks later and states that she has tried increasing fiber intake daily, in the form of fiber-containing cereal and wheat bran, and has been taking Metamucil, which she took intermittently during her previous pregnancy. She has stopped taking Benadryl at night for a sleep aid. She experienced bloating, which she attributes to the increased fiber intake. She asks you if there are alternative management options.

Discussion

Initial management of constipation includes increase in dietary fiber, fluids, and exercise. Dietary fibers increase stool bulk and frequency and reduce transit time. The recommended daily dietary fiber dose is 20–35 g, though these doses are often

Table 3 Rome diagnostic criteria

	Rome II	Rome III[a]
IBS	At least 12 weeks (need not be consecutive) in preceding 12 months of abdominal discomfort or pain with two or more of the following: 1. Improvement with defecation 2. Onset associated with change in stool frequency 3. Onset associated with change in stool form	Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with two or more of the following: 1. Improvement with defecation 2. Onset associated with change in stool frequency 2. Onset associated with change in stool form
Functional constipation	At least 12 weeks (need not be consecutive) in preceding 12 months of the following: 1. Straining > 1/4 of defecations 2. Lumpy or hard stools > 1/4 of defecations 3. Sensation of incomplete evacuation > 1/4 of defecations 4. Sensation of anorectal obstruction or blockage > 1/4 of defecations 5. Manual maneuvers to facilitate > 1/4 of defecations 6. <3 defecations per week Loose stools are not present and there are insufficient criteria for IBS	I. Must include two or more of the following: 1. Straining in at least 25 % of defecations 2. Lumpy or hard stools in at least 25 % of defecations 3. Sensation of incomplete evacuation for at least 25 % of defecations 4. Sensation of anorectal obstruction or blockage for at least 25 % of defecations 5. Manual maneuvers to facilitate at least 25 % of defecations 6. Fewer than three defecations per week II. Loose stools are rarely present without the use of laxatives III. Insufficient criteria for IBS
Functional diarrhea	At least 12 weeks (need not be consecutive) in the preceding 12 months of: 1. Loose (mushy) or watery stools 2. Present > 3/4 of the time 3. No abdominal pain	Loose (mushy) or watery stools without pain occurring in at least 75 % of stools

IBS irritable bowel syndrome
[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

not achieved. Soluble fibers, found in oat bran, barley, nuts, and seeds, attract water forming a gel and improve bowel symptoms in chronic constipation in the general population. Fiber supplement with corn-based biscuit and wheat bran has been shown to increase the number of bowel movements and soften stool consistency in pregnant women [51]. Light exercise should also be recommended, as it can promote regular bowel movements. If symptoms persist despite the above changes, a laxative can be considered (Tables 4 and 5).

Bulk-forming fiber agents, including psyllium, methylcellulose, polycarbophil, wheat dextrin, flax seed, and guar, are not systemically absorbed and are low risk for use during pregnancy. However, their effects may take days to work, and unwanted

Table 4 Types of laxatives and their mechanism of action

Treatment	Examples	Mechanism of action	Side effects
Bulk-forming fiber agents	Psyllium (Metamucil) Methylcellulose (Citrucel) Polycarbophil (FiberCon) Wheat dextrin (Benefiber) Inulin	Increases luminal water binding Increases fecal mass and stool bulk	Bloating and gas
Stool softeners	Docusate	Lower surface tension of stool Facilitates passage of water into stool	Few side effects, cramping
Osmotic laxatives			
Saline agents	Magnesium citrate Magnesium hydroxide	Poorly absorbed osmotic preparations Secretion of water into the intestine	Dehydration and electrolyte disturbance
Poorly absorbed sugars	Polyethylene glycol (Miralax) Lactulose	Increase osmolar tension Secretion of water into the intestine	Bloating and gas Dehydration and electrolyte disturbance
Stimulant laxatives	Bisacodyl (Dulcolax) Senna (Senokot)	Increase intestinal motor activity	Cramping and abdominal pain Dehydration and electrolyte disturbance

side effects include gas, bloating, and cramping. Psyllium (e.g., Metamucil), which has a soluble/insoluble fiber ratio 70/30, increases fecal water content, but patients may complain of unwanted side effects such as gas and bloating secondary to its fermentation in the colon. Methylcellulose (e.g., Citrucel), which is 100 % soluble, is a synthetic polymer fiber that increases fecal mass, stimulates motility, and reduces colonic time. It is resistant to bacterial fermentation. Polycarbophil (e.g., FiberCon) is a hydrophilic resin that is not metabolized by intestinal bacteria. Methylcellulose, polycarbophil, and wheat dextrin (e.g., Benefiber) are less likely to cause gas and bloating.

Docusate sodium, a surfactant and stool softener, is generally well tolerated. Its efficacy and safety in pregnancy has not been established, though there have been no reports demonstrating increased risk in congenital malformations [52, 53]. Docusate is considered likely low risk [13], although there has been one report of neonatal hypomagnesemia from a mother who reported daily maternal docusate sodium use (100–200 mg or more daily) throughout pregnancy [54].

Overall, there is limited data on the use of laxatives during pregnancy. Osmotic laxatives, such as lactulose, polyethylene glycol, and magnesium-containing salts, increase the amount of fluid retained in the gut. Lactulose is a poorly absorbed

Table 5 Safety of medication use during pregnancy

Drug	FDA classification	Comments
Bulk-forming agents		
Psyllium	None	Low risk, preferred after trial of increase in dietary fiber, fluids, and exercise
Methylcellulose	None	Low risk, preferred after trial of increase in dietary fiber, fluids, and exercise
Polycarbophil	None	Low risk, preferred after trial of increase in dietary fiber, fluids, and exercise
Docusate	None	Low risk for short-term use, limited efficacy in treatment of constipation
Osmotic laxatives		Low risk
Magnesium citrate	C	Avoid long-term use (risk of hypermagnesemia, hyperphosphatemia, and dehydration)
Lactulose	B	Low systemic absorption, likely low risk for short-term use
Polyethylene glycol	C	Low systemic absorption, likely low risk for short-term use
Stimulant laxatives		
Bisacodyl	B	Low systemic absorption, likely low risk for short-term use
Senna	C	Low systemic absorption, likely low risk for short-term use
Cascara	C	Safety in pregnancy not well known
Aloe	None	Not recommended
Castor oil	X	Not recommended (possible induction of labor)
Mineral oil	None	Not recommended (may interfere with absorption of maternal nutrients and vitamins, possible neonatal coagulopathy and hemorrhage)
Peppermint oil	None	Likely low risk
Dicyclomine	B	Likely low risk
Hyoscyamine	C	Crosses placenta, little known on effects on fetus
TCA	C (desipramine, amitriptyline) D (nortriptyline)	Crosses placenta, possible association with adverse outcomes in neonate
Rifaximin	C	Associated teratogenicity in some but not all animal studies, no adequate studies in pregnant women

sugar, classified as category B, but can cause bloating, gas, and pain in patients. Polyethylene glycol may result in less bloating and gas and is considered the first-choice osmotic laxative by the American Gastroenterology Association (AGA) during pregnancy [13]. Its systemic absorption is also low, but its safety during pregnancy has not been well established and is classified as category C. Prolonged use could theoretically lead to electrolyte disturbances. Saline laxatives, like

magnesium containing agents, are likely low risk. However, in certain patients (e.g., renal dysfunction), excessive absorption of magnesium may lead to electrolyte and volume overload. Their long-term use during pregnancy is not recommended. Moreover, given its tocolytic properties, magnesium-containing agents should be avoided during the last several weeks of pregnancy.

Stimulant laxatives should be reserved for patients who do not respond to dietary measures, exercise, fiber bulking agents, or osmotic laxatives. Stimulant laxatives increase intestinal fluid secretion and stimulate colonic motility. There is limited data on the use of senna and bisacodyl during pregnancy, and both are classified as categories C and B, respectively. Senna glycosides are minimally absorbed by the intestine and excreted in bile. In rat models senna given during organogenesis was not associated with teratogenicity [55], and in case-control studies, maternal use of senna was not associated with congenital malformation [56]. There have been no animal reproductive studies reported on bisacodyl, though this medication has very little systemic absorption and is likely low risk for short-term use. It can be associated with more abdominal cramping when compared to senna. In general, when possible, the lowest dose and shortest duration of stimulant laxative ingestion needed to control symptoms are recommended during pregnancy.

Cascara, an extract from the dried, aged bark of *Rhamnus purshiana*, is an anthraquinone purgative with laxative properties and is available as an herbal supplement. While its use has not been well studied for during pregnancy, there is no evidence that drugs in this class pose risk to the fetus [53]. Cascara is generally well tolerated and with few side effects, though in high and chronic doses cascara has been linked to several cases of liver injury [57, 58]. Aloe, which has a laxative effect, is not recommended in pregnancy given the possible association with congenital malformations [59]. Castor oil, category X, has a potential association with induction of labor and is therefore not recommended for use during pregnancy. Mineral oil is also not recommended during pregnancy as it may interfere with absorption of important nutrients and vitamins in mothers, as well as its possible association with neonatal coagulopathy and hemorrhage [13].

Linaclotide and lubiprostone are two therapies approved for the management of chronic constipation in the general population. Linaclotide (trade name Linzess), approved by the FDA in 2012, is a guanylin peptide that acts as a selective agonist at the guanylate cyclase-C receptor of intestinal enterocytes. Linaclotide promotes small intestinal secretion of chloride and bicarbonate ions and small intestinal fluid secretion and increases intestinal transit time. In animal studies fetal toxicity occurred at doses toxic to the mother [60]. The safety of its use in pregnant women is unknown. Lubiprostone (trade name Amitiza), approved in 2008, is a prostaglandin analogue and acts locally as a chloride channel activator. At high doses, fetal toxicity was noted in animal studies, but human studies are lacking [61]. Both linaclotide and lubiprostone are classified as category C, and given their relative newness to the market, there are no societal guidelines or recommendations for use during pregnancy.

Case 3

M.L. is a 25-year-old female who recently discovered she is pregnant. She has never been pregnant. She has a history of irritable bowel syndrome (IBS) since college. Because of persistent abdominal pain, she was prescribed amitriptyline over 2 years ago. While taking the amitriptyline, she noted improvement in her symptom, but because of unpleasant side effects, she tapered off amitriptyline. Her symptoms remained manageable and she now takes peppermint oil occasionally for symptoms. For the past year, she noticed increased bloating, as well as generalized mild to moderate abdominal pain associated with belching and passing gas. She does not have any weight loss, blood in stool, worsening of abdominal pain, or changes in bowel habit. She had an unremarkable colonoscopy in her early twenties, and recent labs including work-up for celiac disease were normal. She started a probiotic with some improvement in her bloating. Dietary modifications were recommended, but she has not made any changes in her diet thus far. She is concerned about medication use and control of her symptoms during pregnancy.

Discussion

Traditional management of IBS in the nonpregnant patient focuses on improving individual symptoms, improving global symptoms, preventing unnecessary procedures, and reducing the impact of IBS on the overall quality of life. Smooth muscle relaxants (e.g., antispasmodics) and tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors, and anticonvulsants are potential medical therapies used in the management of abdominal pain and discomfort.

Dicyclomine and hyoscyamine are antispasmodics used for management of IBS and are categories B and C, respectively. In clinical trials dicyclomine improves pain, tenderness, bowel habits, and overall condition [62], and in a meta-analysis of 12 different antispasmodics, including dicyclomine, patients allocated to the antispasmodic group had improvement in global symptoms of IBS or abdominal pain compared to the placebo group (39 % vs. 56 %). Adverse events occurred in 14 % of patients [63] that most commonly included dry mouth, dizziness, and blurred vision. Dicyclomine hydrochloride, an anticholinergic agent, appears to improve tenderness and overall symptoms in patients with IBS but side effects have been noted in up to 69 % of patients at doses of 160 mg/day [62].

There is limited information of dicyclomine (category B) during pregnancy use. Animal studies have not demonstrated fetal harm, and epidemiologic studies in pregnant women taking dicyclomine up to 40 mg/day during the first trimester have not shown fetal abnormalities [64]. Dicyclomine is categorized as compatible with pregnancy [53]. Hyoscyamine (class C) crosses the placenta and little is known on its effects on the fetus.

TCAs have been used to treat functional bowel symptoms and likely work by modulating pain centrally and peripherally. Controlled studies in the nonpregnant population are limited by few numbers of patients and short follow-ups. A meta-analysis showed improvement in abdominal pain scores and clinical response when pooling several TCAs for the use of IBS patients. There are no studies for their use in the pregnant population. Desipramine and amitriptyline are category C, and nortriptyline is category D. TCAs cross the placenta, and their use has been associated with preterm birth and possible complications such as jitteriness, irritability, respiratory distress, and endocrine and metabolic disturbances in the newborn [65, 66]. Few studies have looked at the teratogenic effects on a population level. While Swedish and US studies demonstrated an increased risk of congenital abnormalities in neonates exposed to TCA use during pregnancy [66, 67], another UK study did not find a significant association with their use during the first trimester [68]. The AGA recommends avoidance of TCAs during pregnancy given the limited efficacy data for IBS [17], though risk and benefit should be discussed in women requiring this medication for management of their symptoms.

Peppermint oil in animal models has been shown to reduce calcium influx resulting in the relaxation of gastrointestinal smooth muscle [69]. This mechanism of action may be responsible for its use in the treatment of IBS and abdominal pain. A meta-analysis, pooling the results of four trials comparing peppermint oil to placebo, demonstrated that the use of peppermint oil (ranging from cumulative daily doses of 450 to 600 mg) improved abdominal pain and/or global symptoms. There are few studies looking at the use of herbal supplements during pregnancy and birth outcomes. Low birth weight and preterm delivery do not seem to be increased in women taking peppermint during pregnancy [70, 71], and in a study of the use of peppermint oil for treatment of pruritus in pregnant women, no side effects were noted in patients [72].

Bloating is a common complaint reported by patients with IBS, and these patients often report associated abdominal pain. Impaired gas transit and malabsorption of short-chain carbohydrates may contribute to the symptoms of abdominal bloating and distension. Dietary modifications, such as limitation of FODMAPs (fermentable oligo-, di-, and monosaccharides and polyols), and reduction of fiber intake may improve symptoms of bloating. FODMAP short-chain carbohydrates are poorly absorbed and fermented in the intestinal lumen, causing bloating and abdominal pain. A low FODMAP diet therefore restricts a large number of foods that contain lactose, gluten, as well as many artificial sugars, and some vegetables and fruits in which there is an excess of fructose over glucose. While the exact mechanism of efficacy is not clearly understood, probiotics appear to alter immune response, reducing inflammation, and alter the gut flora composition, resulting in improved IBS symptoms as well. *Bifidobacterium infantis* and *Bifidobacterium bifidum* have been shown to improve symptoms of abdominal pain and bloating [73, 74]. VSL#3 also appears to reduce colonic transit and improve flatulence in IBS patients and bloating in patients with diarrhea-predominant IBS [75, 76]. In a randomized controlled trial of pregnant women receiving probiotics at 2–4 weeks before expected delivery, there were no congenital malformations reported in the

probiotic group. A meta-analysis failed to show difference in birth weight, gestational age, and Cesarean section for maternal probiotic use during pregnancy [77].

Antibiotics may also play a role in the treatment of IBS symptoms. There are potentially important differences in enteric flora of the IBS patient compared to the general population. Lactobacilli and bifidobacilli have been found in lower amounts in stool samples of patients with IBS [78, 79]. Reduction in these beneficial bacteria, which produce short-chain fatty acids that inhibit adherence of invasive bacteria, may favor colonization of the intestine with pathogenic bacteria. Increased hydrogen release during carbohydrate fermentation is associated with bloating and gaseous symptoms, and methane production has been associated with chronic constipation [80]. Rifaximin improves global symptoms of IBS, bloating, and abdominal pain [81–83]. There is limited oral absorption of rifaximin and the exposure to the fetus is expected to be low. Rifaximin is category C and has been associated with teratogenicity in some but not all animal studies [84, 85]. There are no adequate clinical studies in pregnant women.

Inflammatory Bowel Disease

Case 4

S.M. is a 32-year-old female with a history of Crohn's disease (CD) diagnosed 8 years ago, who presents for preconception counseling. She was diagnosed at the age of 24, while in law school, when she developed abdominal pain and bloating. A colonoscopy and cross-sectional imaging showed ileitis and biopsies were consistent with Crohn's disease. She was started on a thiopurine, azathioprine (AZA), and a prednisone taper at diagnosis. Four years after diagnosis, she had recurrence of her symptoms and persistent ileitis, necessitating a second prednisone course as an outpatient and dose increase of her AZA. With the increased dose in AZA, she was noted to have elevations in her liver function tests. AZA was ultimately stopped and prednisone was continued. After discussion with her gastroenterologist, she was started on infliximab (IFX) 5 mg/kg. She has been in clinical and endoscopic remission since then. Prior to starting IFX and while off of AZA, she had one miscarriage at gestation week 8. At the time of her miscarriage, she was in clinical remission and managed with oral prednisone therapy.

Now she is contemplating pregnancy and has been on a stable dose of 5 mg/kg of IFX every 8 weeks for the past 2 years. She has never had any extraintestinal manifestations of CD and has not had any abdominal surgeries. She is a former smoker, but quit after she was diagnosed with CD. Currently she is asymptomatic from the perspective of her Crohn's disease. She is on daily iron supplements and monthly vitamin B12 injections. She recently stopped her oral contraceptive therapy. She has a cousin with ulcerative colitis (UC) who had a proctocolectomy in her twenties and had a difficult time conceiving, but was ultimately successful after in vitro fertilization. She asks you whether her CD affects her ability to conceive given her family and personal history as well as the course of CD during pregnancy.

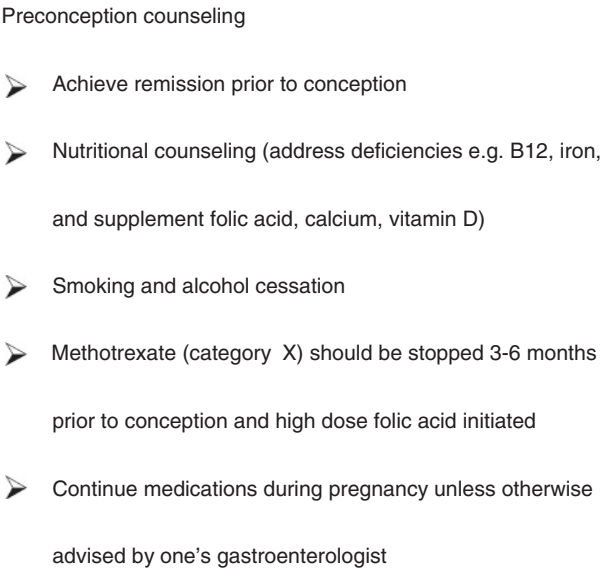

Fig. 2 Management of IBD in patients of reproductive age

Discussion

Inflammatory bowel disease (IBD), CD and UC, often affects women during their childbearing years. Many women with IBD express concern over conception and pregnancy. A multidisciplinary approach between the obstetrician, gastroenterologist, surgeon, and nutritionist is encouraged during preconception and pregnancy (Fig. 2). Women with quiescent disease have similar fertility rates as the general population [86, 87]. While overall fertility is likely to be normal, women with IBD report voluntary childlessness and sexual dysfunction, both of which affect fertility [88]. Active disease is thought to affect fertility and previous pelvic surgery, including restorative proctocolectomy (RPC) and ileal pouch/anal anastomosis (IPAA) which appear to impair conception and reduce fertility [89, 90]. Patients appear to have more spontaneous pregnancies and shorter time to conception and are less likely to undergo in vitro fertilization pre-RPC compared to post-RPC [89].

Disease activity at conception is predictive of disease activity during pregnancy. Patients in remission at conception have a milder disease course during pregnancy and are less likely to relapse postpartum, compared to those with active disease [91–93]. In a study from 12 European countries, 81 % of pregnant women with CD in remission remained in remission by the end of pregnancy, while 19 % relapsed. For those who had inactive disease at conception, the risk of relapse during pregnancy and in the postpartum period was the same as the nonpregnant patient with CD, and the cumulative probability of remaining in remission during pregnancy was the same as that in nonpregnant controls. Disease duration was a risk factor for relapse during pregnancy and postpartum period. However, in this same study, UC pregnant women demonstrated a tendency to relapse during pregnancy. Sixty-five

percent of women with UC in remission remained in remission, while 35 % relapsed. There was an increased risk of relapse during the first and second trimester compared to the nonpregnant UC women [93]. In a meta-analysis, 55 % of patients with active UC at the time of pregnancy remained active during pregnancy, while only 29 % of patients with quiescent UC relapsed during pregnancy. Similarly, 46 % of patients with active CD at conception remained active during pregnancy, and 23 % of patients who were in remission prior to pregnancy relapsed during pregnancy [92]. These findings highlight the goal of achieving and maintaining remission prior to conception.

Women with IBD appear to be at an increased risk of adverse pregnancy outcomes, with an increased risk of preterm birth and low birth weight compared to women in the general population [94–97]. In a large community-based study from Northern California, IBD patients compared to pregnant women without IBD were less likely to have live birth (60 % vs. 68 %) and more likely to have adverse conception outcome, such as spontaneous abortion (23 % vs. 17 %) and adverse pregnancy outcomes, such as preterm birth, small for gestational age and stillbirth (25 % vs. 19 %). Pregnant women with IBD were also more likely to have pregnancy complications, such as abruptio placenta, premature rupture of membrane and infection, when compared to controls (25 % vs. 16 %). There was no increased risk of congenital abnormalities [98]. Therefore, in clinical practice it is recommended to first achieve and maintain quiescent disease at conception and during pregnancy. The general consensus is to wait until patients are in remission prior to conception [88].

Obstetric need should determine the mode of delivery. The European Crohn's and Colitis Organization (ECCO) recommends that active perianal disease or rectal involvement is indication for Cesarean delivery, while IPAA and ileorectal anastomosis are relative indications [99]. Vaginal delivery carries the concern for lacerations and the risk of recurrent Crohn's in the rectovaginal septum and fistula formation. Patients with inactive perianal disease may consider vaginal delivery [88]. The sphincter and pelvic floor integrity is key for the maintenance of fecal continence in patients with IPAA and vaginal delivery may increase the risk of pudendal nerve damage and sphincter injury.

While UC patients with IPAA may report worsening incontinence and increases in stool frequency during pregnancy, these symptoms appear to resolve in the postpartum period. A study of 29 women with UC who delivered after IPAA procedure reported the mean incontinence score increased during pregnancy and subsequently improved postpartum. Thirty-five percent of patients had worsening of daytime continence during the third trimester of pregnancy; 21 % of patients experienced transient changes in continence (reported as seepage) that improved after delivery and 14 % experienced permanent changes (reported as seepage and soilage in one patient). Stool frequency increased in 55 % of patients toward the end of the second trimester and returned to normal in most patients within a few weeks of delivery (permanent increase in stool frequency was reported by 7 % of women) [100]. Another study of 43 UC patients with IPAA reported daytime and nighttime stool frequency increased during pregnancy 5.5–6.6 stools/day and 0.9–1.4 stools/night, respectively. Stool frequency resolved at longer follow-up (greater than 3 months)

postpartum. Daytime and nighttime incontinence also worsened during pregnancy, but improved postpartum [100, 101].

Nevertheless, it is not clear if patients with IPAA necessarily benefit from Cesarean delivery. In one study of 82 patients with UC and IPAA, anal manometry and anal endosonography demonstrated lower mean squeeze pressure and greater sphincter defects, respectively, in those who had vaginal delivery compared to Cesarean delivery [102]. However, stool frequency after pregnancy compared to prepregnancy was not different for women undergoing Cesarean section compared to vaginal delivery in this study and in other studies [100–102]. The presence of colostomy or ileostomy is not considered an indication for Cesarean sections, unless indicated for other reasons.

Therefore, in this patient who is in remission and has not had previous abdominal surgeries, it is unlikely that her CD will affect her fertility. Her previous miscarriage appears to have been during a time when her disease was more active and may have been unrelated to her disease. Her disease course is likely to remain inactive as she is currently in remission on her current regimen.

Case 4 Continued

She continues to express concerns regarding medication use during pregnancy. She is concerned about the potential effects of IFX on the fetus during pregnancy as well as while breastfeeding. She asks if this medication should be stopped prior to conception or during pregnancy.

Discussion

Disease activity at conception and during pregnancy appears to be an important predictor of adverse pregnancy outcomes based on multiple studies. Disease activity has been associated with preterm births, low birth weight, fetal loss, and greater risk of adverse perinatal outcomes [103–107]. In clinical practice, it is recommended that patients achieve and maintain remission prior to conception. Patients are advised to continue medical therapy for IBD with the goal of preventing both relapses during pregnancy as well as improving pregnancy and conception outcomes. Therefore, it is recommended that this patient remain on IFX at conception and during pregnancy. It is important to have a thorough discussion regarding the risks of medication (Table 6) use during pregnancy and the risks of noncompliance through a multidisciplinary approach.

Aminosalicylates are compounds containing 5-aminosalicylic acid (5-ASA). 5-ASAs are category B, except for olsalazine and Asacol HD, which are category C. These medications are considered to be low risk for use during pregnancy by the AGA and ECCO [17, 99]. Mesalamine crosses the placenta and has not demon-

Table 6 Safety of medications used for the management of IBD during pregnancy and lactation

Drug	FDA classification	Pregnancy	Lactation
5-ASA	B/C	Low risk Mesalamine can be continued in both oral and topical forms Consider switching Asacol HD (category C due to DPH coating)	Low risk
Sulfasalazine	B	Low risk and can be continued in pregnancy Supplement with folic acid 2g/day	Low risk
Corticosteroids	C or D	Likely low risk, has been associated with cleft lip with or without cleft palate and decreased infant birth weight Prednisone and prednisolone oral solution, immediate release prednisone, and methyl-prednisolone (category C) Prednisone oral delayed-release tablet (D)	Low risk, consider 4-h delay before breastfeeding
Budesonide	C	Limited information on use during pregnancy, likely low risk	Safety in lactation not known
AZA/6-MP	D	Low risk; recent studies suggest no increase in adverse pregnancy outcomes. Recommend continuing during pregnancy if necessary to maintain remission	Low risk, consider 4-h delay before breastfeeding
Anti-TNF agents	B	Low risk based on limited data. IFX and ADA cross the placenta, while CTP does not No live vaccinations in infants for at least the first 7 months	Low risk
Natalizumab	C	Limited data, safety not known	Safety in lactation not known
Vedolizumab	B	Limited data, safety not known	Safety in lactation not known
Methotrexate	X	Contraindicated	Contraindicated

strated fetal toxicity in animal studies [108]. There is one report of increased stillbirth and preterm birth for mothers prescribed 5-ASA drugs, but there was no accounting for disease activity [109]. However, in other population-based studies as well as a meta-analysis of over 2,000 pregnant women, no significant association of adverse outcomes such as congenital abnormalities, stillbirth, spontaneous abortion, preterm delivery, and low birth weight occurred [110–112]. The reason that Asacol

HD is category C is due to the coating of the tablet. Dibutyl phthalate, an ingredient in Asacol's enteric coating, in animal studies has been associated with skeletal malformations and adverse effects on the male reproductive system. A switch from Asacol to another 5-ASA medication should be considered during pregnancy. Sulfasalazine, composed of a 5-ASA joined to sulfapyridine, is category B and is also considered low risk for use during pregnancy. Sulfapyridine crosses the placenta. A report of hemolytic anemia in infants born to a mother taking sulfasalazine has been noted [113]. However, in an epidemiologic study and in smaller case-control studies of sulfasalazine use during pregnancy, sulfasalazine was not associated with pregnancy complications or congenital abnormalities [114–116]. Sulfapyridine can inhibit folate absorption; therefore, it is recommended that women supplement with folate 2 mg/day. Sulfapyridine and low levels of mesalamine can be detected in breast milk [117, 118]. 5-ASA and sulfasalazine are considered low risk for use in breastfeeding mothers by the AGA and ECCO, though the American Academy of Pediatrics (AAP) reports an incident of bloody diarrhea in an infant exposed to sulfasalazine via breast milk [17, 99, 119, 120].

Corticosteroids cross the placenta, and short-acting steroids such as prednisone, prednisolone, and methylprednisolone reach lower concentration in the fetus than longer-acting dexamethasone. Oral clefts have been reported in newborns exposed to prednisone use during the first trimester in animal studies and in a meta-analysis [121]. Recent population-based studies have failed to demonstrate an association with prednisone use and orofacial malformations and major congenital abnormalities [122–124]. Adrenal suppression in the newborn has been reported after corticosteroid use in pregnancy [125, 126]. There is sparse information on the use of budesonide during pregnancy. Budesonide undergoes extensive first-pass metabolism in the liver and has low systemic bioavailability. In one case series, there were no adverse fetal or maternal effects related to budesonide use during pregnancy [127]. Risks and benefits to the mother and fetus should be discussed when initiating corticosteroids. Corticosteroids are felt to be overall low risk when indicated during pregnancy for management of the IBD patient [17, 99]. Corticosteroids can be excreted in breast milk, with milk/serum concentration ratio of about 0.2 at prednisolone doses $\geq$30 mg and 0.1 at lower prednisolone doses. Peak concentrations occur about 1 h after the dose is given [128]. A 4-h delay before breastfeeding can be considered [99].

Thiopurines, 6-mercaptopurine (6-MP) and AZA, are categorized as category D, based on early experience and case reports. The placenta is a relative barrier to the metabolites of 6-MP and AZA, and metabolites are detected at lower levels in the newborn than that detected in mothers. Multiple epidemiologic studies in the IBD population have not demonstrated an increased risk in small for gestational age and congenital abnormalities in newborns exposed to thiopurines at conception or during pregnancy, while studies have shown mixed results in regard to the risk of low birth weight and preterm birth [129–136]. It is recommended that thiopurines be continued during pregnancy in patients requiring this medication to sustain remission. However, it is generally recommended that thiopurines not be started for the first time in pregnancy, given their lack of efficacy for induction therapy and the

small risk of pancreatitis and bone marrow suppression [137]. In regard to lactation, the levels of metabolites in breast milk appear to be very low, and concentrations of 6-MP in breast milk peak within the first 4 h of drug intake [138–140]. Although the evidence is sparse, there does not appear to be an increased risk in infectious complications in infants exposed to thiopurines via breast milk [141]. Long-term data are not available. A 4-h delay before breastfeeding can be considered to minimize an infant's exposure to thiopurines.

Infliximab (IFX), adalimumab (ADA), certolizumab pegol (CZP), and golimumab (GLB) are antitumor necrosis factors (anti-TNFs) used for the management of IBD. IFX, ADA, and GLB are IgG1 antibodies that are transported across the placenta during the second and third trimester. IFX levels in the newborn cord blood appear to be higher than maternal levels and have been detected in infants born to mothers taking IFX up to gestational week 31 [142, 143]. In a small case series, no short-term infectious complications were seen in infants exposed to IFX in utero [142]. Based on results from a safety registry and epidemiologic studies, IFX use does not appear to be associated with neonatal complications such as low birth weight, spontaneous abortions, and congenital abnormalities [107, 144–147]. Preliminary data from the PIANO study, a prospective registry of pregnancy outcomes in IBD women, demonstrated an increased risk of infections in infants born to mothers on combination therapy of an anti-TNF and immunomodulator at 12 months of age [148]. Data on long-term effects of IFX exposure in utero are not available. ADA like IFX can be detected in the newborn cord blood [143], and based on limited safety data in pregnancy, ADA does not appear to be associated with adverse pregnancy outcomes [146]. CZP is a pegulated Fab fragment that passively diffuses across the placenta. The levels of CZP in the newborn are detected at minimal levels, though clinical data of its use during pregnancy is scarce. In one series, there were no reported congenital abnormalities or infectious complications in 12 newborns exposed to CZP in utero [149]. There are no available data on the use of GLM, which was approved for the treatment of UC by the FDA in 2013, in the pregnant IBD patient.

There are differing opinions about whether anti-TNF therapy should be held late in pregnancy [150–152]. In patients with active disease, it is generally recommended to continue anti-TNFs throughout pregnancy. Some suggest discontinuing anti-TNF therapy in the early third trimester, to minimize infant exposure [153]. However, other providers advocate continuing anti-TNF throughout pregnancy as it appears that levels are present in newborns even when anti-TNFs are stopped prior to gestation week 30 and to minimize the risk of disease relapse in mothers. In one study, 12 patients with IBD in remission on IFX who discontinued IFX at gestational weeks 18–27 did not experience relapse in pregnancy [154]. Since levels of anti-TNF are detected in infants born to mothers on these medications, live vaccines should be avoided for at least the first 7 months However, there is recent data from a prospective multicenter study that anti-TNF levels can be detected in infants up to 12 months. Therefore, delaying live vaccines up to 1 year unless anti-TNF clearance has been documented should be considered. (Reference: Julsgarrd M, Christensen LA, Gibson PR, Gearry RB, Fallingborg J, Hvas CL, Bibby BM, Uldbjerg N,

Connell WR, Rosella O, Grosen A, Brown SJ, Kjeldsen J, Wildt S, Svenningsen L, Sparrow MP, Walsh A, Conner SJ, Radford-Smith G, Lawrance IC, Andrews JM, Ellard K, Bell SJ. Concentrations of adalimumab and infliximab in mothers and newborns and effects on infection. Gastroenterology. 2016; 151(1): 110-9.. In regard to lactation, there are data from small studies on the compatibility of anti-TNF therapy and lactation. The data suggest that little to no IFX is detected in breast milk and is likely compatible with breastfeeding [153, 155, 156].

Monoclonal antibodies to integrin such as natalizumab (NAT) and vedolizumab (VDZ) can be used in patients with IBD. NAT is a monoclonal antibody against the alpha-4 subunit integrin. It is approved for the treatment of Crohn's disease and is category C. There are scant data on the use of NAT during pregnancy. In animal studies on guinea pigs treated with NAT, attributable fetal toxicity and teratogenic effects were not observed [157]; however, reduction in pregnancy rates in female guinea pigs treated with high-dose NAT was observed [158]. In a study looking at 35 women with multiple sclerosis, NAT did not show adverse pregnancy outcomes compared to women with the disease not on disease-modifying therapy [159]. VDZ is a gut-selective monoclonal antibody to alpha-4 beta-7 integrin and is approved for treatment of CD and UC. VDZ is category B. Animal studies of VDZ in rabbits and monkeys at 20 times the dose levels recommended in human did not demonstrate fetal harm. There are no studies on the use of VDZ in pregnant women. The review of VDZ clinical development program revealed that 24 VDZ-treated IBD females became pregnant during the clinical study. Two of a total of 11 live births were premature, and there was one report of congenital defect (agenesis of the corpus callosum) in a mother with a history of spontaneous abortions and ectopic pregnancy who received one dose of VDZ [160]. Methotrexate is contraindicated in pregnancy due to teratogenic effects. It is recommended that MTX be stopped in prospective mothers 3–6 months before trying to conceive and high-dose folic acid be initiated [99].

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Medical Complications of Pregnancy/Headache

Carolyn Bernstein

Clinicians are understandably concerned when a pregnant patient describes headache. Onset, duration, positional worsening, and accompanying features all figure into understanding the pathophysiology and making a determination for proper evaluation and subsequent treatment. Most concerning is the patient who has never had headache prior to the pregnancy who is now presenting with new and severe pain. Three illustrative actual cases will highlight salient features.

Neurologists approach a chief complaint of headache with meticulous wariness. The majority of headaches are benign, meaning that the pain is primary (without concerning secondary cause). Examples of primary headache include migraine and tension-type headache. Migraine is very common, affecting 18% of American women. The condition is most common in women of childbearing age; migraine prevalence decreases postmenopause. It is genetic, with the predisposition running in families, and, often, patients can recall an elderly family member who had "sick headache" even if not formally diagnosed with migraine. The International Headache Society (IHS) has specific guidelines for making the diagnosis. A person must have at least five attacks lasting between 4 and 72 h of moderate to severe intensity, unilateral and throbbing in nature, accompanied by nausea or vomiting, or light and sound sensitivity. Patients often feel that if the headache is not excruciating, then it cannot be a migraine. An accurate diagnosis prior to pregnancy is helpful; migraine incidence decreases substantially during pregnancy. If a migraine patient who has been stable throughout the pregnancy describes a worsening in the third trimester, this should prompt a careful evaluation.

Tension-type headache, formally called "muscle contraction headache" or "hatband headache," is quite common. IHS criteria define this phenotype as a headache, which is bilateral, squeezing, or pressing in description, mild to moderate intensity,

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with few other associated features. Fatigue, muscle spasm, and stress can certainly trigger a tension-type headache, and often rest alone is enough to let the pain improve. Patients are usually able to complete their regular tasks despite a tension-type headache; it is worth recognizing this description, as these headaches are far less worrisome.

A patient describing a new and different headache is concerning. Headaches that are explosive in onset may represent CNS bleeding, such as aneurysm rupture. These are the "thunderclap" headaches. If a patient describes an acute onset with any sort of change in consciousness, she should be directed to emergency evaluation at once. Headaches that are worse with bending over, positional, accompanied by focal numbness or weakness, vertigo, or diplopia (double vision) are also worrisome and should be promptly evaluated. "New and different" or "first or worst" are useful monikers.

Headache evaluation includes a detailed history with documentation of the start and frequency of the headaches, as well as any specific characteristics. Neurologic exam is essential; any focality or sign of increased intracranial pressure such as abnormal funduscopic exam requires further evaluation. Any concern for pre-eclampsia would of course prompt immediate evaluation.

During pregnancy, radiation should be avoided if possible especially during the first trimester although exposure to the fetus from a non-contrast head CT is less than 0.01 rad. The American College of Radiology states that pregnant women can undergo MRI imaging at any stage of pregnancy; it is a risk-benefit decision and should be performed only if absolutely necessary. There is very little data about gadolinium contrast safety, and contrast should be avoided if possible. MRI, MR angiogram, and MR venogram can all be performed without contrast. The neurologist and obstetrician should consult and make appropriate recommendations, explaining potential fetal risk, to the mother. If the evaluating neurologist has concern for a secondary cause of headache, it may well be necessary to image.

Once the patient has been diagnosed, treatment discussion should also be a joint process. Minimizing medication is important whenever possible, but if the mother's disability from even a nonconcerning headache diagnosis such as migraine is great enough to impair her ability to function, medication may be necessary. Depending on the level of fetal development, there may be more options. Some of these will be discussed below. Acupuncture, biofeedback, and cognitive behavioral therapy are options for patients; some of these treatments are covered by health insurance. Massage may also help if the headache is considered secondary to muscle train; dry-needled trigger point injections can be an option as well.

Case One

Susan is a 31-year-old right-handed woman with a 10-year history of migraine with aura. She has two to three episodes each month of scintillating scotoma (visual obscuration surrounded by a glowing border), which last between 10 and 30 min.

After the aura resolves, she develops a unilateral pain in one temple, right more commonly than left, which throbs and pulsates. She is photophobic and phonophobic and often becomes so nauseated that she will vomit. Untreated, the headache lasts about 6 h and may be so severe at times that she is unable to work or focus and must lie quietly in the dark. She has successfully treated with a combination of 10 mg of rizatriptan plus 500 mg of naproxen, which now will abort the entire process within an hour, and if she treats at the onset of the aura, the medication may entirely prevent the subsequent headache. She has been meticulously evaluated and her normal neurologic examination and the intermittent nature of her episodes have affirmed a clinical diagnosis of migraine with aura, meeting ICHD 3-beta diagnostic criteria.

Susan feels that her migraines became more severe when she completed her graduate studies and began working full time as a teacher. She manages her triggers carefully, focusing on regular sleep and hydration, but she credits topiramate, an antiepileptic medication that is also approved by the FDA for migraine prevention, as the most significant intervention in her migraine treatment. Prior to daily medication treatment, Susan experienced at least six migraines each month, and she found the episodes difficult to manage even with abortive medications. She worked diligently with her neurologist to tailor an individual plan for treatment and prevention and has felt well with a low disability scale score (MIDAS) for the past 3 years. Of note is that migraines are associated with an increased risk of preeclampsia.

Six months prior to becoming pregnant, Susan had her Mirena IUD removed and began taking prenatal vitamins; she had tapered off of the topiramate over 3 weeks. She was delighted to become pregnant after 3 months; her migraines have been quiet during the first trimester. Topiramate is class D during pregnancy; its use has been associated with increased risk of cleft lip/palate in a developing fetus [1]. The FDA reclassified this medication in 2011. This is the only malformation associated with topiramate; risk may be secondary to epilepsy as opposed to medication specifically. To date, there is no known association of migraine with fetal malformation. Statistically, migraine decreases with each successive trimester. The Norwegian MIGRA study was reported in 2011 [2]. Participants kept diaries throughout their pregnancies and reported a successive decrease in both the frequency and duration of headaches including self-reported migraine. When migraine patients, both with and without aura, are considering pregnancy, it is important to plan carefully and to minimize medications as much as possible, in particular those with known teratogenic effects [3].

Susan's migraines increased slightly in frequency after her first trimester. She had four to five events per month, each of which was treated with acetaminophen. New data does not show increase in major congenital malformations in women who used triptans during pregnancy compared to healthy non-triptan using controls. A formulation of acetaminophen/caffeine/butalbital is sometimes offered to pregnant women as a migraine abortive. This medication is also class C. Obstetricians sometimes favor its use as it has been available for many years, and there are few adverse outcomes associated. However, both the caffeine and the barbiturate components may affect a developing fetus, and the combination of the three medications can

cause or contribute to medication overuse headache. Susan's obstetrician preferred that she avoid her prepregnancy abortive of rizatriptan and naproxen (note: there is more data for sumatriptan as it was the initial available molecule in this class) [4]. Susan had begun a course of cognitive behavioral therapy prior to her pregnancy and was often able to use meditation to decrease the pain when she did suffer a migraine. She stabilized with respect to the migraines and had a healthy baby girl at 37 weeks of gestation.

Ten days after the delivery, Susan developed a headache that was identical in description to her typical migraine although the pain was continuous. It was unilateral and throbbing. She had mild nausea and both photophobia and phonophobia. Both NSAIDs and some triptans are considered compatible with breast-feeding. Susan took 400 mg of ibuprofen with 100 mg of sumatriptan and the pain decreased slightly but persisted over the next 3 days. After 72 h, a continuous migraine is classified as *status migrainosus*. Susan presented to her neurologist and a thorough neurologic exam was normal. She was given an injection of ketorolac and felt better within 30 min.

The subsequent day, the pain returned. She had an MRI/MRV and was found to have a sagittal sinus thrombosis. Susan was admitted to the hospital and after a hypercoagulable **screen** was drawn, she was started on IV heparin and oral warfarin. Although warfarin is considered safe during breast-feeding, Susan felt more comfortable switching her daughter to formula, and a lactation consultant helped with the transition. Her hypercoagulable screen was negative, and the thrombosis was considered secondary to peripartum hypercoagulability. After 6 months of treatment with warfarin, Susan was able to stop the medication and has done well for 3 years. She was reimaged and the clot had canalized. Susan was counseled that she could have another CVT during a subsequent pregnancy and has chosen to limit her family to one child.

Pregnancy and puerperium are risk for CVT due to prothrombotic state independent of other factors such as infection and cesarean section [5]. Risk increases during the third trimester in particular. One study estimates 12 cases per 100,000 deliveries. During the pregnancy, patients may be treated with low molecular weight heparin; after delivery, the mother may be switched to warfarin [6].

This case illustrates a variation in the normal course of migraine during pregnancy and then a prolonged headache, which raised suspicion for other diagnostic possibilities. Understanding the typical course of migraine in pregnant patients, familiarity with safe treatment options including CBT, and quick recognition of a concerning change in headache duration were instrumental in managing this patient through a worrisome presentation* [7, 8].

Case Two

Barbara is a 28-year-old left-handed teacher with no neurologic history. She is pregnant with her second child and has had an uncomplicated course. Her first pregnancy was significant for hyperemesis gravidarum for which she was admitted to

the hospital during the first trimester for intravenous fluids. At 35 weeks gestation, she develops headache, which is global and nonlocalized. She describes pressing throbbing sensation with brief bursts of more severe pain. Her vision is normal and she denies any focal numbness or weakness. The pain responds to acetaminophen. An intermittent headache persists over the next 2 weeks and she notes fatigue and mild nausea. Barbara goes into spontaneous labor at 37 weeks. Five hours into what has been an uncomplicated labor, she has a generalized convulsion, which lasts 60 s. She is treated with intravenous magnesium and lorazepam and a cesarean section is performed. The baby girl has Apgar scores of nine and nine; Barbara does well after the delivery. She has no further seizure activity.

A detailed neurologic exam is performed; examination is entirely normal. Barbara then has an MRI of her brain. She has a right temporal lobe AVM with a small amount of acute blood, and some hemosiderin product representing subacute bleeding as well. The neurologist reviews Barbara's history. Barbara describes episodes during college of "spacing out" and occasional difficulty with word finding. Of note is that she is left-handed; left-handed people may have dominant right brain function with most speech function located in the right hemisphere, but it is more common for left-handed patients to have dominant left brains or dual brain speech control [9]. The nonspecific headaches that she experienced during the weeks leading up to birth were quite severe at times, but were not prolonged in duration. Again, Barbara had no headache history.

After several weeks postpartum, Barbara underwent resection of the AVM by a vascular neurosurgeon. She was treated with carbamazepine for seizure prophylaxis; of note is that this medication is considered safe during breast-feeding. Her headache had improved and she did not require pain medication. WADA testing was done prior to the surgery. Barbara had word finding difficulty postoperatively but this stabilized over 6 months and she did well.

AVMs are a tangle of arteries and veins connected by fistulas. There is a 3.5 % risk of hemorrhage during pregnancy due to the effects of estrogen. These malformations are most likely to hemorrhage in the fourth decade; they can rupture with devastating effect or hemorrhage in varying amounts [10]. If asymptomatic, the patient can be monitored throughout the pregnancy and surgically treated after. There is a 1–4 % risk of hemorrhage per year. Barbara's lesion was relatively small and was fairly superficial (temporal tip) and therefore easily accessible. However, the blood products on imaging were consistent with repeat hemorrhage over the weeks leading up to diagnosis and support the theory that increased estrogen during the pregnancy was the most likely cause of bleeding as opposed to increased pressure during labor. Had the lesion been diagnosed earlier, there may have been discussion about treating prior to delivery.

Treatment options include surgery, embolization, and radiosurgery. AVMs are graded based on size, venous drainage, and location within the brain according to the Spetzler-Martin scale [11]. Grade I lesions are those which are small, easily surgically accessible and located in "non-eloquent cortex." Barbara's AVM is small and superficial, but, due to bilateral language influence, was a more complicated lesion to approach. Her lesion was discovered in the setting of a first-time seizure;

in retrospect, her severe but short-lasting headaches may well have represented micro-hemorrhages.

There is not conclusive data about the risk of hemorrhage during pregnancy. The rate of rehemorrhage may be higher if a woman experiences a bleed during a pregnancy. Barbara's presentation of seizure during delivery is quite concerning; data does not support higher risk of hemorrhage during vaginal delivery, and it is not clear whether Valsalva increases pressure in the AVM draining veins [12].

Case Three

Janine, a 24-year-old right-handed woman, has no history of headache. She is 10 weeks pregnant; the first trimester has been complicated by weight gain but otherwise normal. Janine had a BMI of 26 prior to the pregnancy. She had struggled to lose weight since she was a teenager. Her primary care physician had worked with her around improving nutrition and increasing exercise; Janine had worked hard to improve her health but despite her efforts, had difficulty consistently monitoring her caloric intake. She stopped using birth control (diaphragm and condoms) 4 months prior to becoming pregnant.

Janine had her first prenatal visit at 10 weeks and told her obstetrician that she was experiencing headaches, which did not respond to acetaminophen. This was a new complaint for her although her mother had migraines. The headaches were perhaps a little worse in the morning and she had global head pain, which improved over the course of the day. Her obstetrician gave her a prescription for butalbital/caffeine/acetaminophen and asked her to check back in 3 weeks. This prescription-only combination is an older formulation for headache. It is class C during pregnancy, and there have been few adverse effects documented on a developing fetus, although it can cause sedation of the baby if used close to the delivery. There are few animal reproductive studies of this formulation. There is a report of an infant who suffered withdrawal seizures after birth; traces of barbiturate were found in the bloodstream (reference here).

In 3 weeks, she returns to see for follow-up. She is having continuous pain and describes blurred vision as well. She is referred to neurology for a headache evaluation.

The neurologist learns that Janine wakes up each day with a severe holocranial headache that is pressing and occasionally throbbing. It remits during the day to some degree but gets worse as Janine become recumbent. She describes a gradual deterioration of her vision to the point where it is difficult for her to read text messages on her iPhone. Janine works on the computer at work, and looking at the screen makes her vision worse. She has some light sensitivity. She then describes a sound of "ocean waves" in her head; the neurologist elicits a description of pulsatile tinnitus with occasional horizontal diplopia with change in position. There is no numbness, weakness, vertigo, phonophobia, or osmophobia. Janine also describes some transient visual obscurations that fade in and out.

Examination in the office is significant only for mild crowding on the optic nerve head, with blurring of disk margins nasally greater than temporally. Otherwise, there is nothing focal or lateralizing, specifically no sixth nerve palsy. The neurologist sends Janine for a non-contrast brain MRI scan after consulting with the obstetrician; the study is normal other than a partially empty sella [13]. Janine then undergoes a lumbar puncture. Opening pressure in the recumbent position is 400. Thirty ccs of fluid are removed; closing pressure is 160. The CSF is sent for routine studies, all of which are normal other than a mildly elevated protein of 60. The subsequent day, Janine reports a greater than 50% improvement in her headache although it still persists.

She then has a consultation with a neuro-ophthalmologist who finds grade one papilledema with constriction of the visual fields. Janine starts a calorie-restricted low-salt diet. She has gained 20 pounds in the first trimester and despite close follow-up with a dietician, she continues to gain weight at a rate of nearly 2 pounds per week for the next 6 weeks. Her headache worsens and she has a repeat spinal tap with opening pressure of 380. Again, 30 ccs of CSF are withdrawn and she improves. Her weight stabilizes, and she does well with respect to the headache until week 30 when she notes worsening of her vision, return of the pulsatile tinnitus, and increased headache severity. A third lumbar puncture shows opening pressure to be 400 [14].

At this point, the neurologist and obstetrician consult about acetazolamide. This medication is class D and is teratogenic in animal studies; however, there has been little documentation of actual risk and, in some instances, may be an appropriate option with an informed patient especially after 20 weeks [15]. When Janine learns of the potential risks, she declines although her fundi show increasing signs of increased pressure. The neuro-ophthalmologist monitors her carefully; fenestration of the optic nerve sheath can be safely done during pregnancy. A V-P shunt is another option although as the uterus enlarges, the shunt may obstruct. Janine stabilizes symptomatically with respect to the headache. Her vision does not deteriorate. Her weight gain decreases and she has a healthy baby girl at 38 weeks. The headache improves post-delivery, and she decides not to breast-feed the baby. She subsequently starts on acetazolamide at 500 mg twice/day and her vision stabilizes. She begins a supervised liquid diet under the care of the bariatric surgery clinic dietician and is able to lose about 4 pounds each month. The headache gradually resolves completely. Funduscopic examination and visual field tests are stable without requiring further intervention.

IIH is a misnomer in many cases. The name of this disorder has progressed from “pseudotumor cerebri” to “benign intracranial hypertension” to “idiopathic intracranial hypertension.” The patient describes symptoms of increased intracranial pressure without focal lesion on evaluation. Presenting complaint is often headache, which can be quite nonspecific. Pain is often worse in the morning after being recumbent during sleep and will improve with upright posture. The headache may remit for brief periods of time, but generally progresses as the pressure increases. The most concerning complication is visual loss, and it is essential to recognize this disorder prior to what may be permanent visual deterioration. Pulsatile tinnitus is often associated; patients describe the auditory rhythmic sound when asked but may

not spontaneously comment on it. There can be transient visual obscurations that often sound much like migraine aura. There is no prodrome or buildup to the headache; rather, it is consistent and often quite severe. The headache may worsen concurrently with weight gain.

Workup includes a thorough evaluation for secondary causes of increased intracranial pressure such as tumor, hemorrhage, or vascular malformation. Classic imaging signs such as "slit-like ventricles" or empty sella are not pathognomic for IIH. There may be flattening of the posterior aspect of the globe that strongly suggests the diagnosis. Lumbar puncture is performed after imaging rules out a mass lesion, and the patient must be recumbent during the procedure. Opening pressure may be quite elevated, as in Janine's case, and fluid is withdrawn after pressure recording to decrease to about 150–170 mm. There are no specific evidenced treatment protocols for IIH. Often, acetazolamide is used as a cerebral diuretic but a lack of safety evidence consensus during pregnancy exists. There is also debate about whether the diagnosis exists in the absence of papilledema. According to the IHS criteria, it is possible to make the diagnosis of IIH in the absence of papilledema based on CSF pressure in concordance with the headache description. The most serious outcome involves irreversible loss of vision. Steroids can usually safely be used during pregnancy in these patients as a short-term therapy to decrease intracranial pressure while preparing for shunt or optic nerve sheath fenestration. Disability from ongoing headache is concerning as well. Documented adverse effects from IIH on a developing fetus are not described. Weight loss and pain control are the key facets of treatment [16].

Other Secondary Causes of Headache

Although not common, a CNS tumor is another possibility for a headache that begins during pregnancy. While a new onset-seizure may be the presenting symptom, a progressive new and different headache should be carefully evaluated. There may be a focal deficit, such as weakness or clumsiness of a limb, signs of increased intracranial pressure, or seizure, both focal and generalized. One symptom of increased CNS pressure is persistent nausea and vomiting; this is often a component of an otherwise healthy pregnancy and care must be taken to look for other more ominous signs. Gliomas are a common type of CNS tumor and range from low grade (slowly developing) to high grade which are often more primitive and invasive. Studies have demonstrated that gliomas may increase during pregnancy as compared to prepregnancy states. Increased blood volume and fluid retention, as well as hormonal mechanisms, may all play a role.

Treatment depends in multiple factors. Surgery is an option, but may be reserved for tumors that are causing neurologic symptoms and are expanding rapidly on serial imaging. The gestational age of the fetus must also be considered, but a craniotomy and tumor resection can be performed. Radiation and chemotherapy are possible as well, although delaying until the fetus is more mature may minimize the development of teratogenicity.

Postpartum Headaches

Unfortunately, women who suffer from a primary headache disorder often revert to baseline postpartum. In particular, migraines which have improved or disappeared as the pregnancy progresses may recur starting as soon as a few days after delivery. This may be secondary to sleep deprivation or be directly associated with changing hormones. Lengthy labor may also predispose to muscle strain that can trigger tension-type headache. Low CSF pressure headache can be caused if there is an inadvertent dural puncture during epidural anesthesia placement; this can be corrected with a blood patch if necessary.

Secondary headache presenting postpartum should raise concerns of thrombotic events or cerebral hemorrhage. Any headache that is new and different or has focal neurologic features on examination must be promptly evaluated [13].

Headache and Breast-Feeding

Breast-feeding may prolong the decrease in frequency of migraine as it may suppress ovulation. It does not have similar effects on other types of primary headache, however. Triptans, sumatriptan, and zolmitriptan, in particular, are often compatible with breast-feeding; NSAIDs may be another option. LactMed maintains a database of medication risk during breast-feeding which is comprehensive and updated frequently [17].

In summary, most headaches experienced during pregnancy are benign and can be safely managed without fetal harm. The obstetrician must be aware of prepregnancy headache history and patterns and should monitor for increase in frequency and severity. Any change in presentation should prompt further evaluation. Migraineurs are delighted to learn that they may improve significantly during the pregnancy and possibly during breast-feeding as well [18]. Serious headaches may present during gestation and expert guidance is essential in management.

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Gestational Diabetes in 2015

Tamara C. Takoudes

Case #1

This is a 41-year-old gravida 1 para 0 Asian woman at 28 weeks who comes in for glucose testing during pregnancy. She is 5 feet 2 inches tall and 115 pounds prior to pregnancy (BMI = 21, normal). Her 1-h 50-g non-fasting glucose is 151 mg/dL (normal < 130–140 mg/dL). One week later she has a 3 h 100 g fasting glucose load and her results are 105/190/143/135). She is diagnosed with GDM based on the Carpenter and Coustan criteria (95/180/155/140) of two abnormal values [1]. She has diabetes counseling with a Registered Dietitian Nutritionist (RDN) and follows the diabetic diet recommended. The fetus is measured on ultrasound and the estimated fetal weight is >90 %. All fasting glucose levels are above the goal of <95 mg/dL; thus, she is started on NPH insulin at bedtime. At 37 weeks she goes into labor and delivers an 8.5 pound female infant. At her 6-week follow-up, she has a 2-h 75-g glucose loading test that is 95 mg/dL fasting and 150 mg/dL at 2 h. She is diagnosed with IGT.

Discussion

Glucose intolerance that begins or is first recognized during pregnancy is the definition of GDM [2]. As pregnancy progresses, maternal insulin resistance rises with increasing placental hormones. GDM is commonly diagnosed in the late second or early third trimester. Risk factors for GDM include previous history of GDM or glucose intolerance, BMI > 30, maternal age > 25 years old, first-degree relatives

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with type 2 diabetes, multiple gestations, previous infant > 9 pounds, previous malformed or unexplained perinatal demise, underlying medical issues such as metabolic syndrome, polycystic ovarian syndrome (PCOS), glycosuria at first prenatal visit, and certain ethnic groups especially Hispanic-American, African-American, Native American, South or East Asian, and Pacific Islanders.

In 2015, controversy still exists about the screening and diagnostic criteria for GDM. Universal screening versus targeted screening for high-risk populations (only patients with risk factors listed above) has been debated. In the United States, only 10 % of patients meet criteria for low risk (absence of all listed risk factors) thus universal screening is generally employed [3]. Universal screening is performed between 24 and 28 weeks as this is when insulin resistance increases. Early screening is important for patients with high-risk factors such as previous GDM, obesity, and strong family histories but no consensus on how or when to screen exists. In our practice, we offer all pregnant patients random glucose or hemoglobin A1c (HgA1c) at the first visit with routine prenatal labs and consider oral glucose challenges if the values are >140 random glucose or >5.7 % HgA1c.

There are two approaches for oral glucose challenges: one-step and two-step methods. The two-step method has been in use longer and involves a non-fasting 1-h value after consuming 50 g of liquid glucose. If the 1-h glucose is elevated, then a second step is performed. This is a 100-g glucose drink consumed with or without carbohydrate loading for 3 days. The threshold for a 50-g test is ≥130, ≥135, or ≥140 mg/dL. If a lower threshold is used, a higher number of patients will require a second step. This involves a 3-h test with a higher sensitivity [4]. The higher the threshold for the 1-h test, the specificity will increase but will have lower sensitivity. If the value after 50-g glucose exceeds 200 mg/dL, then GDM is diagnosed. If the value is between 180 and 200 mg/dL, then a fasting glucose should be checked. If a fasting value is greater than 95 mg/dL, then GDM is diagnosed and no further testing is needed [5]. The 3-h 100-g glucose challenge is considered diagnostic for GDM if two of the four values are abnormal based on Carpenter and Coustan criteria or the NDDG (National Diabetes Data Group) [1]. See Table 1 for the criteria. Both are modifications of thresholds proposed by O'Sullivan and Mahan [6], originally based on venous whole blood samples now converted to plasma samples. The Carpenter and Coustan values are lower because the thresholds derived from the older Somogyi-Nelson method of glucose analysis were also corrected to account for the enzymatic assays currently in use. If only one value of the 3-h 100-g test is abnormal, there is increased morbidity in patients even though frank GDM is not diagnosed. The clinician must decide how to approach these patients taking into consideration risk factors and history to treat as GDM or retest at a later date [7].

In 2008 the HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) data was published and validated the 75-g 2-h "one-step" screening. The 75-g 2-h test is more convenient, better tolerated, and more sensitive for identifying pregnancies at risk for adverse outcome than the 100-g 3-h oral GTT. Increased sensitivity is primarily related to the fact that only one elevated glucose value is needed for a positive test [8] although the cutoffs are also slightly lower. Since this publication in 2008, much controversy has existed about one-step versus two-step testing. Most organizations

Table 1 Diagnostic criteria for the 100-g 3-h GTT to diagnose gestational diabetes mellitus

	Plasma or serum glucose level		Plasma level	
	Carpenter/Coustan		National Diabetes Data Group	
	mg/dL	mmol/L	mg/dL	mmol/L
Fasting	95	5.3	105	5.8
One hour	180	10.0	190	10.6
Two hours	155	8.6	165	9.2
Three hours	140	7.8	145	8.0

Data from: VanDorsten et al. [29]

100-g oral glucose load is given in the morning to a patient who has fasted overnight for at least 8 h. Glucose concentration greater than or equal to these values at two or more time points is a positive test

Two different classification schemes of GDM based upon results of the 3-h GTT results have been proposed. The Fourth International Workshop-Conference on Gestational Diabetes GTT values cited above are based upon the Carpenter and Coustan modification of earlier values. They are lower than those proposed by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus and the National Diabetes Data Group (NDDG), which used cutoff values of 105, 190, 165, and 145 mg/dL (5.8, 10.6, 9.2, and 8.0 mmol/L), respectively. The values are lower because the thresholds derived from the older Somogyi-Nelson method of glucose analysis were corrected to account for the enzymatic assays currently in use

GTT: glucose tolerance test

except the American Congress of Obstetrics and Gynecology (ACOG) recommend using one-step testing (International Association of Diabetes and Pregnancy Study Groups(IADPSG)), World Health Organization, The Endocrine Society, Australian Diabetes in Pregnancy Society and more). The American Diabetes Association (ADA) recommends one- or two-step testing. While the goal of this chapter is not to promote one method over the other, one-step testing has many advantages including earlier diagnosis and thus less delay in intervention as a second oral test is not needed. In addition further studies continue to show that one-step testing may identify more women at increased risk of adverse outcomes [9–11]. More research is needed to explore the cost-effectiveness of the testing.

In our case, the patient was diagnosed with GDM, and initially dietary changes helped but she ultimately needed more treatment than diet and exercise. Once the diagnosis of GDM is made, glucose monitoring with four times daily (fasting and 1- or 2-h postprandial) measurements can help assess the effectiveness of dietary interventions described below. One- or two-hour postprandial glucose can be used although our center uses 1-h as the 2-h assessment may miss a peak in glucose. Postprandial glucose values are considered the gold standard in pregnancy based on data that assessed outcomes for preprandial versus postprandial glucose in GDM patients. Postprandial measurements resulted in a lower HgA1c and less incidence of macrosomia and cesarean delivery for cephalopelvic disproportion as compared to preprandial values [12]. Goal values are variable as hyperglycemia is a continuum and there are no values below which to prevent all complications [8]. The ADA and ACOG recommend fasting blood glucose ≤95 mg/dL, 1-h postprandial ≤140 mg/dL, and 2-h postprandial ≤120 mg/dL.

Table 2 Weight gain recommendations from WHO based on BMI and plurality of gestation

Pregravid weight BMI (kg/m^2)	Energy needs (kcal/kg)	Total weight gain (singleton)	Total weight gain (twins)
<18.5 Underweight	36–40	28–40	No data
18.5–24.9 Normal	30	25–35	37–54
25–29 Overweight	24	15–25	31–50
≥30 Obese	No data	11–20	25–42

The goal of dietary changes is to decrease hyperglycemia, prevent ketosis, provide adequate weight gain based on maternal BMI, and prevent fetal macrosomia [13]. Dietary changes include distribution of calories into three small to moderate meals and two to four snacks per day. Smaller frequent meals decrease postprandial hyperglycemia. Caloric intake is based on maternal BMI; see Table 2. Once the caloric needs are calculated, the distribution of calories is recommended by the American Diabetes Association (ADA) to be about 40 % carbohydrates evenly distributed among meals and snacks, 20 % protein, and 40 % fats with <7 % saturated fats comprising total calories. The least information is known about calorie intake for obese women (BMI > 30) but the ADA recommends restricting caloric intake by 30 % [14].

If there are no medical contraindications to exercise, moderate physical activity is recommended in patients with GDM. Data to support this recommendation is limited in pregnant patients, but in one study pregnant GDM patients showed a decrease in mean HgA1c; fasting and 1-h glucose were seen after 6 weeks of arm ergometry three times a week for 20 min [15].

Follow-up of patients during pregnancy with GDM should include measurement of maternal weight and fetal assessment (see Case #2), but both HgA1c and daily measurement of ketones are optional. HgA1c in pregnancy is lowered by the increase in red cell mass, increase in red blood cell turnover, ethnicity, as well as anemia [16]; therefore, it is not usually helpful in monitoring of patients with GDM. If noncompliance is suspected, then HgA1c may be helpful to correlate with daily logs. Ketones have a controversial association with poor cognitive development on the fetus [17, 18], yet other studies in nondiabetics have shown no difference in long-term neonatal outcome. Development of ketones in GDM is usually from starvation ketosis and not diabetic ketosis as can be the case in preexisting type 1 diabetes. Ketones may be useful to follow especially if a patient is losing weight as strict adherence in order to avoid medications such as insulin result in ketones and weight loss. Maternal starvation and weight loss especially in GDM may lead to fetal growth restriction [19].

In this case, as insulin resistance increased with advancing gestation, the patient could not meet the goal glucose values and needed additional therapy. Oral hypoglycemic medication will be discussed in the following two cases but here insulin was recommended. Most commonly insulin is recommended when the glucose targets are not achieved. New evidence is developing that targeting patients when the fetal ultrasound measured abdominal circumference is more than 75 % may allow

for prevention of fetal macrosomia as well. Meta-analysis of the two largest studies showed this approach limited the incidence of fetal macrosomia but increased the frequency of ultrasound and the number of patients requiring insulin therapy. The number of women with GDM needed to treat with insulin to avoid a newborn with abnormal birth weight was ten [20].

Insulin analogs best studied in pregnancy with good safety profiles and similar to human insulin are lispro (rapid acting), aspart (rapid acting), NPH (intermediate), and Levemir (long acting). Dosing of insulin depends on the patient weight, ethnicity, and timing of hyperglycemia. Generally 0.7–2 units/kg is used and this increases in later gestation as well. If a patients' fasting glucose is elevated, NPH is usually recommended at bedtime, and if postprandial glucose is elevated, rapid-acting insulin is given with a meal. If both fasting and postprandial glucose are elevated, then both NPH and rapid-acting insulin are recommended. The distribution of insulin is about 50 % NPH and 50 % rapid-acting split between three meals. Rough estimates can be used to calculate doses by trimester: 0.7 units/kg up to 12 weeks, 0.8 units/kg up to 26 weeks, and 0.9–1.0 units/kg up to term. In an obese patient, these doses may need to be significantly increased. Twins (discussed in Case #2) will also need increased insulin dosing. Adjustments upward are generally 10–20 % if hyperglycemia persists. Many patients fear that insulin is a permanent treatment and fear injections into the subcutaneous fat especially near the fetus. Reassurance that insulin does not cross the placenta in significant amounts and needles are too small to reach the fetus should be reviewed. High serum glucose rapidly crosses the placenta and increases the risk of macrosomia.

Finally, this patient is diagnosed with impaired glucose tolerance after delivery and has a significantly increased lifetime risk of diabetes. About 20 % of women who have GDM in pregnancy will be diagnosed with IGT after delivery [21]. About 60 % of patients will develop type 2 diabetes after the index pregnancy with GDM. Modifiers that can help decrease that risk may include breastfeeding, weight loss, and exercise. Further studies are in progress to assess the specific decreased risk of T2 DM from breastfeeding [22].

Complications of gestational diabetes are preeclampsia, macrosomia, birth injury to the neonate from shoulder dystocia, maternal trauma from delivery including operative delivery, neonatal demise, and hypoglycemia. Management and care of diabetes decreases these risks. Careful monitoring of the pregnant gravida will be discussed in Case #2.

Case #2

This is a 28-year-old with dichorionic diamniotic twins who presents for prenatal care. She is about 200 pounds and 5 feet 4 inches (BMI = 34). She conceived on metformin and Clomid. She had a hemoglobin A1c checked just after conceiving and it was 6.6 %. She had GDM in her first pregnancy but never had testing in between pregnancies. Her last delivery was complicated by shoulder dystocia of a 10 pound infant born at 39 weeks vaginally.

Discussion

This case highlights multiple issues with diabetes care in pregnancy including infertility problems, medications such as metformin to treat infertility, undiagnosed diabetes prior to pregnancy, effects on glucose by multiple gestations, and pregnancy complications from GDM in pregnancy.

This patient was very likely a pregestational diabetic based on her HgA1c early in pregnancy. Case #1 reviewed that HgA1c may be lower in pregnancy, thus her HgA1c may have even been higher prior to conception. GDM does not increase the risk of congenital fetal anomalies, but elevated HgA1c in the first trimester esp values greater than 7 % have been associated with increased risk of heart, renal, and central nervous system anomalies (see Table 3). Patients with suspected diabetes prior to pregnancy should have complete assessment of other organ systems early in pregnancy such as neurologic (especially eyes), endocrine (thyroid) and cardiac systems. A thorough physical exam, dilated eye exam, screening for thyroid disease with TSH, liver assessment, renal assessment with serum creatinine and urine analysis for proteinuria, and baseline EKG is recommended. Miscarriage is also increased thus early fetal assessment with dating ultrasound should be performed. This patient will need diligent care after delivery as she most likely has type 2 diabetes.

Multiple gestations pose challenges in pregnancy too as the increased placenta mass significantly increases insulin resistance and makes euglycemia harder to achieve. Multiple gestations also increase the risk of hypertension in pregnancy, growth restriction, stillbirth, and premature delivery compounded by the risks of diabetes. Careful surveillance is recommended and outlined in this discussion.

This patient does not require any screening for GDM given her HgA1c but immediate referral for diabetes care is needed. Metformin is a biguanide used in the treatment of both infertility and diabetes. It decreases hepatic glucose production and intestinal glucose absorption as well as increases insulin sensitivity. In our case, metformin was used for conception. The history suggests this patient may have

Table 3 Association of major malformations in IDM with initial maternal glycohemoglobin level. Degree of Elevation of Glycohemoglobin malformations/Infants)

Degree of elevation of glycohemoglobin (malformations/infants)				
Author, date	*n*	Moderate	High	Highest
Miller et al. 1981	106	<7 [2/48 (4.2)]	7–9.8 [8/35 (22.9)]	≥10 [5/23 (21.7)]
Ylinen et al. 1984	142	<6 [2/63 (3.2)]	6–9.8 [5/62 (8.1)]	≥10 [4/17 (23.5)]
Reid et al. 1984	127	<6 [2/58 (3.4)]	6–9.9 [5/44 (11.4)]	≥10 [6/25 (24)]
Key et al. 1987	61	<5.8 [2/45 (4.4)]	5.8–9.4 [4/13 (30.8)]	≥9.5 [3/3 (100)]
Greene et al. 1989	250	<6 [3/99 (3.0)]	6–12 [6/123 (4.9)]	≥12 [11/28 (39.3)]
Hanson et al. 1990	491	<6 [3/429 (0.7)]	6–7.9 [2/31 (6.5)]	≥8 [5/31 (16.1)]
Rosenn et al. 1994	228	<4 [4/95 (4.2)]	4–9.9 [7/121 (5.8)]	≥10 [3/12 (25.0)]
Total	1,405	[18/837 (2.2)]	[37/429 (8.6)]	[37/139 (26.6)]

Adapted from Kitzmiller et al. *Diabetes Care* 1996;19(5)
Data are SD above normal mean [*n*/*n* (%)]

polycystic ovarian syndrome (PCOS) which increases the risk of miscarriage as well as gestational diabetes due to associated insulin resistance [23]. Metformin has both supportive as well as nonsupportive data in regard to decreasing the risk of miscarriage when used in the first trimester. If used throughout pregnancy, metformin may decrease the risk of GDM. One study of over 270 women with PCOS were treated with metformin or placebo until delivery, and metformin did not reduce the risk of pregnancy complications specifically GDM [24]. Specifically for glycemic control in GDM, our center does not use metformin for many reasons including it crosses the placenta and there have been high levels noted in cord blood and up to one-half of women on metformin will need additional insulin therapy (and the use of metformin may delay starting insulin therapy). More safety data about the use of metformin in pregnancy is needed.

In this patient who was on metformin when she conceived, usually the medication is weaned by the end of the first trimester. This patient already has an abnormal HgA1c and thus prompt referral, and institution of insulin is needed if her fasting and postprandial glucose values are not at goal as described in Case #1. Glyburide will be discussed in Case #3.

Weight gain in twins is less clear, but specific recommendations are noted in Table 2 for twins except those that are underweight. This patient would be recommended to gain between 31 and 50 pounds maximum based on the Institute of Medicine guidelines.

Fetal follow-up is more frequent for twins, but specifically for GDM even in a singleton pregnancy, ultrasound follow-up is recommended. ACOG is very nondirective but our maternal-fetal medicine unit recommends fetal testing in GDM patients. Fetal testing is the assessment of fetal well-being by daily kick counts, nonstress test (NST), biophysical profile (BPP, ultrasound), combination of both, or a contraction stress test. Generally estimated fetal weight (EFW) by ultrasound is performed once a month after the diagnosis of GDM is made. If a patient has poor control or suspected pregestational diabetes, then fetal testing should begin by no later than 32 weeks with weekly or 2× a week intervals. If a patient has well-controlled GDM with diet alone, then weekly testing begins at 36 weeks. If a patient has well-controlled GDM on insulin, then weekly testing commences at 32 weeks and 2× a week testing begins at 36 weeks. Any change in maternal or fetal condition can prompt increased testing as well.

Delivery in patients with GDM is a two-part decision as it involves proper timing as well as discussion about the mode of delivery. Delivery in pregestational diabetes is generally recommended between 39 and 40 weeks given association with stillbirth and poorer perinatal outcomes, but GDM is not by itself an indication for delivery. When active versus expectant management was reviewed, no evidence-based recommendation can be made as long as fetal testing is reassuring and the patient is compliant/well controlled [25].

Mode of delivery for GDM is based on the ultrasound EFW. The risk of shoulder dystocia is increased in patients with GDM compared to women without GDM. Approximately 588 cesareans are needed to prevent one case of a permanent brachial plexus injury in a GDM patient [26]. Despite this large number of cesareans, the risk of permanent nerve injury remains, and this is the cutoff that is recommended

Table 4 Rate of shoulder dystocia by birth weight in nondiabetic and diabetic women

Birth weight, g	Nondiabetic women, %	Diabetic women, %
≤4,000	0.1–1.1	0.6–3.7
4,000–4,449	1.1–10.0	4.9–23.1
≥4,500	2.7–22.6	20.0–50.0

Adapted from ACOG Practice Pattern No 7, Oct 1997

by ACOG for both pregestational as well as GDM patients (see Table 4). In this case, the patient had a previous delivery complicated by shoulder dystocia, and thankfully her infant did not have any permanent injuries. Twins have a lower risk of reaching the size of her previous delivery, but shoulder dystocia cannot be predicted by birth weight alone. The recurrence risk ranges from 1 to 17 % (the large range is likely as many patients do not attempt vaginal birth after an index pregnancy complicated by shoulder dystocia) [27]. Her prior pregnancy may have been complicated by poor diabetes control hence the neonatal birth weight was large. Twins have a higher rate of cesarean birth regardless over singleton pregnancies for fetal and maternal indications. This patient chose an elective cesarean given her history and current pregnancy of twins. She delivered healthy twins at 37 weeks after she broke her water weighing about 7 pounds each. After delivery, she was diagnosed with type 2 diabetes and was able to lose weight to avoid insulin therapy.

Case #3

A 32-year-old G1P0 conceives 2 years after bariatric surgery with a laparoscopic Roux-en-Y procedure. She had a diagnosis of glucose intolerance prior to the surgery. She lost 120 pounds; she was 350 pounds prior and now weighs 230 pounds and is 5 feet 6 inches (BMI 56 prior to bariatric surgery now 37). Her fasting glucose is 82 early in pregnancy and her HgA1c is 5.5 %. During the pregnancy she gained about 10 pounds and exercised daily. She monitored her fasting and 1 h glucose intermittently. By 28 weeks, her fasting glucose was 100s and 1-h postprandial values were above 130s. She changed her diet and was managed on glyburide 5 mg. She received iron transfusions and B 12 injections starting at 28 weeks. She delivered a healthy baby boy at 39 weeks by planned cesarean for breech. The neonate was 8 pounds and had normal glucose values after delivery. She breastfed and lost the weight she gained in the pregnancy.

Discussion

Bariatric surgery is more common as the epidemic of obesity especially in the United States increases. Pregnancy outcomes are generally more favorable in a patient who has lost weight but poses more complex issues in relationship to pregnancy. Obesity significantly increases the risk of GDM and yet screening for GDM

can be difficult in patients after bariatric surgery. "Dumping syndrome" is related to simple sugars that rapidly empty into the small intestine causing a release of insulin and hence severe hypoglycemia. These patients cannot be screened for GDM with the usual oral glucose challenges. There is no standard for screening but especially since this patient population is at increased risk of GDM, screening should be pursued. Options include but are not limited to hemoglobin A 1c measurements (as this patient had), fasting glucose, postprandial glucose values done in the office after a meal, and home glucose monitoring especially in the time frame of 24–28 weeks. No standards exist for testing these patients but vigilance is required. In addition, this patient was screened and treated for the vitamin deficiencies most common in bariatric surgery patients such as B12 and iron. Also in this case, she did well with exercise and weight gain in pregnancy but still developed GDM by the third trimester due to increasing insulin resistance.

As discussed previously, the gold standard of treatment is insulin, but some centers are using oral hypoglycemics more commonly due to obvious patient and provider convenience. Our center does not use metformin or glyburide as first-line therapy due to the controversies about placenta passage of the medication as well as lack of long-term data on safety. Regardless, glyburide is very commonly used and is considered in patients with mild glucose elevations especially if they refuse insulin therapy. Glyburide, similar to metformin, has been studied in pregnancy yet clear guidelines and use of these medications vary from practice to practice. Glyburide is a sulfonylurea that stimulates pancreatic islet beta cell insulin release. Both ACOG and ADA endorse the use of oral agents in pregnancy but the FDA has not approved these medications. While some centers use glyburide as a first-line therapy for GDM in women who fail to control glucose with diet alone, our center uses glyburide for women who refuse or are unable to use insulin. Glyburide has less "failures" than metformin (up to 16 % need supplemental insulin with glyburide vs up to 50 % in metformin) thus is preferred as an oral agent over metformin. Glyburide was not originally felt to cross the placenta but follow-up data shows significant levels in the fetal cord blood. Patients need to be counseled on the uncertainties of the affect on the neonatal pancreas. A meta-analysis also showed glyburide-exposed pregnancies had higher rates of macrosomia and neonatal hypoglycemia when compared to insulin [28].

This case demonstrates how a motivated and well-counseled patient can succeed despite her increased BMI.

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Thrombophilia and Thrombocytopenia in the Pregnant Woman

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Pregnancy and Venous Thromboembolism

Introduction

A number of factors contribute to an increased risk of vascular thromboembolism (VTE) during pregnancy including augmented venous stasis secondary to anatomic changes and a heightened activation of the coagulation cascade. Compression of the left iliac vein by the left iliac artery impedes venous return accounting for the preponderance of left lower extremity deep vein thrombosis (DVT) during pregnancy [73]. Evidence of heightened activation of the coagulation cascade comes from measurements of decreased anticoagulant activity such as of protein S, increased procoagulant activity, and decreased fibrinolysis [19, 83]. The "hypercoagulability" of pregnancy peaks in the early postpartum period and is posited to occur in preparation for the hemostatic challenge of delivery [45]. As in the general population, there is significant interest in risk stratifying pregnant women to identify those at high risk that would benefit from anticoagulation.

Two-thirds of all pregnancy-associated DVT occur antepartum distributed evenly throughout the three trimesters, the remaining one-third occurring postpartum [73]. Taking into account that the antepartum period is approximately sevenfold greater in duration than the postpartum period, it becomes clear that the absolute daily risk of venous thromboembolism (VTE) is considerably higher during the postpartum period. In a recent study that assessed more than one million pregnancies in California, the odds of experiencing a thrombotic event was tenfold higher in the first 6 weeks postpartum, and the increased risk persisted up to 12 weeks [43]. The wide range in the absolute risk of VTE that exists during pregnancy is exemplified

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by comparing a woman without a personal or family history of VTE during the antepartum period who has a risk of <0.1 % over 40 weeks and a woman with a personal history of VTE and thrombophilia in the postpartum period, who has a risk 5 % over 6 weeks ([87]; Pabinger et al. 2005). Thus, the risk of VTE in the antepartum and postpartum period is considered separately prior to making recommendations regarding antithrombotic therapy in a given case.

The risk of harm to the patient from antithrombotic therapy forms a crucial part of the equation when estimating the net clinical benefit or lack thereof. Beyond major hemorrhage, the patient may also encounter minor bleeding, allergic reactions, heparin-induced thrombocytopenia (though rare), limited obstetrical anesthesia options, and wound complications following delivery. VTE-related deaths represent a leading cause of maternal mortality in the developed world and yet, fortunately, remain uncommon accounting for 0.8–4.7 deaths per 100,000 pregnancies (Berg et al. 2010; [15]). Major bleeding rates from low-molecular-weight heparin (LMWH) in the antepartum period are extremely low (0 %, 95 % CI, 0–0.6 %) and appear to be increased in the postpartum period (0.3 %, 95 % CI, 0–1 %) [11, 23, 26, 29, 33, 35, 36, 41, 56, 76, 80]. The proportion of major bleeding events that are fatal is about 3.5–4 %, whereas the proportion of VTE that are fatal (as extrapolated from other populations) is about 1.4–2 % [49, 62], that is, approximately a half of that of the fatal bleeding risk. This implies that VTE risk must exceed the major bleeding risk by two- to threefold to achieve a mortality benefit. Generally speaking, a conservative estimate is that an absolute VTE risk of >3 % either in the antepartum or postpartum period would be needed for the antithrombotic therapy to provide a net clinical benefit to the patient [79]. Such estimates naturally raise the question – which populations have a calculated risk high enough to meet such a threshold?

Case 1

A 28-year-old primigravida, heterozygous for factor V Leiden, is seen in the hematology clinic at 12 weeks of gestation. She has no other significant past medical history. In particular she does not have a personal history VTE nor of any bleeding problems. Her family history is notable for idiopathic DVT in a brother, who is the proband. Thereafter, she was found to be heterozygous for this trait upon screening. The patient is currently asymptomatic with an unremarkable first trimester. Based on her heterozygous factor V Leiden status and positive family history for VTE, she is recommended postpartum prophylaxis with LMWH. The patient has a normal pregnancy and delivers a healthy male neonate at 41 weeks of gestation. She is initiated on enoxaparin 40 mg subcutaneously daily on the first postpartum day for a total of 6 weeks.

The Clinical Impression Pregnancy with factor V Leiden

Discussion of Management Pregnancy is a transient, independent risk factor for venous thromboembolism. The incidence of VTE increases tenfold from 1 in 10,000

to 1 in 1,000 during pregnancy [3, 56, 57] and a further tenfold in the postpartum period [43, 73]. This risk is further modified by acquired and inherited risk factors.

The most common genetic determinant of thrombophilia is factor V Leiden, which is present in approximately 5 % of Caucasians (including European, Arab, Jewish, and Indian populations) [74] and, interestingly, is not present in African Black, Chinese, or Japanese populations. The next most prevalent genetic determinant in Caucasians is the prothrombin 20210A mutation [67]. Factor V Leiden refers to a point mutation that converts arginine to glutamine at position 506 in factor V, rendering it resistant to activated protein C-mediated (APC) cleavage [16]. Factor V Leiden was therefore originally termed "APC resistance." The Leiden thrombophilia study found that overall, the relative risk for VTE is increased sevenfold for factor V Leiden heterozygotes and 80-fold for homozygotes [46]. Nonetheless, only about 5 % of factor V Leiden heterozygotes will experience a VTE in their lifetime; the overwhelming majority will remain free of VTE. Prothrombin 20210A mutation results from a single nucleotide transition (guanine to adenine) at position 20210 of the 3′-untranslated region of the prothrombin gene resulting in elevated plasma prothrombin (factor II) levels. Heterozygous prothrombin 20210A mutation is associated with about twofold increase in risk of VTE, whereas the homozygous state is associated with a much higher risk (De Stefano et al. 2001). The deficiencies of natural occurring anticoagulant proteins c and s and antithrombin are rare, but associated with a 10–20-fold increased risk of VTE.

The differences in the VTE risk in the antepartum and postpartum periods and its interaction with an individual patient's risk factors, inherited and acquired, are taken into account to formulate recommendations for antithrombotic therapy. Large prospective cohort studies of patients with heterozygous FVL or prothrombin mutation [20, 37, 50, 51, 84, 86] and randomized control trials [23, 36, 41, 56, 80] have demonstrated a low risk of venous thromboembolism (VTE) in the antepartum period in the absence of prophylactic anticoagulation. For asymptomatic (no personal or family history of VTE), homozygous FVL and prothrombin mutation, antenatal prophylaxis is not recommended per the American College of Chest Physician (ACCP) guidelines [4]; however, the risk of antenatal VTE [40, 55] is deemed to be high enough by many experts to justify antenatal prophylactic anticoagulation. The data on pregnant women with antithrombin deficiency is limited, but given the high risk of VTE in the nonpregnant antithrombin-deficient population, this is regarded as a particularly potent thrombophilia during pregnancy and treated with antenatal antithrombotic therapy (Conard et al. 1990; [9]). Asymptomatic antithrombin-deficient patients are treated with weight-adjusted LMWH, whereas those with a personal history of VTE are treated with therapeutic doses of LMWH; moreover, pooled human antithrombin concentrate is administered around the time of delivery. Previous history of estrogen-associated VTE has been shown to have a high antepartum recurrence in the absence of anticoagulant prophylaxis, as high as 10 % in some retrospective studies (Pabinger et al. 2005; De Stefano et al. 2006), and, hence, warrants antithrombotic therapy. The risk of VTE in the postpartum period is high in potent thrombophilias warranting antithrombotic therapy [4, 82]. In addition, compound heterozygosity for FVL and prothrombin G20210A mutation also con-

Table 1 Inherited thrombophilias and prophylactic anticoagulation

	Observed or estimated absolute risk[a]	Antepartum anticoagulation	Postpartum anticoagulation
Factor V Leiden, heterozygote			
No family history	1.2 (0.8–1.8)	No	No
Positive family history	3.1 (2.1–4.6)	No	Yes
Prothrombin 20210A gene mutation, heterozygote			
No family history	1.0 (0.3–2.6)	No	No
Positive family history	2.6 (0.9–5.6)	No	Yes
Protein C or S deficiency			
No family history	~0.7 (0.3–1.5)	No	No
Positive family history	1.7–6.6 (0.4–14.7)	No	Consider
Antithrombin deficiency			
No family history	0.7 (0.2–2.4)	Yes	Yes
Positive family history	3.0 (0.08–15.8)	Yes	Yes
Factor V Leiden, homozygous			
No family history	4.8 (1.4–16.8)	Consider	Yes
Positive family history	14.0 (6.3–25.8)	Yes	Yes
Prothrombin 20210A gene mutation, homozygous			
No family history	3.7 (0.2–78.3)	Consider	Yes
Positive family history	n/a	Yes	Yes

[a]Observed or estimated absolute risk of VTE, antepartum and postpartum combined, % pregnancies (95 % CI)

- Data based on Table 7 in Bates et al. [4]
- Recommendation for antepartum and postpartum anticoagulation (AC) based on ACCP 9th Edition Guidelines
- Antithrombin deficiency recommendations are based on Bramham et al. [9]

fers a high risk of VTE in the postpartum period, and therefore postpartum antithrombotic therapy is recommended for this group. This is not the case for the weak thrombophilias, where, like during the pregnancy, only clinical vigilance is recommended (see Table 1).

A further consideration for the practicing physician is the eventuality of multiple risk factors coinciding in one patient rendering a cumulative, elevated risk of VTE during the postpartum period, for example, a woman with a weak thrombophilia in the postpartum period and one or more of the following: inflammatory bowel disease, age >35, prior superficial phlebitis, BMI>25 kg/m^2, immobilization, Cesarean section, postpartum complications such as hemorrhage and infection, and smoking (Jacobsen et al. 2008; [88]). Importantly, the literature indicates that a family history of VTE, which can be thought of as a phenotypic manifestation of thrombophilia, portends a further two- to fourfold increased risk for VTE [7]. Clinical guidelines therefore recommend that

pregnant women with a weak, inherited thrombophilia, who do not have a personal history of prior VTE, but do have a positive family history for VTE, undergo clinical vigilance in the antenatal period and prophylactic- or intermediate-dose anticoagulation in the postpartum period [4]. Prior history of VTE, particularly in association with a temporary risk factor, is also considered to be a weak risk factor outside of an estrogen-associated event. Only 3 out of 125 women (2.4%) with prior history of VTE, none with a history of provoked VTE, had antepartum recurrence of VTE in a prospective cohort of 125 pregnant women with a single prior VTE in whom antepartum heparin was withheld (Brill-Edwards et al. 2000). The combination of two or more of these independent risk factors, particularly in the setting of heterozygous FVL or prothrombin G20210A mutation, may confer a VTE risk high enough for consideration of antithrombotic therapy. It is generally recommended that women who suffered an unprovoked VTE or estrogen-associated VTE receive thromboprophylaxis both antepartum and postpartum.

Key Points

1. The daily risk of VTE is significantly greater in the postpartum period than the antepartum period. Distinct anticoagulation recommendations are therefore made for the antepartum and postpartum periods based on the individual patient's risk factors.
2. The inherited thrombophilias present a varying range of risk for VTE rather than a uniformly elevated risk of VTE.
3. Heterozygous Factor V Leiden or prothrombin G20210A mutation in isolation (without a personal history of VTE or a positive family history for VTE or other mitigating factors) can be managed without prophylactic anticoagulation.
4. Potent thrombophilias (e.g., antithrombin deficiency or homozygous Factor V Leiden) in isolation are an indication for prophylactic- to intermediate-dose postpartum anticoagulation. Many experts consider the risk to be sufficiently high to warrant prophylaxis in the antepartum period in addition to the postpartum period.
5. Potent thrombophilias combined with a positive family history of VTE are an indication for prophylactic- to intermediate-dose anticoagulation in the antepartum and postpartum periods.
6. We recommend routine thromboprophylaxis for women with a history of idiopathic or estrogen-associated VTE throughout pregnancy and in the postpartum period.

Case 2

A 32-year-old woman G4P0 with a history of recurrent early pregnancy loss presents to her obstetrician reporting a positive home pregnancy test 4.5 weeks after her last menstrual period. The patient recounts having three spontaneous miscarriages at 6, 7, and 8 weeks of gestation, respectively. She reports being diagnosed with antiphospholipid antibody syndrome following her last

miscarriage and recalls being instructed to present for medical attention promptly following a positive home pregnancy test. She has been taking a low-dose aspirin daily. She has no personal history of thromboembolic disease, venous or arterial. Review of her past records reveals persistently positive lupus anticoagulant. She is initiated enoxaparin on 40 mg daily at this visit in addition to the low-dose aspirin that she takes. The patient carries her pregnancy to term, when enoxaparin is switched to unfractionated heparin twice daily in preparation for labor and delivery. Patient undergoes a Cesarean delivery at 41 weeks due to non-progress of labor. Enoxaparin is resumed in the early postpartum period and continued for 6 weeks.

Clinical Impression Obstetric antiphospholipid antibody syndrome

Discussion of Management A substantial literature supports the association between antiphospholipid antibodies (APLA) and recurrent and late pregnancy loss [24, 34, 48, 70]. The definition for antiphospholipid antibody syndrome (APS) requires meeting one clinical criterion involving either a venous or arterial thromboembolic event or pregnancy complication/loss, in addition to persistently positive lupus anticoagulant or an antiphospholipid antibody (Table 2) [60]. Obstetric APS refers to APS that manifests with pregnancy complications or failure. The strongest association between an APLA and pregnancy loss has been found for lupus anticoagulant with an odds ratio of 3 for any miscarriage and greater than tenfold for late third trimester loss [63]. These risks are moderate for anticardiolipin antibodies, whereas risks are weak or inconsistent for anti-β2 glycoprotein 1 antibodies [1]. There has been considerable effort to improve pregnancy outcomes in obstetric APS. The most striking results were derived from a single-center study of 90 women with confirmed APLA and three or more consecutive miscarriages, without a personal history of thromboembolism, SLE, in whom hormonal, anatomic, and chromosomal abnormalities as a cause of recurrent pregnancy loss had been excluded. Low-dose aspirin was initiated at conception, and participants were randomized to continue aspirin alone or in combination with UFH 5000 units subcutaneously twice daily until 34-week gestation. A significant benefit on live birth rates was observed in women treated with unfractionated heparin (UFH) plus aspirin as compared to aspirin alone, 71 % versus 42 % [71]. A systematic review of randomized trials comparing UFH or LMWH in combination with aspirin or aspirin alone in patients with obstetric APS (five trials, $n = 334$) demonstrated that the frequency of live births was higher in the combination treatment group as compared to aspirin alone (74.3 % vs. 55.8 %), the number needed to treat being 5.6 [53]. Although compelling, these trials had small sample sizes with heterogeneous populations, such that the live birth rate with aspirin alone varied between 40 % and 80 %. In addition, the benefit of antithrombotic therapy in women with late pregnancy loss or pregnancy complications related to placental insufficiency remains unclear. Guidelines from the ACCP recommend UFH or LMWH plus aspirin for women with obstetric APS associated with recurrent early pregnancy losses and refrain on commenting on other subgroups of women [4].

Table 2 Revised classification criteria for APS

Clinical criteria	Laboratory criteria
1. Vascular thrombosis One or more clinical episodes of venous, arterial, or small vessel thrombosis, in any tissue or organ Thrombosis must be confirmed by objective validated criteria 2. Pregnancy morbidity (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation (b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of (i) eclampsia or severe preeclampsia or (ii) recognized features of placental insufficiency (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded	1. Lupus anticoagulant present in plasma, on two or more measurements obtained at least 12 weeks apart 2. Anticardiolipin antibody of IgM and/or IgG isotype measured in the serum or plasma at medium or high titer (>40 GPL or MPL, or > the 99th percentile), on two or more occasions, separated by at least 12 weeks 3. Anti-β2-glycoprotein1 antibody of IgG and/or IgM isotype measured in the serum or plasma (titer >99th percentile), on two or more occasions, separated by at least 12 week

The diagnosis of APS requires that at least one clinical criterion and one laboratory criterion should be met. Adapted from [60]

Key Points

1. The revised classification criteria for APS require that one clinical and one laboratory criterion be fulfilled: (a) evidence of thromboembolic disease, venous or arterial or pregnancy morbidity, and (b) persistent laboratory evidence of antiphospholipid antibodies, lupus anticoagulant and/or anti-cardiolipin antibody and/or β2-glycoprotein1 antibody.
2. In women with obstetric APS as manifested by recurrent early pregnancy loss, there is evidence that combined therapy with heparin and aspirin leads to improved live birth rates; based on this data, we recommend combination therapy during pregnancy for this subset of women with APS.
3. The value, if any, of antithrombotic therapy in women with obstetric APS associated with late pregnancy loss or placental insufficiency remains unknown.

Case 3

A 29-year-old woman is referred by her reproductive endocrinologist for the management of recurrent pregnancy loss. She has a history of four consecutive first trimester miscarriages. She has celiac disease well controlled on a gluten-free diet. The last two pregnancies were achieved with assisted reproductive technology, and she is anxious to undergo a trial of prophylactic anticoagulation should she become pregnant again. This has been suggested by her reproductive endocrinologist, and she has read on the Internet that this could improve her chances of a successful pregnancy. She would like to coordinate this with the start of her next clomiphene cycle. An extensive workup for recurrent pregnancy loss has been negative so far, including negative testing for antiphospholipid antibody. Pathologic analysis of the previous products of conception is not available. She does not have a personal or family history of VTE. She is counseled during the visit that the available literature does not demonstrate a benefit from prophylactic anticoagulation in the setting of unexplained recurrent pregnancy losses and that while prophylactic anticoagulation with LMWH is fairly safe, the risks do include major maternal bleeding. She elects a trial of prophylactic LMWH in the event of pregnancy. She undergoes another cycle of IVF and does achieve pregnancy at which time she starts LMWH. At 7-week developmental age, a spontaneous abortion is diagnosed based on the absence of a fetal heartbeat.

Clinical Impression Utility of low-molecular-weight heparin to improve pregnancy outcomes

Discussion of Management Hypercoagulability with ensuing thrombosis of placental vasculature is one mechanism that has been put forth to explain placenta-mediated pregnancy complications and pregnancy failure. This hypothetical mechanism raises the possibility of a therapeutic intervention with anticoagulants, a prospect that is understandably tempting to both patients and their physicians.

Table 3 Association between thrombophilia and pregnancy complications

Type of thrombophilia	Recurrent first trimester miscarriage	Single second trimester miscarriage	Stillbirth (third trimester loss)	Preeclampsia (mild or severe)
Anticardiolipin antibodies	5.1 (1.3–8.7)	?	9.26 (0.86–99.8)	2.7 (1.65–4.51)
Anti-β2-glycoprotein1 antibodies	2.12 (0.69–6.53)	?	23.5 (1.2–455)	19.14 (6.34–57.77)
Lupus anticoagulant	NA	14.3 (4.7–43.2)	54.2 (2.4, 1198)	1.45 (0.76–2.75)
Factor V Leiden mutation (heterozygote)	[a]	4.1[a] (1.9–8.8)	2.0 (0.4–9.7)	[a]
Factor V Leiden mutation (homozygote)	1.9[a] (1.0–3.6)	8.6 (2.2–34.0)	2.1 (1.1–3.9)	1.23[a] (0.89–1.70)
Prothrombin G20210A mutation (heterozygote)	2.7 (1.4–5.3)	?	2.7 (1.3–5.5)	1.25 (0.79–1.99)

Adapted from Middeldorp et al. [59]

[a]The distinction between heterozygosity and homozygosity cannot be discerned

Key Points

1. Recurrent, unexplained pregnancy loss is defined as the absence of APLA, maternal hormonal abnormalities, maternal anatomic abnormalities, and parental/fetal chromosomal abnormalities.
2. The association between inherited thrombophilia and pregnancy complications/loss is controversial, and the current guidelines do not recommend screening women with recurrent pregnancy losses for inherited thrombophilia.
3. Antithrombotic therapy with LMWH and/or low-dose aspirin does not affect the live birth rate in women with recurrent, unexplained pregnancy loss.

While basic science research on genetic mouse models of thrombophilia has provided evidence of a link between fetal demise and activated coagulation in the placenta [39], epidemiologic studies in humans have not convincingly demonstrated an association between thrombophilia and pregnancy failure or complications outside of obstetric APS [1, 21, 42, 81]. Two recent randomized trials, the SPIN and ALIFE studies, sought to address the efficacy of antithrombotic therapy for women with recurrent pregnancy loss [22, 41]. Women with two or more unexplained pregnancy losses were randomized to low-dose aspirin plus LMWH (enoxaparin 40 mg daily in SPIN and nadroparin 2,850 IU daily in ALIFE) to aspirin 80 mg alone in SPIN or to placebo in ALIFE trial. The pregnancy outcomes did not differ between the treatment and control groups in either study. A Cochrane database systematic review on aspirin or anticoagulants for treating recurrent miscarriage in women without APS subsequently reinforced the findings of the SPIN and ALIFE studies (de Jong et al. 2014). Therefore, the current guidelines recommend against the use of antithrombotic therapy in women with unexplained recurrent pregnancy losses ([4]; Royal College of Obstetricians and Gynaecologists 2011).

Thrombocytopenia in Pregnancy

Case 1

A 32-year-old primigravida is noted to have a platelet count of 54,000 per μl during her first prenatal visit at 8 weeks of gestation. She is asymptomatic and denies any bleeding symptoms. Her past medical history and family history are unremarkable; in particular, there is no history of thrombocytopenia. Her physical exam is normal with no evidence of bleeding gums or a petechial rash. A white blood cell count is 9,000 per μl and hemoglobin 14 g per dl. Other routine antenatal labs are normal, including viral studies for HIV, HBV, and HCV. Serologic testing for *Helicobacter pylori* is negative. Her serum immunoglobulins are normal (IgG 850 mg per dl

(normal 650–1,400), IgM 45 mg per dl (normal 30–60), and IgA 120 mg per dl (normal 50–200)), and an antinuclear antibody (ANA) screening test is negative. In the absence of symptoms, she is monitored conservatively with monthly platelet counts. She remains stable until gestation week 32 when her platelet count drops to 38,000 per μl. Weekly monitoring is initiated at this time. At week 37, with a platelet count of 22,000 per μl, she is administered a total of 2 g per kg of intravenous immunoglobulin (IVIG) over 2 days and simultaneously started on 10 mg of prednisone a day. A rapid recovery ensues with the platelet count increasing to 130,000 per μl after 2 days of IVIG therapy and remaining stable. Epidural anesthesia is safely administered at the onset of labor at week 39 resulting in the uncomplicated birth of a female neonate with a cord platelet count of 225,000 per μl. Prednisone is tapered over the next 2 weeks. Her platelet count is noted to be 180,000 per μl on routine follow-up at 4 weeks postpartum.

Clinical Impression Immune thrombocytopenia (ITP) in pregnancy

Discussion of Management Thrombocytopenia (platelet count < 150,000 per μl) affects about 8–10 % of all pregnancies [13]. A more stringent International Working Group definition of thrombocytopenia (platelet count < 100,000 per μl) limits this occurrence to about 1 % [78]. Table 4 enumerates causes of thrombocytopenia in pregnancy and their basic clinical characteristics.

Gestational Thrombocytopenia and Immune Thrombocytopenia

Gestational thrombocytopenia accounts for about 80 % of thrombocytopenia in pregnancy [12]. With a typical onset in the second to third trimester of pregnancy, most cases are mild (platelet count > 80,000 per μl), rarely < 50,000 per μl. Frequency increases as pregnancy progresses and so does severity of thrombocytopenia. Although gestational thrombocytopenia is thought to be secondary to increased clearance and hemodilution, similar to gestational anemia, it is not an expected occurrence in a pregnancy unlike anemia. This does not impact neonatal platelet count and resolves in the early postpartum period with a tendency to recur in subsequent pregnancies.

Thrombocytopenia occurring in the first trimester, especially with a history of thrombocytopenia outside of pregnancy or neonatal thrombocytopenia, is more consistent with immune thrombocytopenia (ITP) [31]. ITP is the second most common cause of isolated thrombocytopenia in pregnancy accounting for approximately 3 % of cases (Sainio et al. 2000). Both gestational thrombocytopenia and ITP are diagnoses of exclusion, but a platelet count of <50,000 per μl is more consistent with the latter or with other rarer causes of thrombocytopenia. A laboratory evaluation of moderate to severe thrombocytopenia (platelet count < 50,000 per μl) is carried out to rule out systemic disorders, both pregnancy specific and general, and diagnose secondary causes of ITP. This workup includes complete blood counts, evaluation of the peripheral blood smear, basic coagulation tests (prothrombin time, partial thromboplastin time, and fibrinogen), complete metabolic profile, viral studies

Table 4 Typical characteristics of thrombocytopenic disorders of pregnancy

Cause	Prevalence	Clinical characteristics		
		Onset	Severity (platelet count per μl)	Characteristics
Isolated thrombocytopenia				
Gestational thrombocytopenia	~80 %	Second to third trimester	>80,000	No bleeding No fetal thrombocytopenia Spontaneous resolution
Immune thrombocytopenia (ITP)	~3 %	Anytime (typically predates pregnancy)	<100,000	Bleeding and fetal thrombocytopenia possible Treatment for severe cases
Drug-induced thrombocytopenia	<1 %	Anytime	<100,000	Resolution upon discontinuation of the offending drug
Congenital thrombocytopenia	<1 %	Predates pregnancy	<100,000	Bleeding and fetal thrombocytopenia possible
Type IIb vWD	<1 %	Thrombocytopenia often worsens with pregnancy	<100,000	Bleeding possible
Systemic disorders				
Preeclampsia	15–20 %	Mid-second to third trimester	>50,000	No bleeding No fetal thrombocytopenia
HELLP syndrome	<1 %	Mid-second to third trimester	>50,000	Bleeding rare No fetal thrombocytopenia
Acute fatty liver of pregnancy	<1 %	Late third trimester	<100,000	Often associated with DIC No fetal thrombocytopenia
TTP/HUS	<1 %	Anytime	<50,000	Thrombosis and bleeding possible No fetal thrombocytopenia
Antiphospholipid antibody syndrome	<1 %	Anytime	<100,000	Thrombosis and pregnancy loss possible
Viral syndromes (EBV, CMV, HIV, HCV, HBV)	<1 %	Anytime	<100,000	Spontaneous resolution (can also be associated with ITP)

Modified from Gernsheimer et al. [31]

(HIV, HBV, HCV), antiphospholipid antibody syndrome screen (lupus anticoagulant, anticardiolipin antibodies, and β2-glycoprotein-1 antibodies), and, if indicated based on history of hemorrhage, a von Willebrand disease (vWD) panel to rule out type IIB vWD. A discussion of management of ITP in pregnancy follows, with other disorders discussed at the end of this section.

In the absence of randomized trials in this field, guidelines on monitoring and management of thrombocytopenia in pregnancy are based on lower levels of evidence and clinical reasoning [61]. The threshold to monitor platelet counts more frequently than routine prenatal visits is moderate thrombocytopenia (platelet count < 80,000/ μl). Initially counts are obtained every 2–4 weeks. If the platelet count is >30,000 per μl, monthly monitoring until gestation week 34 is appropriate, at which time the frequency is increased to weekly assessments. Table 5 summarizes the American Society of Hematology guidelines for the management of ITP in pregnancy [61]. Treatment is deemed necessary in the first two trimesters for platelet counts of <10,000 per μl or symptomatic thrombocytopenia or for any procedures (a platelet count of ≥50,000 per μl is considered adequate for procedures). From gestation weeks 34–36, treatment is indicated to keep platelet counts over 50,000 per μl in preparation for labor and delivery [69].

Corticosteroids and IVIG are first-line agents for the treatment of ITP in pregnancy as listed in Table 5 [61, 69]. There are no randomized trials or large prospective cohorts of treatment of pregnancy-associated ITP to back evidence-based management. Prednisone is considered safe in pregnancy, although its use in first trimester may be associated with increased risk of cleft lip and palate [66]. Additionally, its use is associated with increased maternal weight gain, hyperglycemia, and worsening hypertension [48]. Thus, the lowest dose that achieves a hemostatically effective platelet count can be considered, such as prednisone 10–20 mg orally daily. Intravenous immunoglobulin (IVIG) 2 g per kg administered over 2 days, with or without prednisone, is an alternative particularly when a more rapid recovery in platelet count is desired such as close to term or for a procedure or when there is a less than adequate response to prednisone. IVIG has the same potential adverse effects here as in the nonpregnant population which includes thrombosis and severe headache.

Table 5 Summary of American Society of Hematology guidelines for medical management of ITP in pregnancy

Treatment indications	Platelet count < 10,000 per μl Platelet count < 30,000 per μl in second and third trimester Symptomatic ITP
First-line agents	Prednisone 10–30 mg per day IVIG 2 g per kg over 2 days
IVIG indications	Steroid failure Initial treatment: platelet count < 10,000 per μl third trimester Initial treatment: platelet count < 30,000 per μl and bleeding
Safe platelet count for delivery	>50,000 per μl
Mode of delivery	Based on obstetric indications

Adapted from Gernsheimer et al. [31]

The options for refractory ITP during pregnancy are limited. Splenectomy can be safely performed in the second trimester but is rarely necessary. Anecdotal reports of successful use of anti-D immunoglobulin in non-splenectomized Rh-positive patients [58] and azathioprine [2] are also available, although these agents have potential fetal toxicities. Intravenous anti-D immunoglobulin may cause hemolytic anemia in both mother and fetus and must be used cautiously. There is ample evidence of safe use of azathioprine in pregnancy in transplant and lupus [68], but a concern for preterm labor and intrauterine growth restriction has been raised. Cyclosporine also appears to be safe in pregnancy when used in inflammatory bowel disease and transplant settings [75], but its use in ITP in pregnancy has not been reported. Delayed onset of azathioprine and cyclosporine limits their usefulness as steroid-sparing agents. Successful rituximab use has also been reported [28], but it is not recommended for use in pregnancy as it crosses the placenta and may cause neonatal immunodeficiency. One retrospective series of 153 pregnancies associated with maternal rituximab exposure was associated with 90 live births, of which 22 were premature, one associated with neonatal death, 11 hematological abnormalities, and two congenital deformities [17]. As the maternal conditions were serious, it is difficult to generalize this literature. Thrombopoietin receptor agonists are contraindicated in pregnancy, as animal studies were associated with postimplantation losses and increased mortality with romiplostim.

Serious maternal hemorrhage remains uncommon in vaginal deliveries even with severe thrombocytopenia, and unusual with platelet counts > 50,000 per μl. Two large cohorts of ITP in pregnancy [27, 90] showed that only about 31–33 % of pregnant patients with ITP required treatment, and 74–82 % of pregnancies resulted in normal deliveries. A total of 37.5 % of patients in the cohort of Webert et al. received epidural anesthesia, most with platelet counts >75,000 per μl. Thus, the mode of delivery is based on obstetric indications. When platelet counts remain <50,000 per μl despite treatment, platelet transfusions can be considered but generally result in minimal to no platelet increase due to antibody-mediated consumption of transfused platelets. Epidural anesthesia and analgesia are generally considered safe for a platelet count greater than 75,000 per μl, but local practices vary [5].

Fetal thrombocytopenia (platelet count < 100,000 per μl) complicates 22–28 % of the cases of ITP in pregnancy [27, 90]. There is no clear correlation between the severity of maternal thrombocytopenia and development of neonatal thrombocytopenia, but moderate to severe neonatal thrombocytopenia (platelet count < 50,000 per μl) occurs in about 10 % of the cases [90]. The best predictor of the severity of neonatal thrombocytopenia is its occurrence in an earlier pregnancy [13]. The risk of major hemorrhage, particularly intracranial hemorrhage, is rare. A small, randomized clinical trial revealed that antenatal steroids do not impact neonatal platelet count or outcomes and, hence, should not be used for this purpose [18]. Neonatal platelet count is tested at the time of birth, preferably via peripheral or cord blood sampling, and further monitoring depends on the severity of thrombocytopenia. Typically, the platelet count reaches a nadir 2–5 days after birth and normalizes in a week.

The risk of ITP is higher in subsequent pregnancies but mothers with a prior history of ITP are less likely to require treatment for ITP in subsequent pregnancies when compared to those with a new diagnosis [90].

Other Causes of Thrombocytopenia in Pregnancy

Preeclampsia is the second most common cause of thrombocytopenia in pregnancy defined as hypertension (systolic > 140 mmHg or diastolic > 90 mmHg) that develops after gestation week 20 associated with proteinuria (>0.3 g per 24 h) [10]. Thrombocytopenia complicates about 50 % of cases of preeclampsia, but platelet count < 50,000 per μl occurs only in <5 % of cases [57]. HELLP syndrome defined as Hemolysis (peripheral smear schistocytosis, LDH > 600 U per L, or total bilirubin > 1.2 mg per dL) Elevated Liver enzymes (aspartate transaminase > 70 U per L), and Low Platelet count (<100,000 per μl) occurs in <1 % of pregnancies, complicating 10–20 % of cases of severe preeclampsia [44]. Acute fatty liver of pregnancy (AFLP) is a rare life-threatening condition occurring in late third trimester with many overlapping features of severe preeclampsia and HELLP syndrome. In addition to severe abnormalities in liver function (total bilirubin > 5 mg per dL), there is evidence of moderate to severe normocytic anemia, thrombocytopenia, hypoglycemia, metabolic acidosis, and acute kidney injury. Severe thrombocytopenia with platelet counts < 20,000 per μl is uncommon in severe preeclampsia/eclampsia, HELLP syndrome, and AFLP. The specific management of these conditions is discussed in chapters dedicated to these conditions, but delivery of fetus is the mainstay of treatment. The use of steroids in HELLP syndrome remains controversial except for fetal lung maturity [92]. Plasma exchange has been shown to improve outcomes in severe HELLP syndrome and AFLP, but the evidence is limited [25, 54]. Disseminated intravascular coagulopathy (DIC) can often complicate these conditions, and its management does not differ from DIC in non-pregnancy patients.

Thrombotic thrombocytopenic purpura (TTP) is a rare life-threatening condition characterized by microangiopathic hemolytic anemia, thrombocytopenia, fever, neurologic abnormalities, and acute kidney injury. Although not specific to pregnancy, TTP is more common in women of reproductive age, with increased frequency in pregnancy [85]. Up to 25 % of cases of TTP have been described in association with pregnancy. The pathophysiology of TTP involves deficiency of von Willebrand factor (vWF) cleaving enzyme ADAMTS13 (A Disintegrin And Metalloproteinase with ThromboSpondin type 1 motif, member 13). Both congenital deficiency (Upshaw-Schulman syndrome) and acquired cases secondary to neutralizing autoantibodies can manifest for the first time during pregnancy. Atypical hemolytic uremic syndrome (HUS), associated with congenital defects in the alternative complement pathways, can also complicate pregnancy. As compared to TTP, renal dysfunction is more common in HUS. The management of these disorders in pregnancy is similar to that of nonpregnant patients [30]. Thus, plasma exchange is the mainstay of the treatment with frequency of exchanges guided by serum LDH and platelet counts. Eculizumab has not been used for pregnancy-associated atypical HUS. The risk of relapse in subsequent pregnancies is 100 % in congenital cases

Key Points

- Thrombocytopenia occurs in approximately 10 % of all pregnancies; most cases are mild and secondary to self-limiting gestational thrombocytopenia.
- Immune thrombocytopenia occurs in approximately 3 % of all pregnancies; the management of ITP in pregnancy is similar to nonpregnant cases with low-dose corticosteroids and IVIG being the backbone of therapy.
- The mode of delivery in ITP is driven by obstetric indications; the goal platelet is >50,000 per μl for delivery.
- A self-limiting fetal thrombocytopenia can complicate ITP in pregnancy; the risk of intracranial hemorrhage is low and typically occurs after delivery.
- Preeclampsia, HELLP syndrome, and AFLP are pregnancy-specific systemic syndromes that can result in mild to moderate thrombocytopenia and occasional DIC.
- TTP and atypical HUS are thrombotic microangiopathies that can complicate pregnancies with a high risk of recurrence in subsequent pregnancies.

and as high as 20 % in acquired cases of TTP/HUS [72]. Hence, subsequent pregnancies require careful monitoring from early pregnancy.

Antiphospholipid syndrome is described elsewhere in this chapter. SLE can be associated with secondary ITP, the management of which is similar to primary ITP. Viral syndromes and drug-induced thrombocytopenia are self-limiting conditions. Type 2b vWD is a rare inherited bleeding disorder associated with mild thrombocytopenia. Increased affinity of platelet glycoprotein Ib to vWF in this condition causes accelerated clearance of vWF and platelets. Women with this disorder may first be recognized during pregnancy when thrombocytopenia becomes more pronounced with gestation [47] as the production of vWF increases. Occasionally, platelet counts can decrease < 20,000 per μl, usually close to term, with rapid recovery after delivery [38]. vWF panel which shows a normal vWF antigen levels, decreased vWF activity, decreased high-molecular-weight vWF multimers, and an abnormally increased low-dose ristocetin-induced platelet aggregation aids in the diagnosis. Levels of vWF and factor VIII should be increased to > 50 IU per dL to cover delivery and any surgical procedures and can be achieved with administration of purified vWF/factor VIII concentrate. Platelet transfusions may be required at the time of the delivery for platelet counts < 50,000 per μl.

Case 2

A 30-year-old G5P0 with a history of recurrent pregnancy losses is seen in hematology clinic at 10 weeks of gestation. Her first pregnancy resulted in a spontaneous abortion of a twin pregnancy at 6 weeks; second, an intrauterine fetal demise at 24

weeks, fetal necropsy associated with liquefaction of intracranial and other body cavities; third, a spontaneous abortion at 13 weeks; fourth and last, an intrauterine fetal demise at 31 weeks associated with fetal intracranial hemorrhage, erythroblastosis, and hydrops. Patient does not have any significant past medical history, and a complete workup of recurrent pregnancy loss is found to be normal except for platelet antigen incompatibility. She is identified as human platelet antigen-1a (HPA-1a) negative with father being HPA1a positive, homozygously. In addition, anti-HPA-1a antibodies are detected in maternal serum. Patient is initiated on IVIG 2 g per kg per week, and prednisone 60 mg daily added at 20 weeks. An elective Cesarean section is performed at 34 weeks after the administration of betamethasone for fetal lung maturity. A female fetus is delivered with cord blood platelet count 14,000 per μl. The neonate is treated with HPA-1a negative platelets to keep platelet count > 30,000 per μl. A head ultrasound is normal and thrombocytopenia resolves in a week after delivery.

Clinical Impression Fetal and neonatal alloimmune thrombocytopenia (FNAIT)

Discussion of Management FNAIT is a devastating disease with an incidence of ~1 in 1,000 to 2,000 pregnancies [8]. It results from alloimmune destruction of fetal platelets by maternal antibodies directed against platelet cell membrane antigens inherited from the father, similar to hemolytic disease of the newborn. In contrast to hemolytic disease of newborn, platelet alloimmunization can occur even in the first pregnancy in FNAIT, and, hence, it is common for the firstborns to be affected. FNAIT is suspected when either neonatal thrombocytopenia occurs within the first 24–48 h after birth or fetal demise resulting from intracranial hemorrhage. Intracranial hemorrhage occurs in about 20 % of cases with 80 % of these occur before 30 weeks of gestation, documented as early as 20 weeks [89].

The laboratory diagnosis of FNAIT is based on the identification of the offending antigen by typing of maternal and paternal platelet antigens and serological detection of maternal anti-platelet alloantibodies. The prevalence of HPA-1a phenotype in Caucasians is about 2.5 %, accounting for 75 % of the cases of FNAIT, followed by HPA-5b and HPA-3a [91]. In Asians, HPA-4b is involved more often. HLA-DR antigen B3*0101 positivity increases the risk of FNAIT in HPA-1a negative mothers.

The management of an infant with neonatal thrombocytopenia depends on its severity. Compatible platelets are transfused for severe thrombocytopenia (<30,000 per μl) with or without IVIG. Screening head ultrasound is obtained to rule out intracranial hemorrhage. Thrombocytopenia usually resolves within 1–2 weeks of birth [6]. Due to recurrence of FNAIT with increasing severity in subsequent pregnancies with incompatible fetus, the management of subsequent pregnancies is imperative. If father is homozygous for the implicated HPA, then the fetus will have a 100 % chance of possessing the antigen, whereas those with heterozygous fathers will have a 50 % chance. Chorionic villous sampling at 8–10-week gestation or amniotic fluid sampling at 18–20 weeks can help identify the fetus at risk in case of paternal heterozygosity, but these procedures carry their own risk of adverse events, particularly if the fetus is thrombocytopenic.

Table 6 Risk stratification and management of fetal and neonatal alloimmune thrombocytopenia

Risk group	Definition	Risk	Management		
			IVIG	Prednisone	Cesarean delivery
1	Previous fetal or neonatal thrombocytopenia or ICH of unknown etiology	Unknown	–	–	–
2	Previous FNAIT but no ICH	Standard	2 g/kg at 20 weeks[a]	0.5 mg/kg at 32 weeks	37–38 weeks
3	Previous FNAIT with ICH at or after 28 weeks gestation	High	1 g/kg at 12 weeks; 2 g/kg at 20 weeks[a]	0.5 mg/kg at 28 weeks	35–36 weeks
4	Previous FNAIT with ICH before 28 weeks gestation	Very high	2 g/kg at 12 weeks	1 mg/kg at 20 weeks	35–36 weeks

Modified from Pacheco et al. [64]
IVIG intravenous immunoglobulin, *FNAIT* fetal and neonatal alloimmune thrombocytopenia, *ICH* intracranial hemorrhages
[a]Alternatively 1 g/kg IVIG plus prednisone 0.5 mg/kg

Management is based on risk stratification with IVIG and steroids forming the basis of the treatment. Table 6 summarizes the risk groups and recommended management [64]. Randomized trials are lacking in this field and most data come from prospective and retrospective cohorts. A small, randomized trial compared low-dose IVIG (0.5 g per kg per week) to standard-dose IVIG (1 g per kg per week) in pregnant females with a history of FNAIT without intracranial hemorrhage and found no difference in outcomes [65]. Pregnancies with very high risk of FNAIT, as our patient, are commonly managed with IVIG 2 g per kg per week starting at 12 weeks of gestation, supplemented by prednisone 1 mg per kg daily at 20 weeks. An elective Cesarean delivery is carried out at 34–36 weeks. In a prospective cohort, no intracranial hemorrhage recurred in seven cases treated with this regimen [14].

Key Points
- FNAIT results from alloimmune destruction of fetal platelets by maternal antibodies directed against incompatible paternal antigens.
- The most commonly implicated platelet antigen is HPA-1a accounting for over 75 % of all cases in Caucasians.
- The most devastating consequence of FNAIT is fetal intracranial hemorrhage occurring in approximately 20 % of all cases, as early as 20 weeks of gestation.
- Management is risk stratified with IVIG and steroids being the backbone of therapy.

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Infectious Diseases in Pregnancy

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Cases UTI, Influenza, TORCH, Parvovirus and Lyme disease

Objectives

To understand the diagnosis, management, and complications of asymptomatic bacteriuria, influenza, TORCH infections, parvovirus, and Lyme disease in pregnant women. To understand the potential effects of these infections in the pregnant woman and her fetus and to review the management of women exposed to or infected with any of these infections. Infection during pregnancy is a broad topic to cover but often will be seen in pregnancy.

Case #1

A 28-year-old female presents to her obstetrician for her 18-week prenatal visit. She has had a healthy pregnancy thus far. Today, she complains of burning with urination. She has noticed increased frequency and urgency but thought it was a normal part of pregnancy. She denies any fevers, chills, back pain, nausea, or vomiting. Her urinalysis is notable for + leukocyte esterase, +nitrite, and >150 WBC/high-powered

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field. Her urine culture is pending at the time of the appointment and she is sent home on oral amoxicillin. Two days later she calls her physician with complaint of nausea, fever to 38.5 C, chills, and back pain. Her urine culture is now growing >100,000 colony-forming units/ml (cfu/ml) of *E. coli* with resistance to amoxicillin. How should this case be managed?

Introduction

Asymptomatic bacteriuria (ASB), cystitis, and pyelonephritis are common occurrences in pregnancy that can be challenging to manage and have the potential to cause serious complications. Physiologic changes in pregnancy, including ureteral dilatation, increased bladder volume, decreased bladder, and ureteral tone, all contribute to urinary stasis and can lead to urinary tract infections (UTI) [1]. Asymptomatic bacteriuria occurs in up to 9 % of pregnant woman and can lead to a symptomatic urinary tract infection or pyelonephritis in 30–40 % of patients if left untreated [2]. Cystitis and pyelonephritis can occur in up to 2 % of pregnancies [3]. Because of the increased risk of UTI in pregnancy, the higher likelihood of progression to upper tract disease, and association with adverse pregnancy outcomes such as intrauterine growth restriction (IUGR), preeclampsia, preterm delivery, and low birth weight infants, screening for asymptomatic bacteriuria and appropriate treatment and management of cystitis and pyelonephritis are important for both mother and baby [4].

Screening and Diagnosis

The Infectious Disease Society of America (IDSA) has published guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults [2]. For asymptomatic women, bacteriuria is defined as two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts $\geq 10^5$ cfu/mL in culture. However, in clinical practice one midstream, clean catch specimen with the above criteria would be considered positive and should be treated in the pregnant patient. Because of an increased risk of complications, the IDSA recommends routine screening for asymptomatic bacteriuria at least once in early pregnancy with a urine culture and treatment if results are positive. This recommendation is based on the increased risk of progression to a symptomatic urinary tract infection or pyelonephritis in 30–40 % of patients. In addition, it is known that antibiotic treatment of asymptomatic bacteriuria in pregnancy is associated with a significant decreased risk of both pyelonephritis and the frequency of low birth weight infants and preterm delivery [5–7]. The exact timing of screening does vary based on organization. The IDSA recommends a urine culture in “early pregnancy.” The US Preventative Services Task Force and The American College of Obstetrics and Gynecology

(ACOG) recommend screening with a urine culture between 12 and 16 weeks of gestation or at the first prenatal visit [8]. In general, rescreening later in pregnancy is not warranted in low-risk patients.

The diagnosis of a urinary tract infection and pyelonephritis differs from ASB only by symptomatology. The presence of dysuria, urgency, and increased urinary frequency should make one consider a diagnosis of UTI. The addition of fever, nausea, vomiting, back pain, or costovertebral angle tenderness on exam should raise the suspicion for pyelonephritis. As the above, a urine culture should be sent with $\geq 10^5$ cfu/mL, the accepted standard for significant bacteriuria. However, lower colony counts such as 10^3 cfu/mL in symptomatic patients with a UTI can occur. Pyuria with >10 leukocytes/microL, hematuria, and a positive nitrite test may also be seen on urinalysis in the setting of a UTI or pyelonephritis. However, it is of increased importance to send a urine culture as well as this can help guide antibiotic choice which is more limited in the pregnant patient. In this case, the initial presentation, urinalysis, and culture support the diagnosis of cystitis. The development of nausea, back pain, and fever is consistent with pyelonephritis and likely occurred due to antibiotic resistance to the initial antibiotic prescribed.

Microbiology

As is the case with nonpregnant women, the majority of urinary tract infections in pregnant women are caused by Enterobacteriaceae, especially *Escherichia coli*, *Klebsiella*, and *Enterobacter* spp. which account for almost 90 % of infection [3]. Other pathogens include *Proteus mirabilis*, *group B Streptococcus* (*GBS*), and *Staphylococcus saprophyticus*. GBS vaginal colonization is associated with preterm rupture of membranes, preterm labor, and neonatal sepsis. However, it can also be a cause of UTI in approximately 5 % of patients [1]. One randomized clinical trial found a significant reduction in rates of premature rupture of membranes and preterm delivery in women with GBS bacteriuria who were treated with penicillin when compared to placebo [9]. Whether GBS bacteriuria is equivalent to GBS vaginal colonization is unclear. However, if GBS bacteriuria is seen at any point in the pregnancy prophylactic antibiotics during labor is recommended.

Complications in Pregnancy

The morbidity associated with asymptomatic bacteriuria, cystitis, and pyelonephritis is significant. Asymptomatic bacteriuria has been associated with IUGR, preterm delivery, and low birth weight infants [2, 10, 11]. In a large, retrospective population-based study of nearly 200,000 deliveries, cystitis was found to be independently associated with preterm delivery, preeclampsia, IUGR, and cesarean delivery [4]. Acute pyelonephritis during pregnancy carries an increased risk of complications

Table 1 Antibiotics for asymptomatic bacteriuria and cystitis in pregnancy

Antibiotic	Dose	Duration	Notes
Nitrofurantoin	100 mg orally every 12 h	Five to seven days	Does not achieve therapeutic levels in the kidneys so should not be used if pyelonephritis is suspected.
			Avoid use during the first trimester if other options are available.
Amoxicillin	500 mg orally every 8 h	Three to seven days	Resistance may limit its utility among gram-negative pathogens.
Amoxicillin-clavulanate	500 mg orally every 8 h	Three to seven days	
Cephalexin	500 mg orally every 6 h	Three to seven days	
Cefpodoxime	100 mg orally every 12 h	Three to seven days	
Fosfomycin	3 g orally as single dose		Does not achieve therapeutic levels in the kidneys so should not be used if pyelonephritis is suspected.
Trimethoprim-sulfamethoxazole	800/160 mg (one double-strength tablet) every 12 h	Three days	Avoid during the first trimester and at term.

The durations listed in the table are based on data from studies conducted in both nonpregnant and pregnant women

such as ARDS, anemia, renal dysfunction, preterm labor, IUGR, premature rupture of membranes (PROM), preeclampsia, and septic shock [4, 12–14]. In summary, infections of the urinary tract from ASB to pyelonephritis are associated with adverse outcomes not only for the mother but also the neonate.

Treatment

The treatment of ASB in pregnancy is outlined in Table 1. As with all urinary tract infections, management should be tailored to the organism and susceptibility pattern seen on culture. In pregnancy, attention must also be paid to the safety of the antimicrobial depending on the stage of pregnancy. Antibiotics frequently used include nitrofurantoin, beta-lactams, cephalosporins, trimethoprim-sulfamethoxazole, and fosfomycin. A short course of antibiotics (3–7 days) is frequently used although the optimal duration of antibiotics for ASB is unclear. A Cochrane systematic review of 13 studies found a trend to lower rate of bacterial clearance in patients treated with a single-dose regimen when compared to short course (4–7 days) [15]. One antibiotic, fosfomycin, however, has been shown in a single dose to have equivalent rates of cure to 7-day courses of other antibiotics, including nitrofurantoin [16]. Unfortunately, up to 30% of women can fail to clear their bacteriuria after a course of antibiotics [3].

Table 2 Parenteral regimens for empiric treatment of pyelonephritis in pregnancy

Antibiotic	Dose, interval
Mild to moderate pyelonephritis	
Ceftriaxone	1 g every 24 h
Cefepime	1 g every 12 h
Aztreonam[a]	1 g every 8 h
Ampicillin	1–2 g every 6 h
PLUS	
Gentamicin[b]	1.5 mg/kg every 8 h
Severe pyelonephritis with an impaired immune system and/or incomplete urinary drainage	
Ticarcillin-clavulanate	3.1 g every 4 h
Piperacillin-tazobactam	3.375 g every 6 h
Meropenem	500 mg every 8 h
Ertapenem	1 g every 24 h
Doripenem	500 mg every 8 h

Doses are for patients with normal renal function. If methicillin-resistant *S. aureus* (MRSA) is known or suspected, see treatment regimens outlined separately in topics addressing MRSA management
[a]Alternative in the setting of beta lactam allergy
[b]Aminoglycosides have been associated with fetal ototoxicity; this regimen should be used only if intolerance precludes the use of less toxic agents

Because of this, it is recommended to repeat a urine culture shortly after treatment to document clearance and periodically throughout the pregnancy [2].

The treatment of cystitis in pregnancy is similar to ASB. However, the provider may not have the urine culture results at the time of diagnosis, and empiric antibiotics can be chosen based on coverage of common organisms such as Enterobacteriaceae. Again, a 3–7-day course is recommended with a repeat culture after completing antibiotics to confirm sterilization. Shorter courses of antibiotics have the potential to minimize side effects and complications for the mother such as *Clostridium difficile*-associated diarrhea and also to decrease antimicrobial exposure for the fetus. According to a recent Cochrane review, there is no significant difference in outcomes for cure rates, recurrent infection rate, and incidence of preterm delivery or rupture of membranes with any one particular antibiotic over another [17]. Please see Table 1 for antimicrobial options during pregnancy. Some antibiotics that are typically used to treat UTI in the nonpregnant patient, including fluoroquinolones and tetracyclines, are contraindicated in pregnancy due to potential effects on musculoskeletal and dental development, respectively.

As described above, pyelonephritis in pregnant women has the potential for serious morbidity and appropriate treatment is paramount. Because of this, initial management of pyelonephritis in the pregnant patient should begin as an inpatient. The case patient above should start parenteral antibiotics and transition to oral antibiotics when afebrile for 24–48 h. Some options for initial therapy could include a parenteral cephalosporin such as cefazolin or ceftriaxone. See Table 2 for additional antibiotic choices. Of note, nitrofurantoin and fosfomycin do not achieve adequate tissue penetration and should not be used for the treatment of pyelonephritis. Because recurrent pyelonephritis can occur in up to 8% of patients, ongoing

suppression with antibiotics such as nitrofurantoin 50–100 mg or cephalexin 250–500 mg daily should be considered for the duration of the pregnancy in cases like our patient [3, 10, 18]. In summary, urinary tract infections are frequently encountered during pregnancy, and risk of progression to upper tract disease is increased. Appropriate workup and treatment is critical to reduce the risk of pyelonephritis and adverse pregnancy outcomes.

Case #2 Influenza and Pregnancy

A 27-year-old woman, currently 20 weeks pregnant, presents to her primary care physician for a routine visit in October. She is offered the flu vaccine but declines, concerned that she always gets "the flu" with the influenza vaccine, and since she is pregnant, she does not want to risk getting sick. She also heard that vaccines might harm her fetus.

Eight weeks later, she returns with a fever of 102 F (39 C) and diffuse myalgias for the last 3 days. A point-of-care test for influenza A is positive. She asks about medications that "cure" this disease. Should she be prescribed oseltamivir?

Discussion

Influenza is caused by three members of the family Orthomyxoviridae. They are divided into influenza A, B, and C. Influenza A is the most common cause of severe disease and epidemics. Influenza A viruses are characterized by their hemagglutinin (H) and neuraminidase (N) surface antigens.

Influenza epidemics occur annually to triennially and are of variable severity. Pregnant patients were overrepresented in admissions to hospital and intensive care in the 2009 pandemic [19]. The reasons for this increased severity of disease are unknown, but might include altered immune response and cardiopulmonary physiology.

Influenza is characterized by a febrile respiratory illness that starts abruptly with chills, high fevers (normally >102 F), myalgia, and headaches. Associated respiratory symptoms include cough, nasal discharge, and sore throat, lasting 5 days to a week. Nausea and vomiting seems to be more common in pregnant patients [20]. While influenza is mostly a self-resolving illness, in older patients and in a disproportionate percentage of pregnant patients, it can be complicated by viral pneumonia, myocarditis, and myositis. Secondary bacterial pneumonia (caused by *S. aureus*, *Streptococcus pneumoniae*, and *H. influenzae*) is a feared complication.

Studies done during influenza pandemics reveal that this disease increases the risk for spontaneous abortion and preterm birth [21]. Fetal malformations have also been associated with influenza, but if this is a result of the disease itself or hyperthermia is yet unknown. This is clear only in the vulnerable time of the early first trimester usually less than 10 weeks.

Clinical diagnosis alone in the setting of an epidemic is accurate approximately 80 % of the time. Laboratory diagnosis in the outpatient setting can be made by either a rapid viral antigen with a sensitivity varying between 50 and 80 % or a molecular diagnostic test using PCR amplification with sensitivity of around 90 %.

Influenza Vaccination in Pregnancy

The most effective strategy for preventing influenza in pregnant women is immunization. Benefit to the infant has also been demonstrated as maternal immunization reduces respiratory illnesses with fever in infants in the first 6 months of life [22].

Both the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) and the American College of Obstetricians and Gynecologists recommend that all pregnant adults receive an annual influenza vaccine. An inactivated and a live attenuated vaccine are available. Currently, the inactivated influenza vaccine should be given to pregnant women as soon as it is available, and it can be given at any point during gestation. The live intranasal influenza vaccine is not recommended for pregnant women, but can be given in the postpartum period. In the Northern Hemisphere, influenza occurs from October through May, and vaccines are available as early as late August.

A common misconception about the flu vaccine is that you can get the flu from the vaccine. This has been studied by two blinded, randomized trials that reported no difference between subjects that received the inactivated flu vaccine and placebo in terms of fever, headache, or muscle aches. Differences were seen in soreness and redness at the injection site among people who got the flu shot [22, 23]. The safety of influenza vaccination during pregnancy is supported by a multitude of studies [24, 25]. A second misconception is regarding thimerosal. Thimerosal is a mercury-containing preservative used in multidose vials of the influenza vaccine. There is no scientific evidence that thimerosal-containing vaccines cause adverse effects in children born to women who received vaccines with thimerosal [26]. However, thimerosal-free formulations of the vaccine are also available.

Treatment of Influenza

In the United States, oseltamivir and zanamivir are FDA Pregnancy Category C drugs, a result of the lack of studies to assess safety in pregnant patients. There is no evidence of adverse fetal outcomes with oseltamivir [27]. Expert opinion recommends prompt antiviral treatment for pregnant and postpartum (2 weeks postpartum) women with confirmed or suspected influenza [28]. Treatment should not be delayed pending laboratorial diagnosis. Early treatment within 48 h of symptom onset has been shown to decrease intensive care admission and mortality [29]. While the evidence for the later treatment is not as strong, treatment is still

recommended. Based on limited data, the dosing of antiviral therapy for treatment of influenza during pregnancy is 5 days, the same as in nonpregnant adults and non-immunocompromised patients.

In addition to antivirals, control of fever is essential in the treatment of influenza in this patient population as fever has been associated with worse fetal outcomes, especially in the first trimester. Of all antipyretics, acetaminophen has a long history of safe use in pregnancy and is widely used.

Infection Control in the Outpatient Setting

When visiting their healthcare providers, pregnant women with suspected or confirmed influenza infection should be given facemasks and instructed on precautions to decrease transmission.

Healthy newborns of mothers with confirmed or suspected influenza should be considered exposed and should follow hospital infection control guidelines. In the wake of the 2009 H1N1 pandemic, the CDC recommends temporary separation of a mother with suspected or confirmed influenza from her newborn until all criteria were met: the mother had received antiviral medications for at least 48 h, was afebrile without antipyretics for 24 h, and is able to control her cough and respiratory secretions. Once the mother and infant are able to initiate close contact, standard precautions and respiratory hygiene apply. The mother's milk should be fed to the newborn by a healthy caregiver until criteria are met for close contact. Unlike other body fluids and secretions, human milk is not considered a body fluid to which standard, droplet, or contact precaution recommendations apply. Milk from an infected mother is not considered infectious. Antiviral medication use by the mother is not a contraindication to breastfeeding. Antiviral chemoprophylaxis of the infant is currently not recommended, due to limited data on safety and efficacy [30] (Fig. 1).

Antiviral agent	Dosage	Approved for	Adverse events
Oseltamivir (Tamiflu®)	75 mg twice a day, oral	14 days and older	Nausea, vomiting, neuropsychiatric disturbances, skin rash
Zanamivir (Relenza®)	10mg (2 inhalations) twice a day	7 years and older, with no history of COPD or asthma	Diarrhea, nausea, sinusitis, cough, dizziness. Severe allergic reaction (airway or facial edema)

Fig. 1 Common antivirals active against influenza A and B

Case #3 TORCH Infections

Ms. B. is a 33-year-old G2P2 13-week pregnant woman that presents to an urgent care center in August with a history of 3 days of sore throat with cervical lymphadenopathy, cough, fever, and malaise. She reports that she has been febrile up to 100.6 F (38 °C). She denies any rashes, recent travel, raw food ingestion, or sick contacts. She has two small cats that were adopted about 3 months ago. She is a kindergarten teacher. Per the patient, a prenatal screen for human immunodeficiency virus (HIV) and syphilis was negative. She is immune against rubella. She is concerned about toxoplasmosis, as her obstetrician had counseled her about this condition and the risk for fetal disease. What tests should be obtained? What is the risk for the fetus? What are some of the other infections associated with congenital syndromes and fetal abnormalities?

Congenital and Perinatal Infections

Congenital and perinatal infections are important causes of fetal mortality and child morbidity. They are grouped in an acronym, TORCH, that reflects a group of infections with common disease manifestations in the fetus and newborn that includes dermal, ocular, and neurological manifestations such as jaundice, purpura, and visual and hearing loss. The TORCH complex encompasses *Toxoplasma gondii*, syphilis, rubella, cytomegalovirus, and herpes simplex virus.

Congenital Toxoplasmosis

Toxoplasma gondii is a protozoan intracellular parasite acquired from ingestion of infected bradyzoites in undercooked, cured, or raw meat or from using kitchen supplies contaminated with raw meat. Soil and water can also be infected by cat feces which can contain oocysts. Because cats develop immunity after primary infection and oocysts are only shed in a primary infection, kittens are a particular risk to susceptible hosts such as pregnant women and patients with immunodeficiencies.

If toxoplasmosis is acquired for the first time during pregnancy, vertical transmission to the fetus via the placenta occurs during the acute parasitemic phase. Symptoms of acute maternal infection can vary from none to fever, headache, malaise, and myalgias, mimicking a mononucleosis-like illness.

Diagnosis is based on serological conversion from negative to positive IgG or IgM antibodies for *T. gondii*. While this is possible in countries where prenatal and serial Toxoplasma serologies are obtained, there is no current recommendation for prenatal Toxoplasma serologies in the United States. Reasons for this include the low incidence of congenital toxoplasmosis and the low specificity of the *T. gondii* serological testing. Some states recommend newborn testing for *T. gondii* IgM [31].

A more common clinical scenario that might confront a physician practicing in the United States is a positive isolated IgM in the context of an unknown prior serological status in a pregnant patient. IgM reactions can be nonspecific or reflect prior infection as it may persist for more than 1 year. In the case of an isolated positive IgM with a negative IgG and unknown prior immune status, a repeat serology should be obtained in 2 weeks to assess if there is IgG seroconversion, hence eliminating the possibility of a nonspecific IgM reaction. If the repeat test is positive for IgM and IgG, seroconversion is documented and treatment should be initiated. In patients with initial positive IgM and IgG or a persistent positive IgM, a reference laboratory should confirm the positive serology.

The risk for congenital toxoplasmosis increases with gestational age at the time of acute disease with a risk of transmission of around 15 % at 13 weeks and 71 % at 35 weeks [32]. Treatment is advocated for pregnant women with probable or definite seroconversion, and the regimen recommended depends on the gestational age and/or signs of fetal involvement. Fetal ultrasonography should also be obtained to assess for fetal abnormalities (hydrocephalus, brain or hepatic calcifications, splenomegaly, and ascites). Amniocentesis at 18 weeks with amniotic fluid PCR for *T. gondii* is recommended, but risk and benefits of this procedure should be discussed with the patient. For all cases of suspected congenital toxoplasmosis, consultation with a national expert is recommended (PAMF-TSL, Palo Alto Medical Foundation Toxoplasma Serology Laboratory or the National Collaborative Treatment Trial Study, in the US) [33].

Treatment with spiramycin is recommended by many investigators in the United States and Europe during the first 18 weeks of pregnancy. In the United States, spiramycin can be obtained after discussion with the Food and Drug Administration via a "compassionate use [IND]" program. This medication will not act on the fetus and will only clear the placenta of the parasite. It should be continued until delivery unless there is any evidence (ultrasound, amniotic fluid PCR) or suspicion of fetal involvement, which requires a switch from spiramycin to pyrimethamine and sulfadiazine on week 18 in order to prevent fetal disease. This regimen is avoided in the first 18 weeks due to the risk of teratogenicity from pyrimethamine. Folic acid (25 mg daily p.o.) should be given to prevent hematological toxicities. Weekly complete blood counts should be monitored and treatment discontinued if significant myelotoxicity.

Congenital Syphilis

Syphilis is caused by the spirochete, *Treponema pallidum*, and it can remain latent for years. Because this organism cannot be cultured using conventional techniques, diagnosis is based on clinical and serological data. Untreated syphilis during pregnancy, especially early syphilis, can lead to stillbirth, neonatal death, or infant disorders such as deafness, neurologic impairment, and bone deformities. Congenital syphilis (CS) can be prevented by early detection of maternal infection and treatment at least 30 days before delivery [34].

A recent report by the Centers for Disease Control and Prevention (CDC) warned of the increased rate in CS during the period 2005–2008 after years of steady decline. Multiple professional organizations, including the American College of Obstetricians and Gynecologists (ACOG) and the CDC, have recommended syphilis screening within the scope of a prenatal visit [34]. In high-incidence populations (sex workers, use of illicit drugs, human immunodeficiency virus infection, and no prenatal care), retesting during the third trimester (28th–30th week) is recommended. All patients who have syphilis should be offered testing for HIV infection.

Penicillin remains the mainstay of treatment, but duration and dosage depends on the phase at which syphilis is diagnosed. Syphilis can be classified as primary, secondary, and tertiary, based on initial symptom presentation. If asymptomatic (latent), it can be divided into early (less than 1 year since negative titers) or late (more than 1 year). Screening tests for syphilis are traditionally non-treponemal specific and include RPR (rapid plasma reaction) and VDRL (venereal disease research laboratory). Positive non-treponemal testing should be followed by confirmatory treponemal testing such as TPPA (*T. pallidum* particle agglutination assay) or FTA-ABS (fluorescent treponemal antibody absorption). If treponemal testing is negative, this may represent a transient biological false positive which can occur in pregnancy.

Primary syphilis is normally characterized by a painless chancre, involving the genital, perineal, anorectal areas, throat/lips, or hands. This normally occurs about 2–4 weeks postexposure and heals spontaneously. Treatment is benzathine penicillin G (BPG) 2.4 million units intramuscularly once. Secondary syphilis can have a broad range of systemic symptoms including rash that involves palms and soles, headache, fever, pharyngitis, and lymphadenopathy. It occurs about 2–8 weeks post resolution of the initial chancre. Treatment is identical to primary syphilis. The hallmark of tertiary syphilis is the formation of gummas (granulomatous lesions). These can occur anywhere but typical lesions involve the heart or large vessels and the central nervous system. Treatment for tertiary syphilis is with BPG 2.4 million units intramuscularly weekly for 3 weeks. If neurosyphilis is suspected, a 10- to 14-day course with aqueous penicillin G 18–24 million units IV is recommended.

The most likely presentation to primary care is for prenatal screening of an asymptomatic patient. Positive screening results in pregnancy even if asymptomatic should prompt a search for prior syphilis testing and for occult symptoms. If by clinical exam there are no signs or symptoms suggestive of symptomatic syphilis, care should be taken to determine how long this latent infection has been present. Treatment with a single injection of BPG as the above is acceptable for primary, secondary, as well as early latent syphilis if clear documentation of negative testing within a year is available. Some experts recommend a second dose of benzathine penicillin G 1 week later in pregnant patients especially in the third trimester tertiary, and late latent syphilis requires weekly penicillin injection for three doses. Severe allergies such as hives or angioedema to penicillin require desensitization as alternatives to penicillin are not recommended because of potential fetal toxicity or failure of treatment to cross the placenta.

While a possibility in any patient receiving treatment for syphilis, the Jarisch-Herxheimer reaction (immune over-reactivation from treponemal destruction) has particular importance in the pregnant patient as it can lead to induction of early labor or fetal distress. Pregnant women should be aware of this potential risk. The non-treponemal test titer or RPR should be repeated at 1, 3, 6, 12, and 24 months with a fourfold titer reduction by 6 months post therapy to ensure resolution.

Most cases of congenital syphilis occur from transmission to the fetus during early syphilis (primary, secondary, and early latent). The frequency of vertical transmission increases as gestation advances, but the severity of fetal infection decreases with infection later in pregnancy. Seventy to 100 % of infants born to untreated mothers will be infected compared to 1–2% of those born to women adequately treated during pregnancy. Therefore, screening for syphilis at the first prenatal visit and repeat testing later in pregnancy for those at highest risk is critical for the prevention of congenital syphilis and its potential adverse fetal outcomes.

Rubella

Rubella, also known as German measles, is a member of the Togavirus family, genus *Rubivirus*. Rubella is a childhood disease that prior to a generalized vaccination plan occurred in 6-year cycles, usually in the late winter. Rubella during pregnancy can result in spontaneous abortion, intrauterine growth restriction, and fetal malformations. Vaccination greatly reduced the incidence of rubella and congenital rubella syndrome. Acute rubella is normally a self-limited disease associated with a maculopapular rash similar to scarlet fever that begins on the face and quickly spreads to the trunk and extremities. Other nonspecific symptoms such as low-grade fever, sore throat, cough, headache, and malaise may also be present. Classically, rubella is associated with tender suboccipital and postauricular lymphadenopathy. Treatment is supportive.

Congenital rubella infection can be catastrophic, not only resulting in spontaneous abortion, intrauterine growth, and congenital defects (classically valvular abnormalities, hearing and visual impairment) but also more subtle late manifestations such as intellectual disability, diabetes mellitus, and thyroid abnormalities. Maternal-fetal transmission is the highest if infection occurs in the first 16 weeks of pregnancy. The incidence of defects may be as high as 80–85 % if maternal rubella is acquired during the first trimester. Little if any risk for congenital rubella syndrome occurs after 18–20 weeks' gestation.

As there is no treatment, prevention and early fetal diagnosis is essential. The CDC recommends documentation of rubella immunity at the first prenatal visit. If the woman is nonimmune, MMR vaccine should be given postpartum since this live vaccine is contraindicated during pregnancy.

In patients with no evidence of immunity and clinical features suggestive of rubella infection, acute rubella can be documented by one of the following: a greater

than fourfold increase in IgG rubella titers in convalescent versus acute serum, the presence of rubella-specific IgM, or a positive rubella culture. In all pregnant patients with acute rubella, fetal infection should be sought by chorionic villous or amniotic fluid sampling with a rubella-specific polymerase chain reaction assay.

Due to the catastrophic effects of congenital rubella infection in early pregnancy, women should be counseled on the risk of maternal-fetal transmission and offered pregnancy termination, especially if congenital infection happens in the first trimester.

Cytomegalovirus

Cytomegalovirus (CMV) is a DNA herpes virus that is the most common congenital viral infection. Maternal infection can be either primary, when a nonimmune woman is primarily infected, or secondary, when maternal immunity was present prior to conception and may be due to reactivation of latent virus versus reinfection. Maternal immunity is more prevalent in the lower socioeconomical status and older and multiparous women.

Adult primary infection resembles a mononucleosis-like syndrome with low-grade fever, myalgia, headaches, rhinitis, pharyngitis, and malaise. About a quarter of all congenital CMV infection occurs after maternal primary infection [35]. Fetal CMV disease presents with a wide variety of manifestations and appears to be more severe if infection is acquired in the first trimester. Clinical manifestations include intrauterine growth restrictions, CNS abnormalities such as microcephaly or chorioretinitis, hepatosplenomegaly, and thrombocytopenia [35]. Mortality is around 5 % of all the newborn affected and long-term morbidity is typically related to neurological involvement [36]. Treatment with antiviral medication during pregnancy has not been proven to be beneficial, and the effects of medications such as ganciclovir, foscarnet, and cidofovir on the early fetus have not been established. Treatment of the neonate for CMV end organ disease is however recommended.

While recommended in many European countries, there is no consensus on baseline prenatal screening for immunity to CMV in the United States. In general, women with a febrile illness or clinical features suggestive of mononucleosis-like illness should be screened for primary CMV infection. As with Toxoplasma, the diagnosis of acute primary CMV is dependent on a fourfold increase in IgG titers between acute and convalescent serum, with IgM titers not helpful as they can remain elevated for prolonged periods.

If acute primary CMV is confirmed, prenatal diagnosis should be offered to pregnant women, given the risk of fetal infection. Fetal infection can be established by amniotic fluid sampling for CMV DNA-specific polymerase chain reaction. Fetal prognosis depends on ultrasound assessment of stigmata of CMV infection. There is evidence that CMV hyperimmunoglobulin might be helpful in decreasing the rate of fetal infection with primary maternal infection.

Herpes Simplex Virus

Genital herpes is the result of infection with either herpes simplex virus (HSV) type 1 or 2. HSV is a DNA virus that belongs to the family Herpesviridae. While classically genital herpes is associated with HSV-2 infection, more recent data shows that HSV-1 appears to be an important cause of genital herpetic lesions as well [37]. Seroprevalence for both HSV-1 and HSV-2 is higher with lower socioeconomical status and multiple sexual partners and among black women. Unlike CMV, HSV transmission happens mostly through direct contact in the birth canal and perineal area during labor and delivery. Rarely, there is in utero transplacental transmission. There are no current recommendations in the United States to screen couples for HSV infection.

The presentation and treatment of genital herpes differs whether it is a primary infection or a recurrence. In primary infection, the presentation is normally more symptomatic and has the potential to be severe. Genital and/or perineal pustular lesions with blistering and ulceration are normally present in primary infection. They last for about 2 weeks. Local pruritus with dysuria that can progress to urinary retention might also be present. Systemic signs such as fever and lymphadenopathy are more commonly present in primary infection. Only about one-third of patients with primary genital herpes are symptomatic [38].

In recurrent disease, or in the first genital manifestation of non-primary infection, symptoms are milder, and the lesions, if present, can be atypical with erythema, irritation, and pruritus rather than blistering lesions alone [39].

Viral shedding is shorter and less intense in patients with recurrent disease, which may partially explain why vertical transmission is less likely in mothers with recurrent disease when compared with mothers with primary infection during pregnancy.

Diagnosis is by means of vesicular fluid sampling for either viral culture or HSV-directed polymerase chain reaction (PCR). Distinction between primary (negative serum antibodies for HSV) and non-primary first genital episode (serum antibodies do not match type in lesion) or recurrence (same HSV type in serum and lesion) is based on serum antibody testing.

Treatment for a first genital lesion is recommended as it reduces the duration of active lesions and viral shedding with better results if given within 24 h of beginning of symptoms. Acyclovir 400 mg three times daily orally for 10 days is the recommended regimen. Acyclovir is a FDA class B drug.

For recurrent infection, the recommendations to treat are not as strong unless the pregnancy is ≤35 weeks of gestation as these normally self-resolve. At 36 weeks of gestation in patients with symptomatic genital HSV infection, recommendations from ACOG state to use acyclovir 400 mg three times daily orally from 36 weeks until delivery as it reduces a asymptomatic viral shedding, and there is evidence that it might reduce clinical HSV recurrences at the time of delivery and hence the need

for cesarean delivery. For these reasons, suppressive therapy after 36 weeks is indicated in women with a history of recurrent genital HSV, even if asymptomatic [40]. Valacyclovir is an alternative but often is more costly and with more limited safety data in pregnancy.

Delivery by cesarean is recommended in mothers with active genital HSV lesions or prodromal symptoms suggestive of HSV infection in the birth canal, as per CDC and ACOG recommendations. If active lesions are not present or do not involve birth canal or the area surrounding it, cesarean delivery is not recommended.

About 5–15 % of neonatal herpes is acquired in the postpartum period. Careful hand washing and covering of active lesions should be enforced in anyone with active lesions and caring for the infant. As long as there are no herpetic breast lesions, breastfeeding is not contraindicated. While acyclovir is excreted in breast milk, there are no contraindications to breastfeeding while on acyclovir or valacyclovir (Figs. 2, 3, and 4).

Meat should be “well done” with no signs of rawness. Smoked, dried or cured meat can be infectious.
Avoid contact with raw meat, wash hands if contact necessary. Kitchen surfaces and utensils should also be disinfected if used with raw meat.
Avoid close contact with material potentially contaminated with cat feces, use gloves if unavoidable. Disinfect cat-litter box with near boiling water prior to refill.
Wash fruits and vegetables

Fig. 2 Preventing toxoplasmosis in pregnant patient

Early (primary/secondary/early latent)	**Benzathine penicillin G** 2.4 million units IM in a single dose
Late (late latent/tertiary)	**Benzathine penicillin G** 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals
Neurosyphilis	**Aqueous crystalline** penicillin G 18--24 million units per day, administered as 3--4 million units IV every 4 hours or continuous infusion, for 10--14 days **OR Procaine penicillin** 2.4 million units IM once daily PLUS **Probenecid** 500 mg orally four times a day, both for 10--14 days

Fig. 3 Treatment of syphilis in pregnant patient (Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010 available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5912a1.htm?s_cid=rr5912a1_w)

Primary or first genital non primary infection	Primary: Acyclovir 400 mg orally, three times daily for 7 to 10 days. First genital episode: Same regimen, but recommendation to treat not as strong as primary infection
Recurrent infection prior to 36 weeks of gestation	Consider treatment with acyclovir if started within 24 hrs, otherwise no clear indication to treat
Symptomatic infection at or above 36 weeks of gestation	Acyclovir 400mg orally three times daily until delivery. Consider cesarean delivery if symptoms persist near delivery. Suppressive treatment from 36 weeks to delivery is indicated if history of genital HSV infection

Fig. 4 Treatment of genital HSV infection in pregnancy (Adapted from ACOG Committee on Practice Bulletins [40])

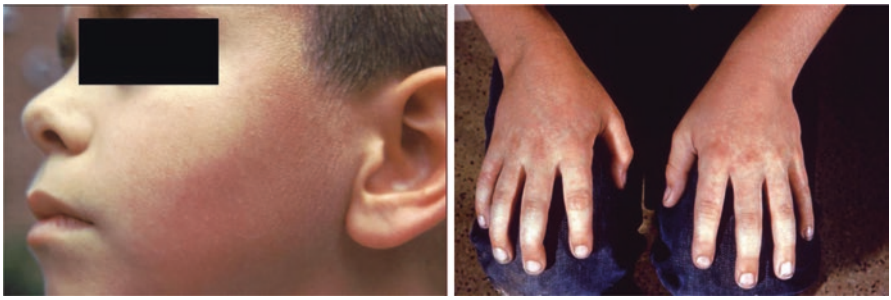

Fig. 5 Slapped cheek-type rash on the face and a lacy rash seen on the hands of a young child (CDC http://www.cdc.gov/parvovirusb19/fifth-disease.html)

Case #4 Parvovirus

A 28-year-old woman presents to her primary care physician at 30 weeks of pregnancy with a chief complaint of feeling ill for the last week. She has had subjective fevers, a mild headache, and joint aches especially in her knees and wrists. She has a 3-year-old son at home who was recently sick with a fever to 39 °C and a rash similar to the one seen in Fig. 5. She is also a physician and thus has had sick contacts in the workplace as well. She wonders what she might have and what effect this illness may have on her baby. She also wonders if there is anything she could have done differently to avoid getting ill during pregnancy.

Introduction

In the above case, the slapped cheek-type rash of the young boy and fever and arthralgias in the woman should make one consider parvovirus B19. It is a common childhood virus that causes erythema infectiosum (EI), also known as fifth disease.

It is an illness that occurs worldwide and one that is typically self-limited. However, it can have implications such as severe anemia and aplastic crisis in the immunocompromised host and rare but serious adverse effects for the fetus if infection occurs during pregnancy [41].

Epidemiology

Infection with parvovirus B19 usually occurs during late winter or early spring and is primarily spread through respiratory droplets [42]. Outbreaks occur on a yearly basis with large epidemics cycling every 4–5 years [41]. It is common in childhood as seen by the prevalence of IgG antibodies to the virus in 2–15 % of children ages 1–5 and 15–60 % of children ages 6–19. By the time a woman reaches child-bearing age, up to 60 % have immunity to the illness from a prior infection [43]. The incidence of acute B19 infection is 3–4 % during pregnancy, and vertical transmission during pregnancy can occur in 25–51 % of cases [43, 44]. The highest infection rate occurs in occupations with close contact with young children such as schoolteachers, daycare workers, and women with nursery or school-age children at home [42].

Clinical Presentation

In children, EI typically presents with a prodrome of fever and headache, followed by a slapped cheek rash on the face and a lacy rash that can be seen on the trunk and extremities as seen above. The rash occurs less frequently in adults and symptoms can mimic a mild cold or even be asymptomatic. For most adults, a symmetric polyarthralgia is one of the most common symptoms and can last weeks to months. The illness in immunocompetent adults and children is typically self-limited, but as discussed below, pregnant women are at risk for fetal complications. The varying presentation of parvovirus B19 in mother and baby can be seen in Table 3. The incubation period is 13–18 days, and the infectivity differs from other rash illnesses in that an infected individual is contagious before the onset of symptoms. This makes prevention of the illness in susceptible or high-risk hosts especially challenging.

Parvovirus in Pregnancy

Parvovirus B19 infection during pregnancy is associated with rare but potentially devastating adverse fetal outcomes including severe fetal anemia, nonimmune hydrops fetalis, and intrauterine fetal death (IUFD). This occurs as a result of the B19 virus' infection of erythroid precursor cells and inhibition of hematopoiesis. Binding sites are found on erythrocytes, but also synovium, placental tissue, fetal

Table 3 Presentation of parvovirus B19 infection

Maternal:
Asymptomatic
Erythema infectiosum/rash
Arthropathy
Anemia
Myocarditis
Fetal:
Fetal loss
Anemia → Hydrops
Myocarditis

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myocardium, and endothelial cells. Severe anemia in the fetus can lead to high-output heart failure and hydrops fetalis as seen by ascites, cardiomegaly, and pericardial effusion on ultrasound exam [43]. Fortunately, this does not occur as often as initially thought. Gratacós et al. prospectively studied 1610 pregnant women in Spain who were <28 weeks pregnant at enrollment. The prevalence of IgG positivity was 35 %. The incidence of acute parvovirus infection during pregnancy was 3.7 %. The incidence of fetal loss due to parvovirus in this large study was 1.66 %. The remaining pregnancies were uneventful, and the 1-year follow-up of infants born to mothers infected during pregnancy showed no serious abnormalities [44].

Similar findings were shown by Enders et al. in another large prospective observational study of 1018 women infected with parvovirus during pregnancy. The observed rate of fetal death was 6.3 %, and death was only observed when B19 infection occurred during the first 20 weeks of gestation. There were six stillbirths, four of which were attributed to B19 infection within the first 20 weeks. This study demonstrated the B19 associated risk of fetal death which was largely confined to the first 20 weeks of gestation. The overall risk of hydrops fetalis in this study was 3.9 %. As with fetal death, hydrops was seen more often when infection occurred earlier in pregnancy (≤32 weeks). A reduced incidence of fetal death with initiation of intrauterine transfusions (IUT) in cases of hydrops fetalis was also seen in this study. The proportion of fetuses that survived after receiving IUT was 11/13 (84.6 %). All of the non-transfused fetuses with severe hydrops died [2]. Although parvovirus appears to be teratogenic in some animals, and some case reports have suggested a link between parvovirus infection during pregnancy and congenital malformations, this has not been supported by epidemiologic and long-term studies [45, 46]. One retrospective study by Rodis et al. looked at outcomes of approximately 110 women up to 7 years after acute parvovirus infection during pregnancy and found no increase in the frequency of developmental delays in children with exposure in utero compared to women with known immunity to parvovirus. In summary, although vertical transmission in

pregnancy can occur relatively commonly, adverse fetal effects remain a rare complication in a minority of fetuses.

Diagnosis and Management

It is not currently recommended to perform routine screening for parvovirus B19 in pregnancy. In the setting of compatible symptoms or a possible exposure to parvovirus, the pregnant woman should be assessed to determine whether she is susceptible to infection or is currently infected. The diagnosis relies primarily on IgM and IgG antibodies, but polymerase chain reaction (PCR) can be helpful in certain situations. The sensitivity of parvovirus B19 IgM is between 80 and 90% and can be seen approximately 10 days after an exposure which is typically right before symptom onset [47]. B19 IgG antibodies develop a few days after IgM antibodies and usually persist for life. The diagnosis and initial management of a pregnant patient with symptoms concerning for parvovirus or with a known exposure is seen in Fig. 6. An isolated positive IgG would suggest prior infection and current immunity with no risk for the fetus. An isolated positive IgM or an IgM and IgG antibody is consistent with a recent infection, and an ultrasound examination should be performed to look for evidence of severe anemia or hydrops fetalis. Serial ultrasounds are typically performed every 1–2 weeks for up to 12 weeks after infection. Ultrasound examinations should include Doppler measurement of the fetal middle cerebral artery (MCA) peak systolic velocity which has been shown to be a sensitive sign for identifying fetal anemia. Signs of hydrops fetalis include scalp edema, ascites, polyhydramnios, and cardiomegaly [41, 43, 48].

Women who are diagnosed with acute infection in the first 20 weeks of pregnancy should be counseled that there is a risk of fetal loss which may approach 10%, as well as fetal anemia and hydrops. Serial ultrasounds can help to detect early signs of anemia and hydrops, and intrauterine fetal transfusions can be used to decrease risk of fetal death. Women who are diagnosed with infection in the second half of pregnancy, as was our case patient, have a much lower risk of fetal death, but fetal hydrops and severe anemia can occur making serial ultrasounds important in this group as well.

Although some studies have found an increased risk of infection in daycare workers and school teachers, the majority of infected women are exposed by their own children in the home [1]. Since the risk of infection at home and in the community exceeds that of the workplace, it does not make sense to exclude pregnant women from higher-risk occupations. The CDC and the American College of Obstetricians and Gynecologists (ACOG) do not recommend routinely excluding pregnant women from the workplace during endemic outbreaks of parvovirus [49]. Also, since transmission of parvovirus B19 can occur before symptom onset, there are no clear strategies to prevent B19 exposures in pregnancy. Patients with preschool or school-aged children at home

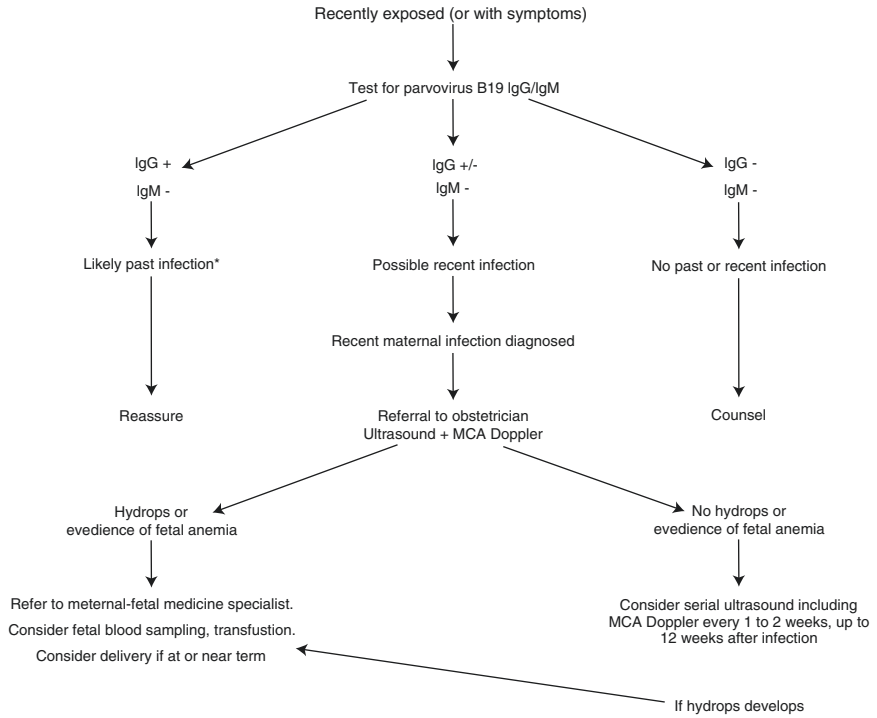

Fig. 6 Management of a pregnant woman exposed to parvovirus B19 (with permission from the Society of Obstetricians and Gynaecologists of Canada [1])

and those working in schools or daycares can be counseled to avoid close sick contacts and sharing food and drink and to use careful hand washing especially during outbreaks.

Case #5 Lyme Disease

A 30-year-old woman presents to her obstetrician in July with a chief complaint of fever and rash of 2-day duration. She is currently 24 weeks pregnant and has no significant past medical history. She recently returned from a trip to Cape Cod, Massachusetts, where she enjoyed hiking and camping. She does not recall any tick bites. She complains of subjective fevers and a red, circular, non-pruritic, non-tender rash in her axilla that she noticed in the shower. She also complains of profound fatigue, malaise, and diffuse muscle aches. She has two small children at home who are well.

Her exam is notable for a temperature of 39.2 C, HR 98, BP 110/80. On exam, she is a fatigued-appearing woman with anicteric, non-injected sclera, supple neck, and no cervical lymphadenopathy. She has a normal cardiopulmonary, abdominal, and neurologic examination. Her skin exam reveals an 8 cm circular, macular, erythematous rash, without central clearing similar to lesion seen in Fig. 7. Her CBC is notable for a mild anemia with hemoglobin 11 g/dL and Lyme serologies return negative. How should this case be managed?

Discussion

Lyme disease is the most common tick-borne infection in North America and Europe. In North America, Lyme disease is caused by *Borrelia burgdorferi*, a spirochete transmitted by the *Ixodes* tick (deer tick) [50]. According to the Center for Disease Control and Prevention (CDC), although Lyme disease has been reported from most states in the nation, 95 % of all cases in 2013 occurred in the northeast and upper Midwest. Transmission occurs through injection of tick saliva during a blood meal. It is important to remember that a feeding of at least 36–48 h is usually required for transmission since Lyme *Borrelia* resides in the midgut of the tick. In addition to avoidance of tick exposure, early tick removal is currently one of the best methods for preventing Lyme disease [50].

The clinical stages of Lyme disease can be divided in three groups: early localized, early disseminated, and late disease (see Table 4) [51]. Our patient presented with signs and symptoms consistent with early, localized infection. Her skin lesion is typical for erythema migrans (EM). EM is a rash that typi-

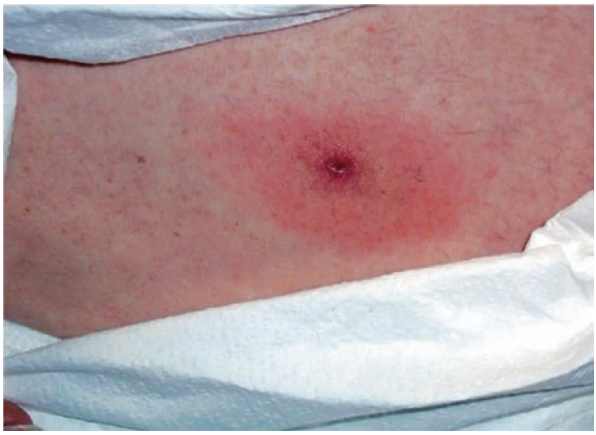

Fig. 7 A single erythema migrans lesion of 8.5×5.0 cm on the abdomen. The lesion is homogeneous in color, except for a prominent central punctum (presumed site of preceding tick bite) (Reprinted with permission from Oxford University Press)

Table 4 Stages and symptoms of Lyme disease

Stage	Symptom
Early localized	Erythema migrans
	Virus-like illness (e.g., fatigue, malaise, fever, chills, myalgia, headache)
Early disseminated	Common:
	Cardiac (e.g., atrioventricular block)
	Dermatology (e.g., multiple erythema migrans lesions)
	Musculoskeletal (e.g., arthralgia, myalgia)
	Neurologic (e.g., lymphocytic meningitis, facial nerve palsy, encephalitis)
Late	Arthritis (e.g., monoarticular, oligoarticular)
	Neurologic symptoms (e.g., encephalomyelitis, peripheral neuropathy)

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cally occurs at the site of the tick bite within 1–2 weeks (range 3–30 days). It is painless, non-pruritic, round or oval, and >5 cm in diameter and can subsequently expand with central clearing. Many patients also have nonspecific symptoms such as fever, headache, myalgias, and fatigue [50]. Early disseminated infection is characterized by multiple EM lesions, cardiac and/or neurologic findings such as facial nerve palsy. Late Lyme typically occurs weeks to years after infection and symptoms can include Lyme arthritis and/or neurologic complications [51].

The CDC and Infectious Disease Society of America (IDSA) guidelines recommend serologic testing to help support the diagnosis of Lyme disease in symptomatic patients. The mainstay is a two-tier approach as outlined in Fig. 8. Initial testing is with the more sensitive enzyme-linked immunosorbent assay (ELISA). If this is equivalent or positive, the more specific, Western blot is done for confirmation. Of note, EM alone is sufficient for a diagnosis of Lyme disease based on clinical grounds. As in this case, the serologic testing during early, localized disease is insensitive, and patients should be treated based on clinical findings alone. Up to 40–60 % of patients with early localized disease will have negative serologic testing, and diagnoses could be missed if Lyme is not clinically suspected [52].

Lyme Disease in Pregnancy

There has long been concern that Lyme disease, if contracted during pregnancy, could cause fetal harm or give rise to its own congenital syndrome. Other spirochetal diseases, such as syphilis, can cross the placenta and cause well-described effects on the fetus. The possibility of transplacental infection with *B. burgdorferi* has been documented in a number of case reports [53–57]. In 1983, the first case of

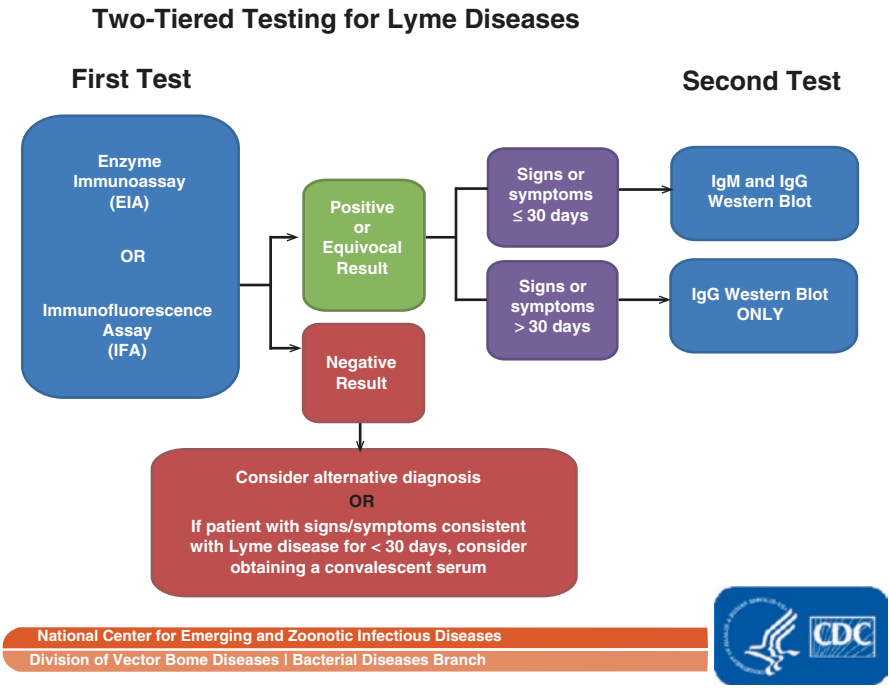

Fig. 8 The Two-tier Testing Decision Tree describes the steps required to properly test for Lyme disease (Reprinted with permission from CDC)

presumed transplacental transmission of *B. Burgdorferi* was reported by Shirts et al. in a 27-year-old woman who presented with fever in the third trimester. The infant was delivered at 34 weeks via cesarean section for non-reassuring fetal status and the mother received cefamandole. Infant complications included hyperbilirubinemia, hepatosplenomegaly, and rash. A *Borrelia*-like spirochete was seen on peripheral blood smear from the infant and in the lumen of the placental cord vessels. The infant did well following ampicillin treatment [56]. Schlesinger et al. later reported another case of transplacental transmission of *B. burgdorferi* in a woman who developed an EM rash in her first trimester but was not treated. The infant born at 35 weeks died within 2 days of birth and was found to have multiple cardiac defects. Postmortem examination did reveal spirochetes in multiple organ systems in the infant [55].

Whether transplacental transmission of *B. burgdorferi* actually increases the risk of an adverse pregnancy outcome is unclear. The individual case reports of cardiac malformations, stillbirth, cerebral edema, and rash have suggested a possible association between Lyme disease in pregnancy and neonatal harm [53, 55, 57]. However, clinical, serological, and epidemiological studies have failed to demonstrate a definite causal association between infection in pregnancy and

adverse pregnancy outcomes [58–60]. In one of the largest prospective studies to date, Strobino et al. looked at over 2000 pregnant women in Westchester County, New York, an area with high endemnicity for Lyme disease. They collected clinical questionnaires and Lyme serologies at the first prenatal visit and delivery. They found that maternal exposure to Lyme disease before conception or during pregnancy was not associated with fetal death, congenital malformations, or prematurity [59]. This same author also found no association between congenital heart defect and maternal tick bite or maternal Lyme disease within 3 months of conception or during pregnancy in a retrospective case-control study [61]. Although rare cases suggestive of congenital Lyme have been reported in the literature, the majority of women who are infected do not transmit the disease to their infant.

Treatment of Lyme Disease

The IDSA guidelines on the treatment of Lyme disease can be seen in Table 5. The management of pregnant woman with Lyme disease differs only in that doxycycline is contraindicated in pregnancy because of the risk of permanent tooth discoloration and possible effect on fetal bone formation. In this patient with early, localized Lyme disease, amoxicillin 500 mg three times per day for 14–21 days would be appropriate. In cases where parental therapy is preferred such as neurologic abnormalities, and some cardiac conditions including high-degree AV block, ceftriaxone is the drug of choice in nonpregnant and pregnant patients alike. It is important to know that *Ixodes* ticks can be co-infected and transmit Lyme in addition to other pathogens such as *Anaplasma phagocytophilum* and *Babesia* spp. If symptoms are not compatible with Lyme disease after a tick bite or symptoms fail to resolve after appropriate antibiotic therapy, these co-infections should be considered [62]. Amoxicillin, which would be used to treat early Lyme disease in pregnant patients, is not effective against either *Anaplasma or Babesia*, and further investigation and alternative therapies would need to be explored.

In the case of a known tick bite, the IDSA recommends antibiotic prophylaxis with a single dose of doxycycline 200 mg given within 72 h of tick removal for select patients meeting all the following criteria: The attached tick can be identified as an adult or nymphal *Ixodes* tick and has been attached for ≥36 h based on exposure or engorgement; local rate of *Borrelia burgdorferi* in ticks is ≥20 %; and doxycycline is not contraindicated. In this case, a tick bite was not recognized, but if it had been, prophylaxis would not be recommended. This is because of risks of doxycycline in pregnancy, in combination with the lack of data to support short courses of amoxicillin as a prophylactic regimen, and the excellent efficacy of antibiotic treatment of Lyme disease if infection does develop [50]. Since prophylaxis in pregnancy is not a recommended prevention of Lyme

Table 5 Recommended antimicrobial treatment of patients with Lyme disease

Drug	Dosage for adults	Dosage for children
Preferred oral regimens		
Amoxicillin	500 mg 3 times per day[a]	50 mg/kg per day in 3 divided doses (maximum, 500 mg per dose)[a]
Doxycycline	100 mg twice per day[b]	Not recommended for children aged <8 years For children aged >8 years, 4 mg/kg per day in 2 divided doses (maximum, 100 mg per dose)
Cefuroxime axetil	500 mg twice per day	30 mg/kg per day in 2 divided doses (maximum, 500 mg per dose)
Alternative oral regimens		
Selected macrolides[c]	Azithromycin 500 mg once daily, clarithromycin 500 mg twice per day	Azithromycin 10 mg/kg per day, clarithromycin 7.5 mg/kg twice per day
Preferred parenteral regimen		
Ceftriaxone	2 g intravenously once per day	50–75 mg/kg intravenously per day in a single dose (maximum, 2 g)
Alternative parenteral regimens		
Cefotaxime	2 g intravenously every 8 h[d]	150–200 mg/kg per day intravenously 3–4 divided doses (maximum, 6 g per day)[d]
Penicillin G	18–24 million U per day intravenously, divided every 4 h[d]	200,000–400,000 U/kg per day divided every 4 h[d] (not to exceed 18–24 million U per day)

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[a]Although a higher dosage given twice per day might be equally as effective, in view of the absence of data on efficacy, twice-daily administration is not recommended

[b]Tetracyclines are relatively contraindicated in pregnant or lactating women and in children <8 years of age

[c]Because of their lower efficacy, macrolides are reserved for patients who are unable to take or who are intolerant of tetracyclines, penicillins, and cephalosporins

[d]Dosage should be reduced for patients with impaired renal function

disease with avoidance of possible exposure, the use of tick repellents, such as DEET (*N*,*N*-diethyl-3-methylbenzamide), and early removal of ticks remain important tools to reduce infection rates [63].

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Thyroid Disease During Pregnancy: An Overview for the Primary Care Physician

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Case I

A 27-year-old gravida 2 para 1 visited her primary care physician after having a positive pregnancy test. She had an uncomplicated first pregnancy and was not evaluated for thyroid disease during that pregnancy, but two years after the delivery of her daughter, she was diagnosed with Hashimoto's thyroiditis. At diagnosis, her TSH was elevated at 12 mIU/L, her free thyroxine (FT4) was low at 0.4 mIU/L, and she had positive thyroid peroxidase (TPO) antibodies. She was started on 50 mcg of levothyroxine daily. Her TSH stabilized at 1.1 mIU/L and FT4 was within the reference range. Prior to planning her second pregnancy, she contacted her endocrinologist for advice, who recommended she continue her current levothyroxine dose but to increase her weekly dose from 7 to 9 pills of 50 mcg pills upon her first missed menses or positive pregnancy test and to promptly contact her health care provider.

The patient's initial TSH obtained at 6 weeks gestation was elevated to 3.1 mIU/L, 2 weeks after increasing her levothyroxine dose. The patient, who had already increased her dose to 9 pills weekly, was counseled again to increase her dose with a goal to meet her first trimester-specific reference range of 0.1–2.5 mIU/L. Her TSH was retested at 12 weeks gestation and was within this range at 2.0 mIU/L. Her TSH was retested monthly during her second and third trimesters and remained stable so no further changes were made to her levothyroxine dose for the remainder of the pregnancy. She had an uncomplicated term delivery of a healthy infant.

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Review of How the Diagnosis Was Made

Hypothyroidism due to Hashimoto's thyroiditis was diagnosed prior to the second pregnancy with TSH, FT4, and TPO antibodies. Effectiveness of therapy was evaluated by TSH values regularly during pregnancy.

Lessons Learned

Physiologic changes in thyroid function occur during normal pregnancy. hCG stimulates thyroid activity; as hCG increases during the first trimester, thyroid-stimulating hormone (TSH) decreases [1–3] and then gradually increases and plateaus. Free T4 (FT4) initially increases with the increase in hCG and then decreases after the first trimester. TBG and total T4 both increase during pregnancy. Gestation-specific reference intervals for TSH exist during pregnancy [4–6], which should alleviate the misinterpretation of thyroid function tests [6]. Dashe et al. constructed a nomogram in 13,599 singleton pregnancies and a separate nomogram in 132 twin pregnancies to estimate expected reference ranges throughout gestation [7]. However, in iodine-deficient populations, no gestation-specific levels have been established [8]. According to the American Thyroid Association guidelines, trimester-specific reference ranges for TSH as defined in populations with optimal iodine intake should be applied [9]. If not available, TSH in the first trimester should fall between 0.1–2.5 mIU/L, 0.2–3.0 mIU/L in the second trimester, and 0.3–3.0 mIU/L in the third trimester [9]. FT4 is optimally measured by T4 in dialysate or ultrafiltrate with online extraction, liquid chromatography, or tandem mass spectrometry; but if not available, TSH is a more reliable estimate of thyroid function [9].

New-onset hypothyroidism during pregnancy is a rare occurrence. Allan et al. screened 9403 healthy women between 15 and 18 weeks gestation, of which 172 women (1.8 %) had a TSH from 6 to 9.9 mIU/L and 37 women (0.4 %) had a TSH greater than 10 mIU/L [10]. Casey et al. screened 17,298 women before 20 weeks gestation; similarly, 404 women (2.3 %) had elevated TSH and 32 women (0.2 %) had both an elevated TSH and a suppressed FT4 [4].

Both overt and subclinical hypothyroidism are associated with adverse pregnancy outcomes. Casey et al. found a significant ($p < 0.05$) increase in both placental abruption and delivery at less than 34 weeks gestation in women with subclinical hypothyroidism compared to age-matched euthyroid women [4]. In the Generation R Study, thyroid function tests and birth outcomes were studied in 5971 women with singleton pregnancies and no current or past thyroid disease except for a low (3.4 %) incidence of subclinical hypothyroidism. Five percent of women had a preterm delivery at less than 37 weeks gestation, 4.4 % had a spontaneous preterm delivery at less than 37 weeks gestation, and 1.4 % delivered at less than 34 weeks gestation (defined as very premature delivery) [11]. Using the ATA guideline of normal gestation-specific TSH values, the authors found that women with elevated

TSH had an increased incidence of overall preterm delivery but not of spontaneous preterm delivery. Women with hypothyroxinemia had a 2.5-fold increased risk of preterm delivery, a 3.4-fold increased risk of spontaneous preterm delivery, and a 3.6-fold increased risk of very preterm delivery. Women with TPO antibody positivity had a 1.7-fold increased risk of preterm delivery, a 2.1-fold increased risk of spontaneous preterm delivery, and a 3.6-fold increased risk of very preterm delivery [11]. LaFranchi et al. found greater rates of maternal complications including gestational hypertension and c-section in women with overt and subclinical hypothyroidism [12]. Higher c-section rates may be in part due to the associated increased incidence of breech presentation at term in mothers with elevated TSH [13].

In addition to preterm delivery, there are serious outcomes on fetal morbidity and mortality in hypothyroid women. In a study of 9403 women with singleton pregnancies, the fetal death rate after 16–18 weeks gestational age was fourfold higher in the 2.2 % of women with a TSH greater than 6 mIU/L (3.8 % vs 0.9 %), which rose to 8.1 % among women with a TSH greater than 10 mIU/L [10]. In women with a TSH greater than the 97.5th percentile compared to euthyroid women, birth weight less than 1500 g, NICU admissions, and respiratory distress were all significantly increased [4]. Another prospective population-based study of 1017 women with singleton pregnancies found that those with overt hypothyroidism had an increased risk of fetal death, fetal loss, circulatory system malformations, and low birth weight [14]. Those with subclinical hypothyroidism also had increased risk of fetal distress, preterm delivery, poor vision, and neurodevelopmental delay [14].

Much research has focused on maternal hypothyroidism and fetal neurodevelopmental effects. During the first 14 weeks of gestation when brainstem and cerebral neurogenesis occurs, the fetus's source of free T4 is entirely maternal. From 14 weeks onward, during neuronal maturation and synaptic development, the fetus begins producing and supplying its own thyroid hormones [15]. Man et al. studied the offspring of 365 otherwise uncomplicated pregnancies. Hypothyroxinemic mothers were defined as women with two or more values below the normally elevated levels or who received no thyroid hormone replacement or inadequate therapy. IQ levels in the 4-year-old and 7-year-old offspring of these mothers were significantly less ($p < 0.05$) compared to euthyroid mothers [16]. In another study, children of women with untreated hypothyroidism during pregnancy averaged 7 points lower on IQ testing and had a significant percentage (19 % vs 5 % of controls) of IQ less than or equal to 85 [17]. The Generation R Study looked at expressive language at 18 months and nonverbal cognitive function at 30 months in 3659 children, of which all mothers had normal TSH. The authors found a significant increased odds ratio of expressive language delay in mildly and severely depressed FT4 levels compared to controls. The odds ratio was also significantly increased for nonverbal cognitive delay but only with severely depressed FT4 levels [18]. Li et al. compared women with subclinical hypothyroidism and low T4 and TPO antibodies with control groups matched for gestational age, gender, birth condition (Apgars), birth weight, and other factors. IQ and motor function score of offspring at 25–30 months old were significantly lower ($p < 0.01$) in all three groups compared to their matched controls [19]. A study of over 5700 children found that only girls of

mothers with elevated TSH had a significant increased odds ratio of inattention and ADHD symptoms at age 8 as measured by a teacher-administered test [20].

Infertile women who are euthyroid but thyroid peroxidase antibody (TPO-Ab) positive have also been shown to have poor pregnancy outcomes. A prospective study of 484 euthyroid women undergoing assisted reproductive technology, of which 72 (15 %) were TPO-Ab positive, found that TPO-Ab-positive women treated with levothyroxine had no difference in pregnancy rate compared to placebo-treated TPO-Ab-positive women and the TPO-Ab-negative control group but did have an increase in miscarriage rate. Delivery rate was lower in both groups of TPO-Ab-positive women compared to the negative control group, but there was no difference in delivery rates between the two TPO-Ab-positive groups [21].

Euthyroid women with autoimmune thyroid disease are at risk for obstetrical complications. Negro et al. randomized 115 TPO-Ab-positive women with a normal TSH to treatment with levothyroxine (57 women) versus placebo (58 women). The control group consisted of 869 TPO-Ab-negative women. Primary outcome measure was the rate of obstetrical complications. Levothyroxine was dosed by initial TSH value obtained in the first trimester. Both groups of TPO-Ab-positive patients had higher initial TSH values compared to the control group. Untreated TPO-Ab-positive patients had significantly elevated TSH values throughout gestation and significantly lower free T4 values after 30 weeks gestation and a significant increase in miscarriage and preterm delivery compared to the other two groups ($p < 0.05$ for all). These results suggest that treatment with levothyroxine in euthyroid women with TPO antibody positivity can reduce the risk of miscarriage and preterm delivery to control levels. The authors recommended levothyroxine treatment for all pregnant women with TSH greater than 2.0 mIU/L or high TPO antibody titers [22].

Given the above risks, should all pregnant patients be screened for hypothyroidism? Vaidya et al. screened 1560 pregnant women during their first obstetric visit using TSH, FT4, and FT3. TPO antibodies were checked in 85 % of patients. 26.5 % of patients were considered high risk, defined as a personal history of thyroid disease or autoimmune disease or a family history of thyroid disease. Of the patients, forty (2.6 %) had an elevated TSH, and the prevalence was significantly higher in the high-risk group (6.8 %) compared to the low-risk group (1 %). However, twelve of the forty low-risk patients (30 %) had an elevated TSH. The authors concluded that targeted screening of only the high-risk group would miss approximately one third of pregnant women with overt or subclinical hypothyroidism [23]. However, universal screening versus case finding has not been shown to decrease adverse outcomes. Negro et al. randomly assigned 4562 pregnant women to a universal screening group or a case-finding group. Women in both groups were labeled as high risk or low risk depending on their history. High-risk women in both groups and low-risk women in the universal screening group were tested for TSH, FT4, and TPO antibody; low-risk women in the case-finding group were tested during pregnancy, and results were reviewed postpartum. Patients were treated with levothyroxine if TSH was greater than 2.5 mIU/L. Euthyroid TPO-antibody-positive patients were retested in the second and third trimesters. Similarly, hyperthyroid women were screened and treated as indicated. In the case-finding group, 20 (4.4 %) of

patients versus 34 (1.9 %) of low-risk patients had hypothyroidism. Similarly, in the universal screening group, 4.0 % of high-risk patients and 2.5 % of low-risk patients screened positive. Adverse outcomes examined included miscarriage, cesarean delivery, preterm delivery, and NICU admission. No differences were seen in adverse outcomes between the universal screening and the case-finding groups, but screening and treating the low-risk patients resulted in a significantly decreased rate of adverse outcomes compared to the untreated low-risk patients not identified during pregnancy [24].

The Controlled Antenatal Thyroid Screening study (CATS) was a prospective randomized controlled trial whose aim was twofold: to identify subclinical hypothyroidism (SCH) in early gestation and to evaluate levothyroxine (LT4) intervention therapy in SCH. Women were initially randomized into screening (sample measured immediately) and control groups (sample stored and measured after delivery). Women identified in the screening group with SCH were started on LT4 150mc daily in the late first to early second trimester, at a median gestational age of 13 weeks and 3 days. The primary outcome was the IQ of children at age 3 years, which was not significantly different between the control and the screening groups. Two other tests, the child behavior checklist and the behavior rating preschool, also showed no difference between the two groups. This trial showed no benefit for antenatal screening and treatment for SCH, as it appears to have been implemented too late to be impactful in early childhood cognitive function [25].

However, challenges in screening may occur. In euthyroid women with TPO antibody positivity who are at risk for miscarriage and preterm delivery, LT4 therapy is associated with a decreased risk of these complications [22]. Another prospective study of 1560 pregnant women concluded that screening only pregnancies with risk factor for thyroid disorders would miss approximately one third of pregnant women with either overt or subclinical hypothyroidism [23]. No national organization recommends screening of low-risk pregnant women.

In patients with known hypothyroidism, thyroid function can be optimized in pregnancy by paying close attention to those with known thyroid disease. Mandel et al. reviewed 12 women with primary hypothyroidism on LT4 before, during, and after pregnancy. All patients experienced an increase in their TSH, and 9 of 12 patients (75 %) required an increase in their LT4 dose during pregnancy [26]. A prospective study of 63 pregnant women taking LT4, 83 % of whom evaluated were in the first trimester, showed that 49 % of initial TSH values were outside the normal laboratory reference range. The rate of fetal loss was significantly higher (29 % versus 6 %) in women with abnormal initial TSH compared to initial TSH within the reference range [27].

Thyroid dysfunction in early pregnancy has been associated with miscarriage. Of 1013 women in whom LT4 had been started at least 6 months prior to conception and whose TSH was measured in the first trimester, 62.8 % had a TSH greater than 2.5 mIU/L, with 29.1 % greater than 4.5mIU/L and 7.4 % greater than 10mIU/L. Miscarriage risk was increased in women with TSH greater than 4.5mIU/L (odds ratio 1.8) which further increased in women with TSH greater than 10mIU/L (odds ratio 3.95) [28].

In patients with planned pregnancies, preconception TSH levels should be optimized. Of 53 pregnant women with hypothyroidism in whom preconception TSH was less than 2.5 and in the normal range 6 months prior to pregnancy, 17 had to increase their levothyroxine dose due to an elevated TSH at the first prenatal visit. 50 % of women with a preconception TSH of 1.2–2.4 mIU/L required an increase in their levothyroxine versus only 17.2 % of women with a preconception TSH of less than 1.2 ($p < 0.02$). The authors concluded that preconception TSH levels should not only be in the normal range prior to conception but should not be greater than about 1.2 mIU/L; therefore, fewer dose adjustments during pregnancy would be needed [29]. In another study of 25 hypothyroid women planning pregnancy, 14 were assigned to partially suppressive treatment and 11 continued their current levothyroxine dose. Women who received partially suppressive therapy showed higher (normal) FT4 and lower TSH at the first postconception evaluation. Women who continued their current dose were twice as likely to have an increased TSH later in pregnancy. The authors noted that a partially suppressive dose may be worthwhile in light of the effects of maternal hypothyroidism on future offspring [30]. Alexander et al. studied 19 hypothyroid women on preconception levothyroxine, of whom 17 resulted in term births. A mean levothyroxine dose increase of 47 % was required, with the median onset of the required increase at 8 weeks gestation. However, the requirements increased as early as 5 weeks gestation [31].

To minimize the risks of untreated hypothyroidism, the American Thyroid Association recommends that treated hypothyroid patients who are newly pregnant should self-increase their levothyroxine dose by 25–30 % if they have a missed menstrual cycle or have a positive home pregnancy test and promptly notify their caregiver. One way this can be accomplished is to increase their weekly dose of 7 pills to 9 pills [9].

Case II

A 24-year-old gravida 1 para 0 at 9 weeks gestational age by last menstrual period presented for evaluation of nausea, vomiting, and intermittent palpitations. She had no known medical problems, although her mother had Graves' disease. Physical exam was notable for a heart rate of 110 beats per minute, exophthalmos, and a diffuse goiter. Transvaginal ultrasound showed a normal appearing single fetus with cardiac activity whose measurements were consistent with her stated gestational age. Her thyroid-stimulating hormone (TSH) was undetectable and her free thyroxine (T4) was elevated. Thyroid receptor antibodies (TRAb) were drawn. She was started on propylthiouracil (PTU) and antiemetics, which resolved her symptoms. TRab returned and were positive. She was transitioned to methimazole (MMI) in the second trimester. Her thyroid function tests were drawn monthly and were stable within treatment range. The remainder of her pregnancy progressed normally with no complications.

Review of How the Diagnosis Was Made

This patient presented with signs and symptoms of thyrotoxicosis. Laboratory evaluation was consistent with hyperthyroidism. The etiology of her hyperthyroidism was suspected to be Graves' disease due to the physical findings and confirmed with the positive thyroid receptor antibodies. A normal intrauterine pregnancy was confirmed by a pelvic ultrasound.

Lessons Learned

Maternal complications of uncontrolled or untreated hyperthyroidism include hypertensive disorders of pregnancy, preterm labor, congestive heart failure, placental abruption, and thyroid storm. Fetal and neonatal complications include intrauterine growth restriction, small for gestational age, prematurity, stillbirth, fetal and neonatal hyperthyroidism, and congenital malformations.

Laboratory diagnosis of hyperthyroidism in pregnancy can be challenging due to the physiologic changes in thyroid function during pregnancy. Total T4, free T4 (FT4), total triiodothyronine (T3), and thyroid-binding globulin (TBG) are elevated in normal pregnancy. Additionally, FT4 analogue assays may underestimate the actual FT4 value. TSH suppression and/or FT4 elevation appear transiently in approximately 10 % of pregnancies in the first trimester [3]. TRAb may be useful in establishing a diagnosis. Radioactive iodine is contraindicated in pregnancy.

It is important to differentiate the etiology of thyrotoxicosis as gestational versus clinical. The majority of patients with thyrotoxicosis have gestational thyrotoxicosis. Gestational thyrotoxicosis, which is hCG mediated, appears in the late first and early second trimesters and resolves as hCG decreases. Patients may be asymptomatic with a suppressed TSH only or may have hyperemesis gravidarum with suppressed TSH and mildly elevated FT4. No goiter is usually present on physical exam in areas of iodine sufficiency and patients are TRAb negative. The course is self-limited and no antithyroid medication is indicated. A serum TSH in the first trimester less than 0.1 mIU/L should prompt a history and physical exam, and FT4 measurements should be obtained. T3 and TRAb may be helpful to establish a diagnosis of hyperthyroidism [9]. In women with gestational hyperthyroidism and hyperemesis gravidarum, management includes supportive therapy, treating dehydration and hospitalization if indicated. Antithyroid drugs are not recommended [9].

Approximately 0.1–4 % of pregnant women with thyrotoxicosis have a clinical, rather than a gestational etiology for their symptoms. Of these, Graves' disease is the most frequent. Other etiologies include thyroiditis, toxic nodule(s), and hydatidiform mole.

Thyroiditis is a rare diagnosis in pregnancy, the etiology of which is postinfectious or autoimmune mediated. Because so few cases have been reported, the percentage of patients who have complications is unknown. Clinical findings include a

goiter, which may be painful (De Quervain's or postinfectious etiology) or painless (autoimmune etiology). Patients are TRAb negative and may be TPO negative or positive in those with an autoimmune etiology. Similar to gestational thyrotoxicosis, the course is self-limited and no antithyroid treatment is indicated [32].

Hydatidiform mole is another hCG-mediated form of thyrotoxicosis in pregnancy. Onset appears following mole formation and resolves if hCG decreases after treatment of the molar pregnancy. Like gestational thyrotoxicosis, patients may be asymptomatic with a suppressed TSH alone or may have hyperemesis gravidarum with a suppressed TSH and elevated FT4. Patients do not have a goiter and are TRAb negative [32].

Graves' and toxic nodular goiter, whose etiology is autoimmune or of nodular autonomy, have a variable onset whose course is persistent until addressed. Like other etiologies of hyperthyroidism, patients may be asymptomatic with a suppressed TSH alone or may have hyperemesis gravidarum and symptoms of thyrotoxicosis with a suppressed TSH and elevated FT4. Clinical findings include a goiter, TRAb positivity, or positive thyroid ultrasound findings. Antithyroid treatment is indicated due to the complications described at the beginning of this segment [32]. Evidence is lacking to recommend for or against a thyroid ultrasound to differentiate the cause of hyperthyroidism in pregnancy. Radioactive iodine scanning or uptake should not be performed in pregnancy [9]. Additionally, thyrotoxic women who are not pregnant but desire to conceive should be euthyroid prior to attempting pregnancy [9].

The use of the antithyroid drugs PTU and MMI during pregnancy and their potential effects on the developing fetus have been evaluated in multiple studies. MMI may have increased transplacental passage compared to PTU [33], and its use in the first trimester has been associated with aplasia cutis and choanal atresia [34]. Cord serum PTU levels at term are higher than maternal levels, suggesting the fetus has a slower clearance of PTU [35]. In a case-affected control analysis of 18,131 cases of congenital malformations and first-trimester medication use, 127 infants were born to mothers who took antithyroid medication; 47 took PTU and 80 took MMI. 52 groups of malformations were analyzed. Significant associations were found between PTU and situs inversus, unilateral renal agenesis/dysgenesis, and cardiac outflow tract anomalies and between MMI and situs inversus, choanal atresia, and omphalocele [36]. Another study examined 6,744 women with Graves' disease, of whom 1426 took MMI, 1578 took PTU, and 2065 took no antithyroid medication during the first trimester. Overall, there was a 4.1 % rate of major anomalies with MMI compared with 2.1 % in the control group and 1.9 % in the PTU group. Anomalies included aplasia cutis, omphalocele, and a symptomatic omphalomesenteric duct anomaly [37]. A Danish nationwide cohort study of 817,093 children born from 1996 to 2008 found that MMI/carbimazole (CMZ) and PTU were associated with an increased risk of birth defects diagnosed before age 2. The prevalence was an excess of cases per live birth (5.7 % for nonexposed and 5.4 % for history of antithyroid drug use prior to pregnancy compared with 8 % for PTU alone, 9.1 % for MMI/CMZ alone, and 10.1 % for MMI/CMZ with a switch to PTU in early pregnancy). The odds of

developing a birth defect were 1.41 for PTU, 1.66 for MMI/CMZ, and 1.82 in MMI/CMZ with a switch to PTU in early pregnancy. Specific birth defect associations were seen in the different groups. Children exposed to MMI/CMZ had a combined odds ratio of 21.8 and exhibited aplasia cutis, eye and circulatory anomalies, choanal and esophageal atresia, omphalocele, and omphalocele-mesenteric duct anomalies. Malformations involving the face, neck, and preauricular sinus or cyst with fistula were seen in PTU-exposed children. Those receiving both medications had an increase in urinary tract anomalies [38]. A subanalysis of the same cohort examined the severity of birth defects associated with PTU exposure in early pregnancy. Of 14 cases identified, 11 children were exposed to PTU only and 3 to MMI/carbimazole with a switch to PTU in early pregnancy. The prevalence of face and neck defects and urinary system anomalies were both increased, with hazard ratios of 4.92 and 2.73, respectively [39]. Although any antithyroid drug use in pregnancy may pose a risk, both hyper- and hypothyroidism threaten pregnancy outcomes more than antithyroid drugs. Ideally, patients with preexisting Graves' disease should be permanently treated with surgery or 131-I prior to pregnancy [40].

Given the above data, in the first trimester, PTU is preferred, and following the first trimester, switching to MMI should be considered. The lowest dose of medication should be prescribed with the goal to maintain maternal T4 in the upper third of normal to slightly elevated range for pregnancy (FT4 1.7–2.2 ng/dl, T4 12–14 μg/dl). Maternal FT4 and TSH should be monitored every 2–6 weeks, as medication requirements often decrease during the third trimester. Patients with a past or present history of Graves' disease should have TRAb obtained at 20–24 weeks gestational age [9].

Case III

A 28-year-old gravida 2 para 1 at 10 weeks gestational age presented for evaluation of a self-discovered small lump on the right side of her neck. She recently found out she was pregnant and was concerned this may affect her pregnancy. Her mother was diagnosed with stage 1 papillary thyroid cancer 6 months ago. On physical exam, she had fullness of the right neck. No lymphadenopathy was present. Thyroid ultrasound showed a 1.4 cm solid nodule with calcifications located in the left upper lobe and no evidence of lymph node metastases. A fine needle aspiration was performed. Biopsy revealed malignant cells consistent with papillary thyroid carcinoma. TSH was 1.5. The patient was started on levothyroxine to suppress her TSH. The patient had repeat thyroid ultrasounds in her second and third trimesters which showed no change in the size of the nodule and no development of lymph node metastases, and her TSH remained low and stable. She had an uncomplicated vaginal delivery and underwent a total thyroidectomy 8 weeks postpartum. Pathology showed a stage 1 papillary thyroid cancer. Her levothyroxine was increased. She stopped breastfeeding 6 months postpartum and underwent 131-I therapy.

Review of How the Diagnosis Was Made

This patient presented with a thyroid nodule and ultrasound findings concerning for malignancy. Fine needle aspiration confirmed malignancy.

Lessons Learned

The prevalence of thyroid nodules in pregnancy ranges from 3 to 21 % [41–43]. Higher prevalence is dependent on parity, possibly due to the increased iodine requirement during pregnancy with subsequent deficiency [42]. The effect of pregnancy on nodule growth is variable but has been associated with an increase in size of existing nodules and also with the development of new nodules [43]. In pregnant women with thyroid nodules, the prevalence of malignancy ranges from 12 to 43 % [44–46]. In the California Cancer Registry from 1991 to 1999, Smith et al. found a prevalence of 14.4/100,000 women who were listed as having obstetric deliveries and a diagnosis of thyroid malignancy, of which the majority (10.8/100,000) were diagnosed within 1 year after delivery. 3.3/100,000 women were diagnosed within 9 months prior to delivery, and 0.3/100,000 were diagnosed at delivery [47]. Risk factors for thyroid malignancy in pregnancy include family history of thyroid disease; childhood radiation therapy; rapid nodule growth, cough, or dysphonia; and palpable cervical lymph nodes [48]. The optimal diagnostic strategy for thyroid nodules detected during pregnancy is based on risk stratification. All women should have a complete history and physical exam, serum TSH testing, and a thyroid ultrasound [9]. Thyroid ultrasound is the most accurate tool for nodule diagnosis. In nodules measuring less than 10 mm, fine needle aspiration (FNA) is not indicated unless there is a high-risk history, any suspicious ultrasound criteria, or clinical symptoms. Ultrasound findings suspicious for malignancy include hypoechoic areas, irregular margins, chaotic internal vasculature, nodules that are taller than they are wide in the transverse projection, and microcalcifications [48]. Two or more criteria identify neoplasia in 87–93 % of cases [49]. Although FNA appears to be safe in any trimester [9] and cytologic diagnoses appear accurate [44, 45], it may be deferred until after delivery in nodules thought to be benign on ultrasound.

Pregnancy is not thought to impact the prognosis of thyroid carcinoma, and surgery may be generally deferred until postpartum [9]. In five studies comparing the prognosis of women with differentiated thyroid cancer (DTC) during or within 1 year postpartum, no significant difference was seen in tumor recurrence or death between pregnant/postpartum women and controls [50–54]. Additionally, prognosis did not differ whether women had surgery during pregnancy or postpartum. In contrast, one study showed a poorer prognosis (persistence and relapse) in women diagnosed during pregnancy or within 1 year postpartum compared to controls. Most of the tumors in the pregnant/postpartum women were estrogen receptor positive, which may suggest an association between poor prognosis and estrogen-mediated growth [55].

In women with medullary thyroid carcinoma, the impact of pregnancy is unknown, and surgery is recommended for a large primary tumor or extensive lymph node involvement [9].

Surgery during the second trimester of pregnancy has not been associated with increased maternal or fetal risk. In five studies assessing outcomes following thyroid surgery during pregnancy, no maternal or fetal complications were reported [45, 56–59]. In contrast, a 2009 study showed that 201 pregnant patients had a higher risk of endocrine and general complications and longer lengths of stays and hospital costs compared to 31,155 nonpregnant patients [60]. However, results were difficult to interpret due to baseline differences between the two groups and because patients undergoing thyroid and parathyroid surgery were grouped together for analysis.

When a decision is made to defer surgery until postpartum, a neck ultrasound each trimester should be performed. Second trimester surgical intervention is recommended for rapid growth or the development of lymph node metastases before midgestation [9]. It is also recommended that thyroglobulin (Tg) be measured each trimester. Low-risk pregnant women with thyroid carcinoma may be started on thyroid hormone therapy to suppress TSH to 0.1–1.5 mIU/L [9].

In pregnant women who have benign nodules on FNA, repeat FNA and/or surgery is not required unless rapid growth is observed. Additionally, there is no evidence that levothyroxine decreases nodule size during pregnancy [9]. In those with 'suspicious' nodules on FNA, approximately 30 % are malignant. Similarly, surgery is not required unless rapid growth or lymph node metastases occur, and levothyroxine therapy is not recommended [9].

Due to the lack of documented maternal and neonatal complications with subclinical hyperthyroidism, it appears safe to suppress TSH levels during pregnancy in women who have previously treated thyroid cancer and are on levothyroxine therapy. The degree of suppression is dependent on the preconception risk of recurrent disease, with the goal of maintaining TSH in the preconception range during pregnancy. In women with persistent disease, goal TSH is <0.1 mU/L. In those with high-risk tumors free of disease, goal TSH is 0.1–0.5 mU/L. In those with low-risk tumors free of disease, goal TSH is 0.3–1.5 mU/L (low normal range). Lastly, in women who have not had 131-I, who are free of disease, and who have an undetectable Tg and normal neck ultrasound, the goal TSH is also 0.3–15 mU/L [9]. Approximately 9 % of women in the first trimester, 21 % of women in the second trimester, and 26 % of women in the third trimester will require an increase in their dose of levothyroxine [61]. It is recommended to check TSH every 4 weeks until 16–20 weeks gestational age and once again between 26 and 32 weeks gestational age [9].

Women with thyroid cancer often receive ablative 131-I therapy as part of their treatment. Two studies have evaluated the long-term outcome of fertility and future pregnancies. Neither study found an increase in the risk of infertility, miscarriage, congenital malformations, stillbirth, preterm birth, low birth weight, neonatal mortality, death during the first year of life, or childhood cancers [62, 63]. However, there is likely an increased risk of miscarriage in the months following 131-I ther-

apy, which may be due to suboptimal thyroid function response to levothyroxine. Therefore, it is recommended that pregnancy be deferred for at least 6 months after 131-I therapy and that levothyroxine dose should be stabilized prior to attempting pregnancy [9].

The impact of pregnancy on DTC has also been studied. In 60 women with a history of DTC and a subsequent pregnancy, there were no recurrences in the 38 disease-free patients and no accelerated tumor growth in those with residual disease [64]. Similarly, 70 women with a history of DTC and a subsequent pregnancy compared with 109 women with a history of DTC and no subsequent pregnancy showed no difference of recurrence between the two groups [65]. A more recent analysis of 64 women considered disease-free by Tg, and ultrasound and physical exam showed no evidence of cancer recurrence [66]. In contrast, a retrospective analysis of thyroid cancer survivors showed that 8 of 36 women who became pregnant on average 4.3 years after completing 131-I for DTC had a >20 % increase in Tg postpartum. Of these 8 women, 3 had known persistent disease and 5 were "disease-free." No change in Tg was seen in those with a Tg level <3.2 ng/ml and a negative neck ultrasound [67]. In another study, 6 of 63 women (0.95 %) demonstrated cancer progression during pregnancy, which was correlated to persistent disease prior to the pregnancy [68]. In conclusion, pregnancy does not appear to be a risk for tumor recurrence in women with a history of thyroid cancer who are free of structural or biochemical disease. However, in those with structural or biochemical disease at conception, pregnancy may "represent a stimulus to thyroid cancer growth" [9].

In low-risk patients with a history of previously treated DTC and no structural or biochemical evidence of disease prior to pregnancy, ultrasound and thyroglobulin monitoring is not required. In patients with baseline high Tg or structural disease, ultrasound monitoring should be performed each trimester [9].

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Cardiovascular Disease in Pregnancy

Jill B. Whelan and Loryn S. Feinberg

Case 1: Congenital Heart Disease, Bicuspid Valve

A 27-year-old woman presents at 14-weeks gestation for evaluation of a heart murmur. She has no prior past medical history and is taking prenatal vitamins. She was recently diagnosed with a heart murmur at an annual exam with her new primary care provider three months prior to the visit. She underwent a transthoracic echocardiogram which demonstrated a mildly thickened bicuspid aortic valve, with evidence of moderate aortic regurgitation. The aortic root and ascending aorta were well visualized, with mild root dilation of 37 mm and high-normal ascending aortic dimension of 35 mm. She had normal left ventricular cavity size and systolic function. She denies symptoms of shortness of breath, chest pain, dyspnea, palpitations, or peripheral edema. She exercises daily, walking two miles on flat ground without limitation. On examination, her blood pressures were 126/56 mmHg in the right upper extremity and 131/54 mmHg in the left upper extremity. She has a 2/4 diastolic murmur at the left lower sternal border, and her lung sounds are clear bilaterally, without appreciable rales or wheezing. Her laboratory tests showed normal hematocrit and platelet counts, and chemistry panel demonstrated normal electrolytes and renal function. On review, her grandfather had an aortic valve replacement when he was 56 years old, and her father carries the diagnosis of aortic stenosis. She is thrilled about her first pregnancy but is worried about the consequences of her valve disorder. She undergoes dedicated MRA imaging of the thoracic aorta, which

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shows aortic root dimension of 38 mm, ascending aortic dimension of 35 mm, aortic arch dimension of 29 mm, and descending aortic dimension of 24 mm. There is no evidence of aortic coarctation, and there is no aortic flow reversal in the descending aorta. She was counseled regarding the presence of a congenital bicuspid aortic valve, mild aortic dilation, and the need to follow these findings over time. However, there was determined to be no contraindication to pregnancy. She underwent evaluation with a cardiologist in her second and third trimester, without development of clinical symptoms suggesting changes in valvular pathology. She delivered a healthy baby girl at 38 6/7 weeks without complication.

Aortic insufficiency (AI) or regurgitation is generally well tolerated in pregnancy due to a combination of reduced systemic vascular resistance and shortened diastole due to a rise in heart rate, which can reduce the severity of the regurgitant volume. In young women, AI may be due to a congenital bicuspid valve, rheumatic heart disease, infective endocarditis, an autoimmune disorder (i.e., rheumatoid arthritis), or a dilated aorta, such as in certain connective tissue disorders (Marfan syndrome, Ehlers-Danlos syndrome). Typically, symptoms are correlated with severity of regurgitation and the presence of left ventricular dilation and dysfunction. Severe aortic regurgitation with left ventricular dysfunction or acute onset regurgitation is poorly tolerated [1]. In this patient, the presence of a congenital bicuspid aortic valve has led to the development of moderate AI, and she has thus far remained asymptomatic.

Assessing maternal and fetal risk, ideally prior to conception, is central to the management of heart disease in pregnancy. Risk prediction scores of cardiac disease in pregnancy were studied by the CARPREG investigators, who examined four clinical features in the general population including prior arrhythmia or cardiac event, NYHA functional class > II or cyanosis, left heart obstruction, and systolic left ventricular dysfunction with LVEF < 40 %. They determined maternal cardiac event rates of 5 %, 27 %, and 75 % for the presence of 0, 1, and >1 of these clinical features (Tables 1 and 2) [2]. Adverse maternal cardiac events consisted of pulmonary edema, symptomatic arrhythmia, stroke, cardiac arrest, or death. More recently, the ZAHARA investigators expanded the clinical predictors of adverse maternal and fetal outcomes while studying a large population of congenital heart disease patients [3, 4]. In these risk models, severe aortic insufficiency with NYHA class III

Table 1 New York Heart Association functional classification

NYHA class	Symptoms
I	Cardiac disease present, but no symptoms and no limitation in ordinary physical activity, e.g., no shortness of breath with walking (>3–4 city blocks), climbing stairs (two flights), etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (<100 m). Comfortable only at rest
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients

Table 2 Predictors of maternal cardiovascular events and risk score based on the CARPREG study

Cardiovascular event prior to pregnancy (heart failure, transient ischemic attack, stroke, or arrhythmia)
Baseline NYHA functional class > II or cyanosis
Obstructive left ventricular lesions (by echocardiography: mitral valve area <2 cm^2, aortic valve area <1.5 cm^2, peak LV outflow tract gradient > 30 mmHg)
Left ventricular systolic dysfunction (ejection fraction <40 %)

Adapted from Regitz-Zagrosek et al. [1] and Thorne et al. [5]
One point assigned per predictor. Risk estimation of cardiovascular maternal complications: 0 points, 5 %; 1 point, 27 %; >1 point, 75 %
LV left ventricle, *NYHA* New York Heart Association

Table 3 Modified World Health Organization (WHO) classification of maternal cardiovascular risk principles

Risk class	Risk of pregnancy by medical condition
I	No or mild increase in maternal morbidity, and no discernable increased risk of maternal mortality
II	Moderate increase in maternal morbidity and small increased risk of mortality
III	Potential for severe maternal morbidity and significantly increased risk of mortality. Expert counseling regarding risk in pregnancy required. If pregnancy is decided upon, multidisciplinary cardiac and obstetric monitoring needed throughout pregnancy, childbirth, and puerperium
IV	Extremely high risk of severe maternal morbidity or mortality; pregnancy contraindicated. If pregnancy occurs, termination should be discussed. If pregnancy continues, care as class III with multidisciplinary team

Adapted from Regitz-Zagrosek et al. [1] and Thorne et al. [5]

or IV symptoms was thought to be poorly prognostic of maternal and fetal outcomes. However, moderately regurgitant valves tended to be less symptomatic and typically did well with conservative medical management. According to the modified World Health Organization (WHO) risk classification, which integrates known maternal cardiovascular risk factors including conditions with contraindications to pregnancy (Tables 3 and 4) [5], moderate AI represents a modified WHO class II classification. Patients who are WHO class II have a small increased risk of maternal mortality or moderate increase in morbidity, and these patients are recommended to be evaluated by a cardiologist and high-risk obstetrician each trimester for clinical assessment. Modified WHO classification is a useful metric for assessing maternal and fetal risk of cardiac lesions that are established prior to pregnancy.

The evaluation of regurgitant valvular lesions should include a complete evaluation of symptoms, echocardiographic evaluation of regurgitation severity, left ventricular dimensions, and systolic function [6]. Ideally, valvular dysfunction should be assessed prior to pregnancy to establish the stability of the regurgitation over time, to counsel on maternal and fetal risk, and to initiate therapy appropriate for pregnancy. Patients with severely regurgitant valves are recommended against pregnancy prior to valve repair or replacement. In moderate-to-severe regurgitant valves, exercise

Table 4 Modified WHO classification of maternal risk by cardiovascular disease

Conditions in which pregnancy risk is WHO I
Mild pulmonic stenosis, patent ductus arteriosus, or mitral valve prolapse, if uncomplicated
Repaired atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage
Isolated atrial or ventricular premature contractions
Conditions in which pregnancy risk is WHO II to III
WHO II (if otherwise asymptomatic and uncomplicated)
Uncorrected atrial or ventricular septal defect
Tetralogy of Fallot, repaired
Majority of arrhythmias
WHO II–III (depending on individual)
Mild left ventricular systolic dysfunction
Hypertrophic cardiomyopathy
Valvular regurgitation or stenosis (native or prosthetic) not considered WHO I or IV
Marfan syndrome in the absence of aortic dilation
Aortic dilation (<45 mm) associated with bicuspid aortic valve
Repaired aortic coarctation
WHO III
Prosthetic mechanical valve
Systemic right ventricle
Fontan circulation
Cyanotic congenital heart disease (unrepaired)
Complex congenital heart disease
Marfan syndrome with aortic dilation of 40–45 mm
Bicuspid aortic valve with aortic dilation of 45–50 mm
Conditions in which pregnancy risk is WHO IV (pregnancy contraindicated)
Pulmonary arterial hypertension (of any cause)
Severe left ventricular systolic dysfunction (LVEF <30 %, NYHA III–IV)
Prior peripartum cardiomyopathy, with any residual left ventricular systolic dysfunction
Severe mitral stenosis, severe symptomatic aortic stenosis
Marfan syndrome with aortic dilation of >45 mm
Bicuspid aortic valve with aortic dilation of >50 mm
Severe aortic coarctation

Adapted from Regitz-Zagrosek et al. [1] and Thorne et al. [5]
WHO World Health Organization, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association

testing is recommended to fully characterize the patient's functional capacity, the hemodynamic consequences of the lesion, and evaluate for inducible pulmonary hypertension. Symptoms during pregnancy can typically be managed conservatively with judicious use of diuretics for congestive symptoms and afterload-reducing agents, such as hydralazine. Angiotensin Converting Enzyme (ACE) inhibitors and angiotensin receptor blockers, which are also afterload-reducing agents, are strictly contraindicated in pregnancy due to their teratogenicity.

In acute severe regurgitation refractory to therapy, surgery may be unavoidable. If the fetus is mature enough, delivery should occur prior to surgery. In patients with any valvular regurgitation, vaginal delivery is preferable, and symptomatic patients should receive regional anesthesia with epidural or spinal to minimize the cardiovascular consequences of catecholamine surges. In some cases, an assisted second stage of labor may be appropriate [1].

Congenital bicuspid aortic valves are often associated with an underlying aortopathy, and it is important to screen for concomitant aortic dilation and aneurysm. Likewise, there is an important link between bicuspid aortic valves and coarctation of the aorta, and individuals with bicuspid aortic valves should be screened for this condition as well. Approximately 50 % of patients with bicuspid aortic valve and aortic valve pathology (aortic stenosis or aortic regurgitation) have dilation of the ascending aorta [7]. Also, dilation is often maximal at the distal end of the ascending aorta, which cannot be adequately visualized with transthoracic echocardiography, and Magnetic Resonance Imaging (MRI) or Compted Tomography (CT) of the chest should be performed prior to conception. Pre-pregnancy surgery should be considered when the thoracic aortic diameter reaches 50 mm [8]. Immer et al. [9] found that increased aortic root dilation during pregnancy in patients with bicuspid aortic valve carries a significant risk of type A aortic dissection.

Our patient underwent a transthoracic echocardiogram, with visualization of the aortic root, which was mildly dilated. The entire ascending aorta, aortic arch, and descending aorta were not fully visualized. Dedicated MRI of the aorta without contrast administration (an optimal choice to decrease radiation exposure) showed stable dilation of the aortic root and no evidence of coarctation, thoracic aneurysm, or dissection. She underwent a normal pregnancy, with regularly scheduled follow-up with her cardiologist. In the setting of congenital bicuspid aortic valve disease, screening of first-degree relatives, including children, siblings, and parents, is recommended [8].

Case 2: Arrhythmia in Pregnancy

A 31-year-old woman presents to the emergency department at 35-weeks gestation with acute shortness of breath, chest pressure, and sudden onset of palpitations for the preceding 30 minutes. Her medical history is notable for a history of hyperthyroidism for which she received radioactive iodine ablation. She takes levothyroxine 75 mcg by mouth daily, which was recently increased in the first trimester. Six years ago, she had presented to the emergency department with thyrotoxicosis and a supraventricular tachycardia. Her initial vital signs demonstrate a heart rate of 164 beats per minute, blood pressure of 109/56 mmHg, and respiratory rate of 26 respirations per minute. An electrocardiogram is shown in Fig. 1. Laboratory values are not yet obtained. Carotid sinus pressure is applied at the bedside, which decreases the rate to 146 beats per minute (bpm) briefly. Adenosine 6 mg IV once is administered, with a two-second pause and termination of the arrhythmia with conversion

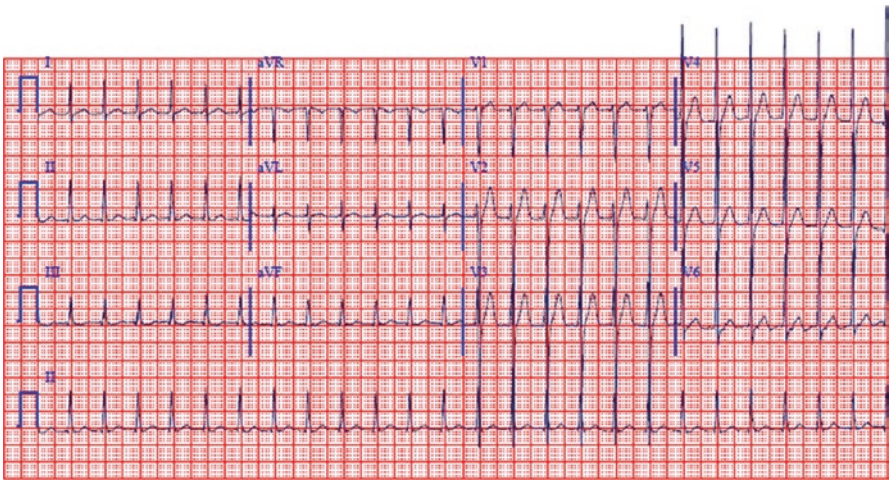

Fig. 1 ECG of supraventricular tachycardia

to sinus rhythm at 83 bpm. Her shortness of breath and chest discomfort resolve. She is admitted for further monitoring on telemetry, but she remains in sinus rhythm for 24 hours (h) and is discharged home without medication changes. Twelve days later, she re-presents with recurrent symptoms and is found to have a supraventricular tachycardia at 157 bpm. She is given adenosine 6 mg IV once, with resolution of the tachycardia and reestablishment of sinus rhythm. During the preceding 10 days, she noted intermittent palpitations for 1–2 min before resolving either on their own or with vagal maneuvers. She is admitted for monitoring and started on digoxin 0.125 mg daily. She undergoes induction of labor on hospital day three, with placement of an epidural, and delivery of a healthy baby boy at 37 0/7 weeks gestation. On hospital day six, she undergoes an electrophysiology study and atrioventricular nodal reentrant tachycardia (AVNRT) ablation. She is discharged on hospital day seven in stable condition.

Premature extra beats and atrial tachyarrhythmias are more frequent and may even manifest for the first time, during pregnancy. The sensation of palpitations is common in pregnancy, with sinus tachycardia, premature atrial contractions, and premature ventricular complexes representing the most common findings [10, 11]. Premature beats manifest most frequently during the second trimester. They are not associated with adverse maternal or fetal outcomes and require treatment only if symptoms are intolerable to the mother. The occurrence of atrial fibrillation or atrial flutter is relatively rare during pregnancy and is usually associated with hyperthyroidism or structural cardiac disease [1], such as underlying valvular disease, congestive heart failure, or congenital heart disease.

AVNRT is the most common supraventricular arrhythmia in pregnant and nonpregnant women. In patients with a preexisting history of supraventricular tachycardia, the incidence of recurrence during pregnancy is as high as 20–44 % in case studies [12, 13]. Previously highly symptomatic tachyarrhythmias should be

treated with catheter ablation prior to pregnancy, when possible. During pregnancy, as in our patient, most supraventricular arrhythmias represent a WHO class II risk category, with a small increase in maternal mortality and a moderate increase in morbidity.

Typically, supraventricular tachyarrhythmias are not well tolerated in pregnancy, if rapid and sustained. Thus, the general preference is to restore sinus rhythm. AVNRT or atrioventricular reentrant tachycardia (AVRT) involving an accessory pathway can often be terminated by successful vagal maneuvers, such as having the patient perform the Valsalva maneuver and cough vigorously or by applying carotid sinus pressure. If vagal maneuvers fail, adenosine is the first drug of choice and can be administered safely and intravenously in pregnancy for diagnostic and therapeutic purposes [13, 14]. Adenosine interrupts conduction down the accessory atrioventricular nodal pathway by prolonging the refractory period of the atrioventricular (AV) node and revealing the underlying atrial arrhythmia. Intravenous metoprolol can be used if adenosine fails and serves to slow the ventricular rate to control symptoms but will not typically convert the rhythm to sinus. Direct current synchronized cardioversion is also safe in all stages of pregnancy [13] and is used typically in situations of hemodynamic instability or arrhythmias refractory to medical therapy.

Digoxin is considered safe in pregnancy and can be used to control the ventricular rate but is not an effective medication to use in the acute setting [13]. Other agents, such as specific medications acting on the AV node (beta-blockers, non-dihydropyridine calcium channel blockers; most class C agents) (Table 5), may also be safe and tolerated during pregnancy to treat the symptoms of the arrhythmia. Antiarrhythmic drug therapies can be toxic to the developing fetus and should be discontinued prior to conception [13]. Major controlled studies of antiarrhythmic drugs during pregnancy are lacking. Typically, antiarrhythmic therapy is reserved for hemodynamic compromise or refractory or recurrent arrhythmia. Specific antiarrhythmic medications are considered safer to use in pregnancy, such as sotalol (class B), flecainide

Table 5 Federal drug administration pregnancy categories

Risk class	Risk of medication in pregnancy
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)
B	Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women
C	Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
X	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, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits

(class C), and ibutilide (class C) [13]. They have not demonstrated any adverse fetal effects, but experience with these medications in pregnancy is limited. Amiodarone is usually recommended against in pregnancy. It is a pregnancy class D medication and its use in pregnancy should be restricted to arrhythmias that are resistant to other drugs or are life threatening [15]. Bypass tract or atrioventricular nodal ablation is possible during pregnancy if necessary and is best performed during the second trimester when the fetus has undergone initial development and the mother and fetus can still be adequately shielded from radiation exposure.

Case 3: Valvular Stenosis, Mitral Stenosis

A 28-year-old Indian American woman presents for evaluation at 8-weeks gestation with a recent diagnosis of rheumatic mitral stenosis (MS). This is her second pregnancy, and the first was an uncomplicated pregnancy with vaginal delivery and home birth three years ago with a midwife while living in India. She was noted to have a murmur on exam by her current midwife and referred for further evaluation. She underwent a transthoracic echocardiogram one week ago which demonstrated mild dilation of the left atrium and a characteristic rheumatic deformity of the mitral valve with severe mitral stenosis and a calculated mitral valve area of 1.3 cm^2. Prior to her pregnancy, she did not experience dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, or peripheral edema. She does note occasional palpitations that she describes as "skipped beats" for the last four weeks, occurring approximately every other day. She does not exercise regularly and is able to care for her three-year-old son, cook, and clean the home without limitations.

On examination, her blood pressure is 110/64 mmHg and heart rate 64 beats per minute and regular. She is noted to have jugular venous distension at 10 cm of H_2O and a 2/6 apical systolic murmur with a soft opening snap, followed by a 2/4 diastolic rumble. Her lung exam is clear, without rales. She has no evidence of peripheral edema. Her electrocardiogram shows normal sinus rhythm with no abnormalities. Her other medical problems include a history of hypothyroidism, for which she takes levothyroxine 37.5 mcg daily.

Four months later, at 24-weeks gestation, she presents to the emergency room with one week of dyspnea on minimal exertion. She is now experiencing mild shortness of breath at rest. Her vital signs show a blood pressure of 96/54 mmHg and pulse rate of 116 beats per minute. A chest x-ray shows bilateral perihilar infiltrates consistent with mild-to-moderate pulmonary congestion. Duplex of the lower extremity shows no evidence of deep venous thrombosis. Her laboratory values are notable for normal chemistry values, including a potassium of 4.6 mEq/L, a blood urea nitrogen of 11 mg/dL, a creatinine of 0.7 mg/dL, a troponin I of 0.01 ng/mL, and a N-Terminal pro-brain natrideretic peptude (NTproBNP) level of 2675 pg/mL. Her electrocardiogram shows an irregularly irregular narrow complex rhythm without organized atrial activity consistent with atrial fibrillation with a rapid ventricular response. She is admitted to the hospital and started on furosemide 40 mg

IV daily with improvement in her symptoms. She is started on therapeutic low molecular weight heparin twice daily and metoprolol 25 mg orally twice daily and spontaneously converts to sinus rhythm on hospital day two. She is discharged from the hospital on day four on furosemide 20 mg oral daily, metoprolol succinate 25 mg once daily, and therapeutic low molecular weight heparin. At 37-week gestation, she undergoes a planned induction of labor with an interdisciplinary team. Low molecular weight heparin is discontinued 12 h prior to induction and anesthesia. An epidural is placed, and she receives an assisted second stage of labor with low forceps extraction and delivers a healthy baby girl. In the immediate postpartum period, she is restarted on therapeutic low molecular weight heparin 12 h after delivery. She notes increased shortness of breath at 18 h after delivery, and a chest radiograph reveals mild pulmonary vascular congestion. An EKG shows atrial fibrillation at 108 bpm. She is restarted on furosemide 20 mg IV daily with resolution of her symptoms.

Rheumatic heart disease is the most common etiology of mitral stenosis in reproductive-aged women. It remains a major problem in developing countries and is still seen in developed countries, especially in immigrant populations. In general, stenotic valves confer a higher risk to the pregnant patient than regurgitant valves, and left-sided valve diseases involving the mitral and aortic valves have a higher complication rate than right-sided valve lesions of the tricuspid and pulmonic valves [1–3, 16]. Physiologic changes during pregnancy can cause previously asymptomatic patients to become symptomatic, as the heart rate may increase by 25 % and blood volume can expand by 40–50 % during pregnancy, leading to a marked increase in stroke volume and cardiac output. In stenotic valve disease, these hemodynamic changes increase the transvalvular gradient and decrease the filling time of the left ventricle and, thus, increase left atrial pressures, resulting in pulmonary venous congestion, pulmonary edema, and congestive heart failure. The presence of atrial fibrillation with a rapid ventricular rate often causes further clinical deterioration. Additionally, the rapid increase in venous return during labor and delivery, partially related to autotransfusion of maternal blood into the circulation from uterine contractions and from relief of inferior vena cava compression from the gravid uterus, may cause a further surge in preload to the left atrium, which can stress the heart further.

Management of MS is related to the severity of stenosis, the presence of symptoms, and timing of diagnosis. Moderate or severe MS is typically poorly tolerated during pregnancy [16], even when the patient is previously asymptomatic. Two main predictors of adverse outcomes during pregnancy include mitral valve area < 1.5 cm^2 and abnormal functional class prior to pregnancy. If diagnosed prior to pregnancy, patients with severe MS regardless of symptoms (valve area < 1 cm^2) or moderate symptomatic stenosis (valve area 1–1.5 cm^2) should be considered for percutaneous mitral balloon valvuloplasty (PMBV) or mitral valve replacement if PMBV is not appropriate. If a patient is pregnant and congestive heart failure cannot be managed with medical therapy, valvuloplasty can be performed resulting in a significant hemodynamic benefit and usually favorable pregnancy outcome [16, 17]. However, valvuloplasty-related complications including cardiac tamponade,

systemic embolization, maternal arrhythmias, initiation of uterine contractions, fetal distress, and fetal loss have been reported, in addition to radiation exposure to the fetus [16]. Optimal management of the pregnant patient with MS is focused on reducing left atrial pressures with careful diuresis and improving left ventricular filling with heart rate control, typically using beta-blockers. Judicious diuresis is crucial to avoid hypotension and volume depletion which may result in decreased uteroplacental perfusion and intrauterine growth restriction.

With pressure and volume overload, mitral stenosis can lead to left atrial stretch and dilatation and place the patient at increased risk of atrial arrhythmias, the most common of which is atrial fibrillation. Patients with valvular atrial fibrillation or atrial flutter require systemic anticoagulation as they are more prone to thromboembolic events than the general population with atrial fibrillation. With any episode of atrial fibrillation, continuous anticoagulation is recommended throughout pregnancy and up to 12 weeks postpartum, when the hypercoagulable state of pregnancy resolves. It is important to screen patients with mitral stenosis for symptoms of atrial arrhythmias, which includes sensations of palpitations, skipped beats, or rapid heart rates. This patient is presenting in the second trimester when intravascular volume is highest with congestive heart failure and atrial fibrillation. Mitral stenosis represents at least a WHO class III risk classification, with significant increased risk of maternal mortality and severe morbidity. She requires immediate treatment with intravenous diuretics, medications for heart rate control, and admission for monitoring. She should be started on unfractionated heparin (UFH) continuously for therapeutic anticoagulation of valvular atrial fibrillation, due to her risk of intracardiac thrombus and systemic embolism. UFH does not cross the placenta and does not expose the fetus to anticoagulation, as does warfarin. Unlike warfarin, heparin does not confer teratogenic effects and is, therefore, considered safer for the fetus. Low molecular weight heparin (LMWH) may also be utilized, using a twice daily weight-based dosing schedule. During pregnancy the volume of distribution for LMWH is variable, and it is essential to monitor anti-factor Xa levels drawn four hours after administration to establish an appropriate dose. Appropriate levels of anti-Xa should range between 0.7 and 1.2 U/mL.

Most patients with MS with NYHA class I/II symptoms can safely undergo vaginal delivery. Patients with class III/IV symptoms or with pulmonary hypertension who do not undergo valvuloplasty should be considered for cesarean delivery [1]. In patients with symptomatic moderate-to-severe mitral stenosis, anesthesia with regional epidural is recommended with an assisted second stage of delivery to decrease pain, abrupt hemodynamic changes, and the adverse cardiovascular effects of repeated, prolonged Valsalva maneuver. Additionally, patients need close monitoring during the immediate postpartum period (12–24 h) when uterocaval venous obstruction is relieved, and sudden increased venous flow to the heart can result in pulmonary edema. Patients with rheumatic valvular disease who traditionally require antibiotic prophylaxis for dental procedures do not routinely require antibiotic prophylaxis for vaginal or cesarean delivery, as long as infection is not suspected and aseptic measures are followed [6, 18].

Case 4: Prosthetic Valve

A 26-year-old woman with a history of intravenous drug abuse and infective aortic valve endocarditis requiring bioprosthetic aortic valve replacement six years prior presents at 7-weeks gestation with her second child. She denies intravenous drugs abuse since prior to the surgery. Her most recent transthoracic echocardiogram three months ago demonstrated a well-seated and normally functioning bioprosthetic aortic valve with mild perivalvular regurgitation and normal transvalvular gradients and otherwise normal left ventricular function and left ventricular cavity size. She denies symptoms of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, palpitations, or chest pain. She is reassured that she does not need to start any new medications, and she is told to continue aspirin 81 mg daily that she is taking for prevention of bioprosthetic valve thrombosis. She has an uneventful pregnancy course and follows up during her second and third trimester with her cardiologist without concerns for clinical deterioration. She delivers a healthy baby boy at 39 and 3/7 weeks.

The selection of artificial valves in women of childbearing age is controversial. Typically, most agree that selection of bioprosthetic valves is safer for mother and child during this period, although their use is associated with an increased risk of structural degeneration in younger patients, which also may be accelerated by pregnancy [19]. In general, patient with bioprosthetic valves will, on average, require repeat valve replacement in 10–15 years after initial placement due to degeneration. This exposes patients to repeated surgical risk associated with open-heart surgery versus the advantage of valve longevity attributed to mechanical valves. However, mechanical valves and their complicated anticoagulation requirements confer increased maternal morbidity and mortality with the possibility of valve dysfunction, valve thrombosis and heart failure, and a higher risk of fetal complications, including fetal demise. The risk of valvular complications during pregnancy depends on the type and age of the valve, position of the valve (i.e., mitral vs. aortic), left ventricular function, and presence of atrial arrhythmias. In patients with well-functioning bioprosthetic valves, the management is similar to that in patients with native valves. There is no indication for systemic anticoagulation in patients with bioprosthetic valves, but aspirin, which is recommended for all prosthetic valves, may be continued in the setting of pregnancy [6]. Patients with bioprosthetic valves should be educated about the possibility of valve dysfunction and should be monitored for signs and symptoms of this. A baseline echocardiogram prior to pregnancy is important to assess the function of the prosthetic valve, including transvalvular gradient; the presence of valvular regurgitation, in addition to evaluating for pulmonary hypertension; ventricular cavity sizes and systolic function; and hemodynamics. In this patient, she has evidence of mild valve degeneration, with mild thickening and regurgitation of the valve. With mild valve dysfunction and normal left ventricular function and no symptoms of congestive heart failure, she is at minimal (WHO class I) risk during this pregnancy. Additionally, according to the American Heart Association, antibiotic prophylaxis in patients with a prior history of endocarditis or with biologic or mechanical prosthetic valves who are undergoing uncom-

plicated vaginal delivery or cesarean section is considered optional, as these patients are considered high risk. Many practitioners have a tendency to give antibiotics prior to delivery in high-risk patients [18].

Over the next 5–8 years, however, this patient may become symptomatic from aortic valve dysfunction. At that point, she may require a repeat sternotomy and valve replacement, and she will still be of reproductive age. Prior to this time, it will be important to establish with this patient her desire for future childbearing. She should be counseled regarding the surgical risk of repeat valve replacement, and there should be consideration for replacement with a mechanical aortic valve during her next surgery due to its longevity. Pregnancy is generally considered high risk in patients with mechanical valves, as management of adequate therapeutic anticoagulation is challenging, and it puts the mother and fetus at risk of complications. One of the reasons for this complication rate includes the fact that pregnancy is a prothrombotic state, and patients with prosthetic mechanical valves are at a higher risk of valve thrombosis throughout pregnancy. In a large review, this risk was found to be 3.9 % with warfarin throughout pregnancy, 9.2 % when unfractionated heparin was used in the first trimester and warfarin in the second and third trimester, and 33 % when unfractionated heparin was used throughout pregnancy. Maternal death complicated these groups in 2 %, 4 %, and 15 % and was usually related to valve thrombosis [10]. According to the American College of Cardiology (ACC) American Heart Associtaion (AHA) guidelines, all pregnant patients with mechanical prosthetic valves must receive continuous therapeutic anticoagulation throughout pregnancy [6].

The need for anticoagulation must be weighed with the risk of fetal complications related to anticoagulation. Warfarin is the anticoagulant of choice for mechanical valves, but it freely crosses the placental barrier. It can adversely affect fetal development, particularly in early pregnancy, and increases the risk of serious bleeding in later stages of development. Fetal embryopathy syndrome, characterized by cognitive impairment, optic atrophy, and fetal bone and cartilage malformations, is highest during the 6th through 12th weeks of gestation [1]. Some patients may elect to hold warfarin between these developmental weeks with transition to dose-adjusted UFH or LMWH, which does not cross the blood-placental barrier. Others may elect to use heparin throughout the pregnancy, decreasing fetal risk but increasing maternal risk of prosthetic valve thrombosis, systemic embolism, and heparin-induced thrombocytopenia. After 36 weeks, however, warfarin should be stopped in all pregnant patients, with transition to UFH or LMWH prior to planned delivery and regional anesthesia.

Case 5: Peripartum Cardiomyopathy

A 33-year-old woman of Ghanaian descent presents in labor at 37 and 4/7 weeks with a twin gestation. At 42 h, she is taken to cesarean section delivery for failure to progress. Cesarean section is complicated by uterine atony and postpartum hemorrhage requiring three units packed red blood cells and two liters of crystalloid for

hemodynamic stabilization with application of Bakri balloon and eventually emergent uterine artery embolization. Hematocrit drops to 21.3 % from 37.6 % and stabilizes at 28.2 % after transfusion. The twin baby boys are healthy with Apgar scores of 8 at 5 min after delivery. At 36 h after delivery, she develops increasing shortness of breath at rest and a new oxygen requirement. Her physical exam reveals bilateral rales at the lung bases, without wheezing, and 2+ bilateral lower extremity edema to just below the knees. A chest x-ray demonstrates bilateral perihilar infiltrates consistent with mild pulmonary edema and small left-sided pleural effusion. A proBNP level is 2,579 pg/mL. A transthoracic echocardiogram is performed on postpartum day 2 and shows left ventricular cavity dilation of 5.9 cm (normal < 5.3 cm) and reduced global left ventricular systolic function with an ejection fraction of 35 %. She is admitted to the Intersive Care Unit (ICU) and started on IV furosemide boluses with clinical improvement in her symptoms.

Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy that can occur from the last month of pregnancy up until five months postpartum and is characterized by left ventricular dysfunction developing during this time frame in the absence of any identifiable or preexisting cause of heart failure. The incidence of PPCM occurs in up to one in 3000 to 4000 births, with variation based on genetic and cultural factors [20]. It is suspected to be the consequence of an imbalance of oxidative stress in which infections, inflammation, and autoimmune processes play a role. Predisposing factors include maternal age greater than 30 years; multiparity and multiple childbirths; history of preeclampsia, eclampsia, or postpartum hypertension; ethnicity (particularly of African descent); low socioeconomic status; or tocolytic therapy with beta-agonists [1]. Heart failure in PPCM is manifested by symptoms such as fatigue, dyspnea, nonspecific chest pain, abdominal distension, symmetric peripheral edema, orthopnea, or paroxysmal nocturnal dyspnea. Transthoracic echocardiography is the appropriate diagnostic test of choice for assessing left ventricular function when PPCM is suspected.

Standard medical management of pregnant patients with decompensated heart failure includes oxygen, diuretics, and vasodilators, such as nitroglycerin or hydralazine. Diuretics should be used judiciously to manage symptomatic shortness of breath and pulmonary congestion, as they can cause placental hypoperfusion. Angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), which are a standard of care in systolic heart failure, are contraindicated in pregnant patients due to fetal teratogenicity (class D) and should not be initiated until after delivery. When ACE inhibitors are needed during breastfeeding, benazepril, captopril, and enalapril are preferred due to reduced excretion in breast milk compared to other agents [21]. Beta-1 selective beta-blockers (most class C) are indicated in patients with heart failure but should not be initiated until the patient is hemodynamically stabilized and her volume status has been optimized. Anticoagulation should be considered in patients with very low ejection fraction <30 % and is recommended in patients with intracardiac thrombus or evidence of systemic embolism.

The prognosis after PPCM is variable; when compared to other etiologies of cardiomyopathy, PPCM generally has a more favorable survival rate [22].

Approximately 50 % of women completely recover normal heart size and function, usually within six months of delivery, but ejection fraction can continue to improve up to two years postpartum. Prognosis is more favorable when the ejection fraction at initial diagnosis is >30 %. The remainder of patients either experience persistent stable left ventricular dysfunction or continue to experience clinical deterioration over time. Predictors of poor prognosis include those with an initial left ventricular ejection fraction <30 % at diagnosis, echocardiographic left ventricular cavity dilation >6 cm, or elevated troponin at diagnosis [23].

Women with a history of peripartum cardiomyopathy should be risk stratified by a cardiologist prior to planning future pregnancies. Subsequent pregnancies carry a recurrence risk of peripartum cardiomyopathy up to 30–50 % [1]. As in this patient, women with a history of peripartum cardiomyopathy and a persistently low ejection fraction are considered modified WHO criteria class IV with respect to future pregnancies. If pregnancy occurs in patients with LVEF less than 40 %, this is a predictor of high-risk maternal and fetal complications, and these patients should consider termination, especially if symptomatic at baseline assessment. If asymptomatic, the pregnancy is still considered high risk, and these patients should be monitored monthly with a tertiary care interdisciplinary team of high-risk obstetricians, anesthesiology, and cardiologists trained in caring for pregnant patients. If LVEF is less than 20 %, maternal risk, including that of death, may be high, and termination of pregnancy should be advised.

Case 6: Myocardial Infarction in Pregnancy

A 42-year-old woman presents to the emergency department at 34 and 1/7 weeks gestation with severe substernal chest pressure associated with nausea. She has a medical history significant for hypercholesterolemia and type I (juvenile onset) diabetes mellitus. She is an executive at a public relations firm and has recently been under stress preparing for a quarterly review. She was in a board meeting today when she had sudden onset chest discomfort at an intensity of 4/10 for the last hour that escalated to 6/10 and was associated with pain radiating down her left arm. A co-worker accompanied her to the emergency department due to ongoing pain. She also has noted contractions for the last hour that are increasing in frequency and severity. Nitroglycerin is administered sublingually, and the chest pain decreases from 7/10 to 3/10. Her initial electrocardiogram (EC6) is shown in Fig. 2. An ST-elevation myocardial infarction (STEMI) is suspected, and she is taken emergently to the catheterization lab. She is given an intravenous heparin bolus and clopidogrel 600 mg once. An acute 99 % proximal plaque thrombosis of the left anterior descending artery is diagnosed during coronary angiography, and a bare metal stent is placed with good angiographic result. Her chest pain post-procedure has resolved, and ST segment elevations have returned almost to baseline on a repeat electrocardiogram. Her uterine contractions have become less frequent. She is admitted to the critical care unit for monitoring for 48 h and eventually discharged

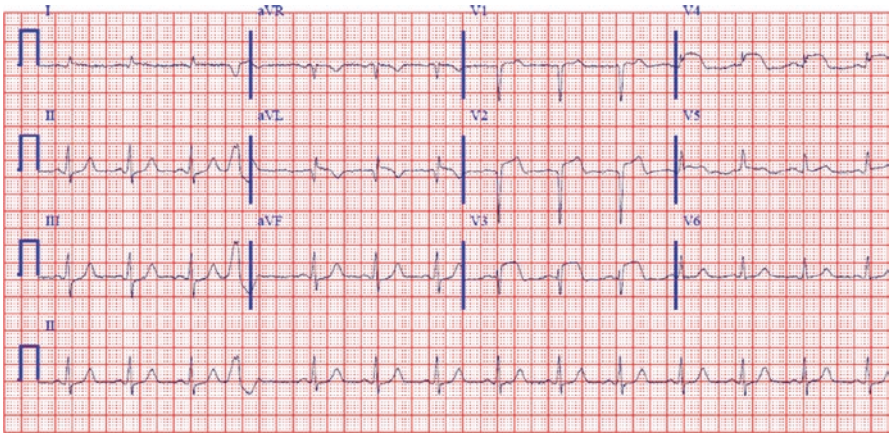

Fig. 2 ECG of supraventricular tachycardia infarction

in stable condition on aspirin 81 mg daily and clopidogrel 75 mg daily. Three weeks later, at 37-weeks gestation, she is instructed to discontinue clopidogrel in anticipation of delivery. She is induced at 37 and 5/7 weeks gestation with placement of an epidural and delivers a healthy baby girl via vaginal delivery after 15 h of labor.

The incidence of acute myocardial infarction (MI) in pregnancy is rare, complicating 3–6 out of every 100,000 pregnancies [24, 25]. While this is an uncommon event in childbearing women, the risk increases three to four times in pregnancy due to increased hypercoagulability, higher myocardial oxygen demand related to increased cardiac output, and decreased oxygen supply with anemia and decreased diastolic blood pressures. Additionally, as women become pregnant later in life with increasing frequency and comorbid conditions such as diabetes mellitus and tobacco abuse, the risk of coronary artery disease increases. The risk of myocardial infarction is also strongly related to major cardiovascular risk factors, such as hypertension, hyperlipidemia, older age, and a positive family history of extensive or early coronary artery disease. Though relatively uncommon, ischemic heart disease is the most common cause of cardiac disease leading to maternal death [26].

Ischemic heart disease can be caused by many different pathologic processes. Coronary artery vasospasm and coronary dissection more frequently result in acute coronary syndrome during pregnancy than the general population; however, classic obstructive atherosclerosis with plaque rupture or fissure with overlying thrombosis is still the leading cause [24]. Pregnant women at higher risk include older patients in their third trimester, who have had multiple prior pregnancies. Other conditions that contribute risk include the presence of preeclampsia or eclampsia, thrombophilia, postpartum infections, and severe postpartum hemorrhage [24, 25]. The diagnosis of acute coronary syndrome is the same in pregnant patients as nonpregnant patients and consists of the clinical history, electrocardiographic changes, and cardiac biomarkers. The diagnosis of a myocardial infarction is often delayed, as more subtle complaints can be attributed to pregnancy-related symptoms. For

non-ST-elevation MI (NSTEMI), troponin levels are superior for diagnosis during labor and delivery, since CK and CK-MB enzymes are increased twofold within 30 min of delivery. However, severe postpartum hemorrhage with shock may also lead to elevated troponin levels with ischemic ECG changes and transient left ventricular wall motion abnormalities. STEMI is a clinical diagnosis based on symptoms and electrocardiographic changes and should not be delayed to wait for cardiac biomarkers to be processed, which can be normal in the acute setting.

Treatment of acute coronary syndrome may be modified in pregnancy to avoid added risk. In general, aspirin, nitroglycerin, beta-blockers, and heparin are considered safe in pregnancy. Statins, ACE inhibitors, and ARBs are contraindicated during pregnancy, and there is no established data for P2Y12 (i.e., clopidogrel, prasugrel, ticagrelor) or glycoprotein IIb/IIIa inhibitors (i.e., abciximab, eptifibatide, tirofiban), though P2Y12 inhibitors are used if necessary (e.g., the presence of an aspirin allergy or if stenting occurs). Emergent coronary angiography should be performed if primary percutaneous coronary intervention is anticipated, such as during an STEMI or if there is refractory ischemia despite optimal medical therapy. Alternatively, medical management may be considered in appropriate patients with an NSTEMI or unstable angina who remain asymptomatic and stable following initiation of therapy. Ideally, the myocardium should have two to three weeks to recover after myocardial injury prior to labor and delivery. In addition, if used, P2Y12 inhibitors need to be continued uninterrupted for at least three weeks after stent implantation and need to be discontinued five days prior to delivery in order to safely administer regional anesthesia, which assists with minimizing oxygen demand on the heart muscle during labor and delivery.

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Musculoskeletal Pain in Pregnancy

John-Paul D. Hezel

Case #1: Foot Pain and Pain Medications

NS is a 35-year-old female G1P0 now 31 weeks pregnant who presents with left heel pain. She states that it began insidiously about 1 month ago and was not related to any specific event. She reports some pregnancy-related back pain but denies any numbness, tingling, or other radicular symptoms into the feet. The pain is located on the plantar aspect of the foot, is worse in the morning and after sitting at her desk for a while, and is relieved by rest and non-weightbearing. She denies prior foot or ankle injuries.

Her past medical and family history is unremarkable, she has no known drug allergies, and her current medications include prenatal vitamins. She works as an accountant and lives at home with her husband. She denies tobacco or alcohol use. Her review of systems is negative other than for her presenting symptoms.

On physical examination, NS is 5 foot 3 inches tall and weighs 175 pounds, which is a 25-pound gain since prepregnancy. She is a well-appearing female, accompanied by her husband, in no apparent distress. She ambulates with an antalgic gait favoring her left lower limb. She has a wide base of support and purposefully walks on her left toes, refusing to heel-strike. She has full plantar flexion, dorsiflexion, eversion, and inversion range of motion and strength in the ankle. There is tenderness to palpation directly over the medial plantar surface of the heel. There is no other bony or soft tissue tenderness and no erythema or swelling. Her calcaneal squeeze test is negative for reproduction of her symptoms, and she has good distal pulses and capillary refill. X-rays were deferred.

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Discussion

Weight gain during pregnancy leads to a multitude of anatomic changes that affect the lower limb. These biomechanical factors likely play a larger role in limb pain than do hormonal changes [1]. Increased lordosis of the low back and relaxation of the peripelvic muscles, primarily the hip abductors that are responsible for stability of the lower limb, can lead to a redistribution of forces through the knee and into the foot. Women become more flat-footed, leading to greater pronation [2] and alteration of pressure points throughout the plantar surface [3]. In combination with pregnancy-related pedal edema [4], ligamentous laxity in the foot and ankle also places more strain on soft tissues. The plantar fascia, a thick band of connective tissue running from the heel to the toes, often becomes stretched or inflamed, a condition known as plantar fasciitis. In the general population, plantar fasciitis is related to overuse or can be instigated by an injury, changes in activity patterns, or poor footwear, though the natural history of the disease is not understood [5]. Obesity is present in 70 % of nonpregnant individuals with heel pain [6], so in pregnant women who have gained weight, the altered kinetic chain and compression directly on the plantar fascia can lead to acute inflammation or chronic disorganization of the tissue, causing severe pain with weightbearing. The most common complaint is pain when taking the first couple of steps in the morning or after a period of inactivity [7], such as when getting up from a desk at work. The relative immobilization of the foot leads to tightening of the connective tissues, and only after moving around or stretching do they begin to loosen up.

When working up a gravid woman with foot pain, plain films are reserved to rule out a fracture from a traumatic event or if looking for degenerative changes, evidence of osteonecrosis, or dislocation. The majority of times, diagnosis based upon physical examination is sufficient. There is tenderness directly over the plantar fascia and pain is often reproduced in the heel with walking. Tenderness in the posterior heel along the insertion of the Achilles onto the calcaneus is more suggestive of Achilles tendinosis or enthesopathy than plantar fascial pain, though the two pathologies can coexist. Pinching the calcaneus between the thumb and index finger is important to help differentiate between plantar fasciitis and a calcaneal stress fracture. If the squeeze test is positive and the history is consistent with a possible bony abnormality, an MRI may be indicated to rule out the stress injury. Calcaneal stress fractures or reactions can be treated with a walking boot until pain abates. These are relatively uncommon, however, and in the vast majority of plantar heel pain, the fascia is the pain generator.

Managing foot pain during pregnancy is completely conservative. The mainstay of treatment is proper footwear, finding a comfortable walking shoe that gives support to the heel and to the arch. Full-length off-the-shelf inserts with a medial arch support may help correct pes planovalgus and realign the ankle, redistributing forces on the plantar surface of the foot, though there is no established evidence that they decrease pain [8]. Stretching of the foot in a dorsiflexed position, using a belt or band or towel, before getting out of bed in the morning alleviates pain with that first

step, and manual and active stretching of the gastrocnemius and soleus is beneficial [9]. If the woman can tolerate exercise, structured physical therapy to learn hip stability and balance drills is also recommended. Treating the entire leg, not just the foot, can accelerate relief of symptoms and help prevent other musculoskeletal pain. Massage to the foot, to the calf, and into the thigh and hip, foot ice baths, elevation, relative rest, night splinting, and rolling a ball or frozen water bottle on the bottom of the foot are other methods of treatment that have some success. In the extreme cases, a walking boot for 7–14 days may help with acute pain. It is important to direct the patient to remove the boot periodically throughout the day, as stiffness in the ankle and atrophy of the calf from long-term disuse can lead to unintended pain and weakness. Corticosteroid injections have been shown to give short-term relief of plantar fascial symptoms up to 6 months [10], so while these injections do not fix the problem, they may be necessary to keep women active and on their feet.

A common question during pregnancy is about the safety of over-the-counter pain medications. Nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen and naproxen, may pose danger to the fetus [11], particularly during the third trimester. For this reason, the Federal Drug Administration has categorized all NSAIDs as Class D after 24 weeks, meaning that there is some evidence of NSAIDs causing human fetal risk [12]. They should only be used in the case of life-threatening illness or when the use of safer drugs is ineffective or not an option. In contrast, acetaminophen (Tylenol) has not been associated with significant fetal risk and is categorized as Class B during all three trimesters [13]. This designation means that there are no good randomized controlled trials in human subjects and that no adverse effects have been found in animal reproduction models. Though there has been some correlation made between acetaminophen use in pregnant women and increased incidence of ADHD in 7- to 11-year-olds [14], acetaminophen has been widely accepted as the pain medication of choice and should be the initial pharmacotherapy if needed during pregnancy.

Case #2: Knee Pain and Exercise Guidelines

AW is a 31-year-old female runner G1P0 now 21 weeks pregnant who presents with right knee pain. It began insidiously about 3 weeks ago as she increased her per week mileage for an upcoming marathon. She is an accomplished long-distance runner, having completed six marathons during her twenties. She usually begins training 4 months before a race, but when she found out she was pregnant, she decided to accelerate her regimen to compete before her second trimester was complete. Her pain was initially exacerbated only with running, but now it hurts when going up and down stairs. She also reports stiffness when getting up from sitting more than 30 min, which is common in her work as an accountant. She denies swelling, instability, or mechanical symptoms. She denies any prior injuries and has never experienced knee pain before this month.

AW's medical history is uncomplicated and she is only taking vitamins as prescribed by her obstetrician. Other than running, she bikes occasionally and strength trains once a week, focusing primarily on ballistic activity. She changes her running shoes every 400 miles and prefers a stiff shoe. She recently switched brands because she was finding her old pair was causing irritation of her Achilles.

On examination, AW is a well-appearing female who walks with a nonantalgic gait. She demonstrates a compensated Trendelenburg sign on single-leg stance bilaterally, but it is worse on the symptomatic right side. She has pes planovalgus with valgus tilt of her ankle when viewed from behind. She has full extension of the knee but some discomfort on full flexion. All special tests – including those for the cruciate and collateral ligaments and menisci – are negative. There is no joint effusion and only mild tenderness over the medial joint line.

X-rays are negative for fractures, dislocations, degenerative changes, or other bony abnormalities.

Discussion

Patellofemoral pain (PFP) is the most common running injury, accounting for between 25 and 40 % of all knee pain [15]. The classic teaching is that it is caused by maltracking of the patella in its femoral groove during repeated flexion of the knee. The lateral quadriceps is thought to overpower the medial quadriceps, pulling the patella laterally. Often the articular cartilage on the undersurface of the kneecap can wear away, a related disorder called chondromalacia patella, which is often used interchangeably with PFP and runner's knee but that means something a bit different in terms of pathology. There is some evidence that patellofemoral arthritic changes contribute significantly to PFP, primarily in the setting of patella alta [16]. The most common symptoms of patellofemoral pain syndrome or "runner's knee" are generalized anterior knee pain with running, difficulty going down stairs, and stiffness with the knee flexed for an extended period, described usually as pain when getting up from a seated position [17].

Though quadriceps weakness does likely play a role in PFP, quadriceps tightness is often more prevalent in patients with anterior knee pain. Knee restriction places more pressure on the patella, causing stiffness after a period of immobility. Trigger points in the quadriceps can also decrease joint range of motion and refer pain to the knee joint, despite the knee itself having no structural problem. Treatment for PFP thus begins with regaining or maintaining knee flexion when compared to the asymptomatic side. Active quadriceps stretching, soft tissue mobilization with a foam roller or PVC pipe, manual tissue work with a therapist or chiropractor, and dry needling to release active trigger points are all initial strategies to regain this motion.

The knee is like a middle child: it takes all the abuse from the older sibling, the hip, and the younger sibling, the foot and ankle. The gluteal musculature, particularly the gluteus medius, is critical in stabilizing the lower limb during single-leg

stance and ambulation, which is essentially a series of repetitive single-leg activities. The foot and ankle, meanwhile, control alignment of the tibia and subsequently the entire leg and thigh. Weak gluteus medius can lead to a loss of stability and alter pelvic mechanics [18], and a weak or flat foot can lead to a loss of proper alignment, both placing more stress on the knee and leading to anterior joint pain. Women with PFP have been shown to have greater more pelvic drop [19], indicative of weak gluteals, and more hip adduction [20], which may correlate mechanically to weak abduction. Rehabilitation of PFP focuses on correction of biomechanical abnormalities, beginning with the hip, foot, and ankle. Hip abductor and core stability, balance, foot intrinsic strengthening, correction of any dorsiflexion or plantar flexion contracture, and proprioceptive training are mainstays of a therapy program, with some evidence that hip plus knee exercise is better than knee exercise alone [21]. Those with pes planovalgus or rearfoot eversion may benefit from off-the-shelf orthotics with a medial arch support to help control tibial alignment, as there may be a link between tibal rotation and PFP [22].

Patellofemoral pain is more common in women than men [23], because of factors that affect the general population and because of anatomic changes that occur naturally from pregnancy itself. Additional weight puts more stress on the joints; hormonal changes lead to ligamentous laxity and subsequent weakness, especially in the hips and pelvis; and postural changes caused by the gravid uterus can alter gait mechanics [24].

One of the most common questions that runners and other active women have during pregnancy is whether or not they can continue to exercise. While there are no specific guidelines on what women can or cannot do while pregnant, it is widely accepted that they should follow the same recommendations as for nonpregnant women and men: 30 min of moderate-intensity exercise at least 5 days a week [25]. The American Congress of Obstetricians and Gynecologists (ACOG) recommend that in uncomplicated pregnancies, recreational and competitive athletes maintain their level of exercise and modify as medically indicated [26]. This differs from ACOG's recommendation for sedentary women, who instead require a full medical evaluation before beginning an aerobic training program.

Evaluation of a runner with knee pain begins with analysis of walking gait and then with the patient standing barefoot on a single leg, looking for proper balance, signs of hip weakness, and low or high arches of the feet. It is important to check range of motion and strength of the hip, knee, and ankle, paying close attention to any differences between the symptomatic and asymptomatic sides. Palpate the knee for an effusion, which would suggest intra-articular damage, and look for tenderness along the medial and lateral joint lines, patellar and quad tendons, and popliteal fossa. Special tests are used to help rule out ligament sprains or meniscal and articular cartilage injury. Palpation of soft tissues may reveal taut bands and trigger points that can refer pain to the knee and contribute to symptoms.

In the absence of trauma, infection, effusion, mechanical symptoms such as locking, instability or feelings of giving way, suspected arthritis or fracture, or intractable pain, there is no need for plain films or advanced imaging.

Case #3: Back Pain and Imaging Guidelines

HA is 36-year-old G2P1 CrossFit athlete now 25 weeks pregnant who presents with low-back and buttock pain. Her pain is bilateral, though slightly worse on the left side. It had been progressive over the past couple of months, but it worsened suddenly a week ago when squatting in the gym. She did not drop the weight, and she denies feeling a pull, but when the lifting session was complete, she felt more sore than normal. She denies any numbness or tingling but does have occasional pain down the back of the left leg. Pain is worse with walking and bending and relieved by rest. She denies prior injuries, though she describes a history of back pain during her last pregnancy. It was similar in nature, was controlled with positional changes at home and at work, and resolved a couple of weeks after she gave birth. Unfortunately, she states that her current symptoms are much worse than her previous episode.

HA's past medical history is positive for exercise-induced asthma that is well controlled with warming up before a workout and an occasional inhaler. Medications also include multivitamins. She is happily married and works out with her husband twice a week. Her daughter is 4 years old. Family history is unremarkable, as is her additional review of symptoms.

Physical examination reveals a gravid female who walks with a nonantalgic gait with a wide base of support. She exhibits slight anterior pelvic tilt and exhibits good stability on single-leg stance. Pain is reproduced with forward flexion of the lumbar spine, which is limited, and relieved with extension. She has full motor strength in the lower limbs, intact sensation to light touch in all dermatomes, 2/4 deep tendon reflexes at the patellae and Achilles, and no upper motor neuron signs. She has a negative supine straight leg raise. There is tenderness throughout the lumbar paraspinal musculature and over the sacroiliac joints bilaterally. Remaining sacroiliac joint tests are negative for reproduction of pain.

HA refused x-rays because of her pregnancy.

Discussion

Weight gain and stretching of the abdominal cavity by the gravid uterus increase lumbar lordosis and lumbosacral stiffness, weaken core musculature, exaggerate hip flexion, protract the cervical spine, and depress the shoulder blades, all placing more strain on the lumbar paraspinal muscles, particularly during weightbearing. Interestingly, though gait mechanics have been shown to change very little in pregnancy, the hip extensors, hip abductors, and foot plantar flexors are all more active during ambulation to compensate for anterior pelvic tilt [27]. These changes, in combination with the well-established hyperlaxity of the sacroiliac joints and pubic symphysis, all place a pregnant woman at greater risk for back pain. Additional risk factors include pain before pregnancy, back pain during a previous pregnancy [28], and multiparity, though the biggest risk factor is the progression of pregnancy [29].

The majority of back pain, both in the general population and among pregnant women, is axial [28] and mechanical in nature, that is, related to movement. Causes include poor posture, muscle weakness, irritation of the joints in the lumbar spine and pelvis, ligamentous laxity, and a host of other biomechanical factors, including gait abnormalities and prior injuries leading to compensation. Rarely is an anatomic cause found, meaning that back pain can most often be treated according to the resulting dysfunction and constellation of symptoms rather than based upon a specific pathology. While pregnant women are at risk for spondylolisthesis, slippage of one vertebrae over another, there is no greater prevalence of disc herniation in this population [30]. The history and physical examination are thus used to rule out the uncommon pathology, such as symptomatic disc herniation, and to determine modifiable risk factors, extent of functional loss, and anatomic asymmetry and weakness, all with the goal of developing an individualized treatment plan.

Examination of a patient with back pain begins with watching her walk. It is important to take note of asymmetries such as pelvic drop on one side compared to the other, lack of knee or hip flexion, inability to clear one or both feet, hyperlordosis of the lumbar spine, and the base of support (i.e., how wide the feet are spread during ambulation). In the standing position, one must check single-leg balance and make sure that she can go up onto her toes and heels [31]. An inability to do so may be a sign of L5 or S1 nerve root impingement, particularly if the deficit is one-sided and accompanied by dorsiflexor or plantar flexor weakness on strength testing. Manual motor strength of all lower limb myotomes, light touch sensation of all lower limb dermatomes, and deep tendon reflexes at the patella and Achilles are imperative to rule out nerve root compression or peripheral nerve injury. An upgoing great toe when checking a Babinski reflex is a sign of upper motor neuron disease and should be evaluated more closely if only found on one side.

One can determine range of motion of the lumbar spine in the standing position by having the patient bend forward with the knees straight and then by leaning backward, hinging from the lumbosacral spine and hips. If pain is elicited in one direction more than the other, attempt is made to centralize the pain to the low back by having the patient perform repeated flexion or extension, whichever movement does not cause reproduction of her pain. For example, if she has more pain with forward flexion, then she is instructed to perform multiple extensions (10–15 repetitions) either while standing or by doing prone push-ups with the hips stabilized on the exam table, such as when doing the upward dog position in yoga. These extensions should not be done if radicular symptoms are elicited. Immediately following the extensions, forward flexion is rechecked to see if her range of motion improves and if her pain is lessened. If so, it would be a sign that McKenzie therapy, use of a directional preference and pain centralization [32], may help control her symptoms, as this method has been shown to be quite effective in patients with mechanical back pain [33].

With the patient lying down on her back, a supine straight leg raise is performed. A positive test is reproduction of sciatic-like pain, numbness, or tingling down the back of the leg between 30° and 70° of hip flexion, suggestive of a disc herniation. This test is not positive if it elicits only back pain or tightness in the hamstring.

While the patient is supine, the hips are examined for range of motion and for any sign of intra-articular pathology such as a labral tear. Palpation of the pubic symphysis, which may be quite tender, the hip flexors, and adductor compartment also gives clues to the pain generator.

The patient is then placed on her side to test for hip abductor strength, the greater trochanter is palpated for signs of bursitis or tendinopathy, and the gluteal muscles are palpated for trigger points. Finally, with the patient prone, the sacroiliac joints, the lumbar paraspinal musculature, the spinous processes, the quadratus lumborum (QL), and the piriformis are all palpated individually, again looking for the etiology of pain. Tightness or trigger points in QL or piriformis can cause isolated low-back pain or can radiate pain down the back of the leg, mimicking disc herniation. If found, these trigger points respond very well to dry needling and trigger point injections.

In a patient with back pain, it is also imperative to rule out SI joint pathology, especially given that the SI joint is widened during pregnancy. Common SI joint tests such as FABER (flexion, abduction, external rotation) have not been shown to be sensitive. Palpation of the posterior-superior iliac spines and the "dimples" just above the buttocks approximates the SI joints and can help isolate the pain. There are also a series of tests that when positive have been shown to lead to the diagnosis of SI joint dysfunction [34]. An injection of local anesthetic into the SI can help confirm that diagnosis, and it can then be treated with SI belts or girdles to redistribute pressure in the low back, hips, pelvis, and legs [35]. Soft tissue modalities and acupuncture may also be effective.

Though x-rays and MRI are rarely needed when working up back pain in pregnancy, they are safe both for the prospective mother and fetus. According to ACOG, radiation from x-rays "is at a dose much lower than the exposure associated with fetal harm" while MRI is "not associated with risk" to the fetus [36]. This discussion is critical to have with pregnant women given the anxiety surrounding radiation of any kind. Counseling about the risk helps develop a treatment plan in accordance with clinical indications and expectations of the prospective mother.

Guidelines for radiologic workup of back pain in pregnancy are the same as for men and nonpregnant women. Red flags indicating the need for an MRI in the setting of back pain include recent trauma, osteoporosis, insidious onset of unexplained weight loss (or failure to gain weight during pregnancy), unexplained fever or other signs of infection, immunosuppression, prolonged use of corticosteroids, intravenous drug use, prior back surgery, progressive weakness, disabling pain, and focal neurological deficits. These deficits include saddle anesthesia and bowel/bladder incontinence, suggestive of cauda equina; focal weakness, hyperreflexia, increased muscle tone, upgoing plantar response, and sustained clonus, suggestive of spinal cord compression; and weakness, hyporeflexia, atrophy, and fasciculations, suggestive of severe nerve root or peripheral nerve compression. MRI is also indicated when planning an interventional or surgical procedure such as epidural injections or laminectomy/fusion.

Treatment of low-back pain in pregnancy requires a multidimensional approach. The mainstay is activity modification with identification of movement patterns that

can be corrected over a short time frame with altered positioning to relieve stress on the lumbar spine. A few sessions of physical therapy can help implement these changes and teach the patient a basic stretching and strengthening program, and 12-week program of therapy has been shown to reduce pain during the second half of pregnancy [37]. Rest plays a role, but can often be counterproductive, leading to more stiffening of muscles and joints.

ACOG recommends the use of low-heeled shoes with arch supports, using lumbar support when sitting, placement of a board between the box spring and mattress for if the bed is soft, squatting to use the knees when bending to pick up heavy objects, sleeping on the side with a pillow between the knees for additional support, and the use of heat, ice, or massage to relieve painful areas [38].

Case #4: Hip and Pelvic Pain and the Use of Contrast Media

VC is a 27-year-old G1P0 former college soccer player now 29 weeks pregnant who presents with right groin pain. The pain began insidiously 3 weeks earlier when she noticed it when getting out of a car. Her groin hurts now when walking but mostly when getting up from lying down. She denies clicking, catching, locking, or popping, and there was no inciting event. She reports a history of "hip" pain during her sophomore year of college when she was diagnosed with a tear of the labrum. She managed her symptoms conservatively with exercise and did not require injections or surgery at the time. VC states that her current symptoms are different than those experienced in the past.

Her past medical and family history is unremarkable, and her pregnancy to date has been uncomplicated. She takes a standard course of vitamins and has no allergies to medications. She lives in a duplex with her husband and has only occasional pain when going up and down stairs. Her review of systems is positive for a "pins and needles" sensation in the right thigh, but she denies shooting pain down the leg, bowel or bladder incontinence, or any other joint pains.

On examination, this is a gravid-appearing female, unaccompanied, who walks with a nonantalgic and symmetric gait. She can heel and toe walk, though when hopping up and down her right leg, she has pain in the groin. She has full range of motion of the hips with some pain on internal rotation, adduction, and flexion of the hip, negative scour test, and negative supine straight leg raise. She has tenderness to palpation over the pubic symphysis, and her symptoms are reproduced with active sit-ups. There is tenderness over the right adductor tendon as it inserts onto the pubic bone. There is no erythema or swelling. Lumbar spine examination is negative. There are no palpable peripelvic trigger points.

VC did agree to proceed with x-rays, which were unremarkable for fractures, dislocation, or joint space narrowing. She did have slight osseous bumps over both femoral head and neck junctions, consistent with cam-type deformities. Joint spaces were well maintained, and there was no suggestion of osteonecrosis of the femoral head.

Discussion

It is well established that the hormone relaxin peaks during the first trimester of pregnancy and helps to widen the pubic symphysis and both sacroiliac joints in preparation for delivery [39]. It is not well established, however, whether this hormonal effect leads directly to pelvic pain or whether additional biomechanical, metabolic, genetic, or degenerative factors play separate roles. In reality, pregnancy-related pelvic girdle pain (PPGP) is likely caused by a combination of all these and other factors that affect women during and after pregnancy [40]. There is no consensus as to the constellation of symptoms with which women present, though it is generally accepted that sharp, stabbing, dull, or shooting pain posteriorly in the SI joints or anteriorly in the pubic symphysis – or both – is usually the primary complaint.

Groin pain, on the other hand, can come from the hip joint itself or surrounding structures, including but not limited to muscles, tendons, connective tissue, and adjacent joints, most notably the pubic symphysis. Evaluation of groin pain begins with ruling out an inguinal or abdominal hernia, low-back disorders, bone infection such as osteomyelitis, bone tumors, urinary or gastrointestinal disease, rupture of the pubic symphysis, and round ligament pain [40]. The round ligament attaches to the uterus, and as the fetus grows, stretching of the ligament can cause transient sharp lower abdominal pain that radiates into the groin. It is treated with pelvic tilting [41]. A thorough history of prior malignancy, signs of local or systemic infection, inflammatory arthropathy, previous trauma, or recent weight loss is critical. Direct examination of the lumbar spine and SI joints and strength, sensory, and reflex testing of the lower limbs help to rule out disc herniation, mechanical low-back pain, or posterior pelvic abnormalities.

The primary differential for groin pain includes muscle or tendon strain, hip flexor bursitis, femoroacetabular impingement with a labral tear, hip joint degenerative changes, hypermobility, rectus abdominis-adductor aponeurosis injury, or pubic symphysis dysfunction. The pubic symphysis measures 3–6 cm in nonpregnant individuals and can separate an additional 2–3 cm during pregnancy. Persistent widening over more than 10 cm is called diastasis, though the exact measurements do not correlate to severity of symptoms. Pain from symphyseal separation localizes to the lower abdomen or suprapubic area but can also radiate into the buttocks, down the legs, or into the groin on one or both sides [42]. Women often complain of pain on weight-bearing, going up and down stairs, and turning in bed. They often wake up in the middle of the night. There is conflicting literature on the incidence of pubic symphysis separation causing pain, but the mainstay of diagnosis is palpation. Deep pressure over the pubic symphysis may evoke local discomfort or cause referral. A step-off may also be felt. Women may also have pain with sit-ups and activation of the adductors, which attach just adjacent to the symphysis. X-rays are not necessary in making the diagnosis, though with pain recalcitrant to conservative management, imaging, especially after delivery of the child, may be warranted to differentiate between degenerative changes, osteitis pubis, diastasis, or inflammatory arthropathy.

Treatment for women with pubic symphyseal pain includes a pelvic belt or girdle, activity modification, strengthening of the hip abductors and adductors to better support the pelvis, sleeping in the lateral decubitus position, graded exercise program, and corticosteroid injections into the joint [43].

In the absence of recent trauma or specific injury, muscle or tendon strain is unlikely. Hip flexor bursitis is also less common in pregnant females. In those with a history of hip problems or those who have new-onset groin pain with positive labral signs, it is possible and likely that the hip joint is the culprit. Femoroacetabular impingement occurs when the femoral head-neck junction consistently comes in contact with the acetabulum, due to an osseous abnormality on either the femur or pelvis. Overuse and repeated hip flexion and adduction, such as when playing soccer and hockey, can lead to tearing of the labrum, a cartilaginous structure that adds depth and cushioning to the joint. Pregnancy can exacerbate symptoms, and maternal positioning during delivery can lead to new tearing [44].

Evaluation of the hip involves checking flexion, internal and external rotation, and abduction and adduction of the joint. Impingement testing is performed by flexing the hip to 90° than internally rotating and adducting the leg across midline, compressing the femoral head-neck junction against the acetabulum. Reproduction of pain is suggestive of FAI. The scour test is performed by flexing the hip to 90° and then directing a vertical force down the femur, simultaneously rotating or "scouring" the joint through its 360° of circular motion. Reproduction of familiar pain or a catch is positive for a likely labral tear. Pain with a straight leg raise at 20° of hip flexion may also indicate hip joint pathology.

Diagnosis of impingement and labral pathology is confirmed with MRI arthrogram of the hip [44]. The contrast injection allows for visualization of the labrum, which is not always delineated clearly without dye. Contrast media has not been studied in pregnant women, but given its potential risk as evidenced by laboratory and animal studies, it is best to avoid arthograms and intravenous contrast unless the benefits outweigh the risks [36]. In the case of possible hip labral tears, the woman can be treated based on clinical features, reserving advanced imaging for after labor and delivery. Instead of MRI, patients in extreme pain can undergo a diagnostic and therapeutic injection of anesthetic and corticosteroid into the femoroacetabular joint. If the patient feels better after the joint is numbed, it is a positive test for an intra-articular pain generator. Manual therapy to relax surrounding soft tissue and physical therapy for hip and abdominal strengthening and stability are also conservative measures used to avoid more aggressive studies and management. MRI without contrast has been shown to be safe, as detailed above, so if osteonecrosis of the femoral head [45] or other more significant bony disease is suspected, MRI may be warranted.

Given all of the biomechanical changes associated with pregnancy, muscles may be activated differently and lead to trigger points in the peripelvic region. Psoas trigger points can mimic impingement, as passive flexion of the hip contracts already contracted muscle, reproducing pain with very specific referral patterns in the groin and down the front of the thigh. Release of these trigger points with dry needling or via manual therapy can provide immediate relief.

Finally, as women gain weight and the uterus compresses the abdomen, the lateral femoral cutaneous nerve, which runs below the inguinal ligament and into the thigh, can be compressed, a condition known as meralgia paresthetica. Women complain of paresthesias into the upper to mid-anterolateral thigh, and there is decreased sensation to light touch in the nerve's distribution. This condition is exacerbated in the third trimester and is usually self-limited, not requiring any specific treatment, though manual therapy has been shown to help [45].

Case #5: Wrist Pain and the Safety of Corticosteroid Injections

TC is a 38-year-old right-handed G3P3 female, now breastfeeding 8 weeks after delivering her third child, who presents with left wrist pain. It began insidiously about 3 weeks before her delivery and has progressed in the postpartum period. The pain is located on the thumb side of the wrist and is exacerbated by picking up a fork or knife or by lifting her newborn. She reports some minor swelling but denies any trauma, fevers or chills, or other worrisome symptoms. She denies numbness or tingling into the hand but does have some radiation of pain down the thumb. TC has been diagnosed by two orthopedic surgeons with tendinitis and was told that she will need surgery. She has tried three different types of wrist braces without any relief of her symptoms.

TC's past medical history is negative for any musculoskeletal problems during either of her previous two pregnancies. She is very active, lifting weights three times a week with a personal trainer and running twice a week. The use of barbells and kettle bells does not worsen her symptoms. She takes ibuprofen as needed and has no drug or environmental allergies. She lives at home with her husband and kids and is currently on maternity leave. She drinks socially and has never smoked. Family history is positive for cancer and diabetes.

Physical examination reveals a healthy-appearing female with full range of motion throughout the cervical spine and left shoulder, elbow, and wrist. She has full 5/5 motor strength in all muscle groups of the upper limb except for pain-limited weakness in the thumb abductors. Her sensation to light touch is intact in all upper limb dermatomes and peripheral nerve distributions, including over the median nerve. She has tenderness to palpation with mild swelling over the distal radius. There is no erythema, and her radial pulse is intact with good capillary refill in the fingers. She has a positive Finkelstein's test but negative carpal compression, Tinel's over the median nerve at the carpal tunnel, and Phalen's. She has no carpal instability, and her pain is not exacerbated by radial or ulnar deviation of the wrist.

X-rays of the wrist are negative for fractures, dislocations of the carpal bones or the distal radioulnar joint, or any degenerative changes.

Discussion

De Quervain's tenosynovitis is characterized by inflammation and thickening of the sheath around the first dorsal compartment of the wrist where the tendons of the abductor pollicis longus (APL) and extensor pollicis brevis (EPB) are located [47]. Pain is present on the thumb side of the wrist, usually over the radial styloid, and can be associated with swelling, redness, and radiation of pain into the forearm or the thumb. The cause is unknown, though it is common during the third trimester of pregnancy and especially in the postpartum period when breastfeeding [48]. Women

complain of pain when picking up their children or with any movement of the wrist toward the small finger. There may be a sensation of clicking, snapping, or locking of the tendons as they pass over the distal radius. Diagnosis is confirmed by a positive Finkelstein's test in which the patient makes a fist over the thumb and ulnar deviates the wrist, while the practitioner places an ulnar-directed stress over the second metacarpal [47]. Pain is reproduced at the radial styloid and often into the thumb, where patients may also exhibit pain and weakness with resisted extension and abduction. This pain should be differentiated from osteoarthritis of the first carpometacarpal (CMC) joint by performing a careful first CMC grind test [50] and looking at x-rays, which are also important to rule out a fracture.

Though compression of the median nerve at the wrist – carpal tunnel syndrome – is also prevalent in pregnant women [51], it differs from de Quervain's in the location and nature of pain and peresthesias. Whereas de Quervain's pain is usually isolated to the wrist and thumb, pain with carpal tunnel syndrome extends into the first radial three-and-a-half digits and is usually accompanied by numbness and tingling in the same distribution. Pain often wakes patients up at night and is related to overuse, though in pregnancy, increased peripheral edema is thought to compress the nerve [51]. Manual compression of the median nerve at the carpal tunnel reproduces pain, numbness, and tingling throughout the nerve's distribution in the hand and fingers. Reproduction of paresthesias into the radial three-and-a-half digits when tapping the median nerve over the carpal tunnel, weakness of the thumb abductors, and loss of sensation in the median nerve distribution – tested over the palmar tip of the index finger – also suggest the presence of carpal tunnel syndrome. Electromyography and nerve conduction studies are used to confirm the diagnosis in preoperative patients, though these invasive tests are usually unnecessary during pregnancy.

Both de Quervain's tenosynovitis and carpal tunnel syndrome in pregnancy are self-limited [49, 51], but given the intense pain and functional deficits that can occur, conservative treatment in warranted. Initial management of de Quervain's is use of a thumb spica splint to stabilize the APL and EPB and limit snapping and friction of the tendons during ulnar deviation [52]. It has been suggested, however, that symptoms resolve most effectively with a corticosteroid injection to the tendon sheath of the first dorsal compartment, and practitioners may use this as first-line treatment [49]. Splints to limit wrist flexion in those with carpal tunnel syndrome may improve symptoms at night, though injections have also proven useful in this population. Corticosteroid injections during pregnancy have been shown to be safe with no ill effects to the fetus or the mother, as long as no medical contraindications exist [49]. While any injection carries the risk of infection, bleeding and hematoma, pain, and nerve injury, with a wrist injection, the most common side effect is hypopigmentation and fat atrophy [53], the risk of which should be clearly discussed with the woman prior to injection. Discoloration and atrophy of subcutaneous fat occur when a portion of the steroid is injected just beneath the dermis rather than into the sheath. Direct visualization of the tendons or nerve with musculoskeletal ultrasound may help decrease the incidence of these complications. Regardless, hypopigmentation and fat atrophy resolve spontaneously by around 6–12 months postinjection [53].

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Epilepsy in Pregnancy

Kaarkuzhali Babu Krishnamurthy

Case

A 32-year-old woman with partial-onset and secondarily generalized seizures presented for a consultation visit in anticipation of pregnancy. She was the product of a full-term, uneventful pregnancy, had no perinatal complications, and reached developmental milestones normally. She was otherwise healthy and well until age 12 years when she had a witnessed convulsive seizure in school. This was followed a year later by episodes consisting of a sense of fear followed by altered awareness. Although several medications were tried including lamotrigine, levetiracetam, and phenytoin, the only medication that allowed the patient to become seizure-free was carbamazepine. With attempts at discontinuing carbamazepine, or cross-tapering to a different anticonvulsant, the patient had breakthrough seizures. She had been seizure-free for 3 years at the time of presentation. Her menstrual history was notable for menarche at age 12 years, which was 1 month prior to the onset of seizures, and her cycles at the time of presentation were irregular and unpredictable. She had been married for 2 years, and she and her husband were interested in starting a family. After discussion of the risks associated with conception on carbamazepine, the patient decided to move ahead. She was started on folic acid and attempted to conceive for 1 year without success. After referral for in vitro fertilization, the patient become pregnant, and her medications were sequentially increased to provide serum concentrations of 8–10 ug/dL. At 39 weeks, she had an uncomplicated vaginal delivery, giving birth to a healthy baby boy. She had no seizures during or following the pregnancy.

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Discussion

Epilepsy is a common chronic neurologic condition, affecting 1–3 % of the general population with roughly equal male-to-female predominance. In the United States, estimates are that approximately three million people in the United States have epilepsy, with perhaps 500,000 being women of childbearing age [1]. As three to five births per 1000 are believed to be to a woman with epilepsy, epilepsy is one of the most common neurological conditions to be encountered in pregnancy [1]. The majority of people with epilepsy are well controlled, requiring one anticonvulsant to remain seizure-free. Many women with epilepsy have babies, but there are circumstances that are unique to women with epilepsy that obstetricians, neurologists, and other physicians involved in pregnancy care should be aware of.

Women with epilepsy have lower fertility rates than women without epilepsy. In part, this is related to social factors, such as reduced marriage rates seen in women with epilepsy. However, hormonal imbalances also play a part [2]. Women with epilepsy have higher rates of anovulatory cycles; this is more pronounced in women with temporal lobe onset seizures than in those with primary generalized epilepsies [2]. Furthermore, there are additional neurohormonal factors that lead to diminished libido in women with epilepsy, further decreasing sexual behavior and decreasing the possibility of conception [2]. Anticonvulsants themselves can further disrupt the neuroendocrine axis. For example, valproate is associated with the development of polycystic ovarian syndrome, leading to oligomenorrhea and anovulatory cycles [2].

As there may be a risk to the developing fetus from exposure to anticonvulsants in utero, some women may wish to consider a medication taper prior to conception. With a limited number of syndromic diagnoses, such as childhood absence epilepsy, the risk of relapse in adulthood after medication withdrawal is small, but with the majority of adult epilepsies, there is no foolproof way to determine whether or not a patient will remain seizure-free after withdrawal of anticonvulsant therapy. Thus, women must be willing to accept this uncertainty if they choose to come off of antiseizure medications. The risks accruing to the mother with breakthrough seizures can include physical injury due to trauma as well as social or employment harm due to loss of driving privileges. However, the risks to the developing fetus can also be significant, such as higher chances of preterm delivery and for being small for gestational age [3].

An area of active investigation is the effect of fetal anticonvulsant exposure, both on major congenital malformations and, equally importantly, on long-term development. Evaluating the structural risk of fetal anticonvulsant exposure is problematic for a number of reasons. Dose ranges tested on animals may exceed dose equivalencies in human, and malformations seen in animals may not predict human teratogenicity; for example, topiramate causes limb agenesis in rats but is known to be associated with an increased risk of orofacial clefts in humans.

Folate supplementation is a recommendation for all women of childbearing age. Women with epilepsy should not be exceptions to this rule and should receive

supplemental folic acid prior to conception [4]. Women with epilepsy taking phenobarbital or phenytoin have lowered serum and/or red cell folate levels, which are inversely correlated with their anticonvulsant levels [5]. There is no data to suggest that folate administration is harmful to women with epilepsy.

While fetal anticonvulsant syndrome has been described for many decades, given the varied causes of epilepsy, it would be important to verify that it is the presence of anticonvulsants and not the epilepsy that is associated with the increased risk of congenital malformations. Holmes et al. looked at a large cohort of women at the time of delivery and placed their babies in one of three categories: those born to women taking anticonvulsant medications during pregnancy, those born to women who had a history of seizures but were not taking anticonvulsants during pregnancy, and those born to women without epilepsy who were not taking anticonvulsant therapy during pregnancy [6]. The babies were given careful physical examinations to identify major congenital malformations and other signs of presumed fetal anticonvulsant exposure such as distal digit and midface hypoplasia. They concluded that only the infants exposed to anticonvulsants in utero had an increased risk of major congenital malformations; those infants born to women with epilepsy not taking anticonvulsants had no greater frequency of malformations than those infants born to women without epilepsy and not taking anticonvulsants [6].

In reviewing the available data related to congenital malformations in anticonvulsant exposure, it appears to be conclusive that birth defects occur more often in children born to women taking anticonvulsants than to women who do not, with the absolute risk in the range of 4.6 % versus 2.8 % in one study [7]. When analyzed separately, the risk is higher with valproate as monotherapy or included as polytherapy. This finding has been replicated in multiple studies, particularly for the risk of valproate-associated midline craniosacral anomalies such as spina bifida, with this being a dose-dependent phenomenon [8]. Lowering effective serum concentrations, particularly in the first trimester, may decrease this risk. Carbamazepine appears also to be associated with spina bifida, though the absolute risk may be somewhat less than for valproate [9]. The other older anticonvulsants, phenytoin and phenobarbital, carry an increased risk of other midline defects including heart defects and craniosacral and facial anomalies [10].

With the newer agents, lamotrigine has been reported to have a 2.9 % incidence of major congenital malformations when used in monotherapy and 2.2 % for levetiracetam [11, 12]. However, topiramate carries a higher than expected risk of oral clefts with an absolute rate of 0.36 % in neonates exposed to topiramate compared with 0.07 % in children born to women without exposure to topiramate [13].

In the absence of major and obvious structural malformations, do children exposed to anticonvulsants in utero suffer from cognitive or behavioral aberrancies that may be related to the early exposure? Thanks to new cohort studies, we now know that the answer with certain anticonvulsants may be yes. The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study is a prospective study monitoring a cohort of children born to women with epilepsy who took one of four anticonvulsants in monotherapy during pregnancy: phenytoin, carbamazepine, valproate, or lamotrigine. All mothers enrolled in the study had IQ testing performed, as this

is a major predictor of child IQ, and data was maintained on their epilepsy types and presence or absence of seizures during pregnancy. The children were tested at regular intervals (ages 2, 3, and 4.5 years). The most significant finding, borne out over time, is that children exposed to valproate in utero had lower IQs than children exposed to the other medications, and this finding is dose dependent, suggesting that women who must take valproate for seizure control should be maintained on the lowest dose possible for seizure control [14]. Additionally, verbal skills were further impaired across all exposures compared to nonverbal skills, although the significance of this finding is unclear as there are additional reasons why this may have been present [14]. When examined through use of a retrospective questionnaire study, children exposed to valproate in monotherapy or as polypharmacy when in utero have a higher likelihood of requiring additional educational supports during school, perhaps related to these cognitive effects [15].

Other neurological syndromes may also be seen in association with anticonvulsant use, particularly with valproate. Exposure to this medication in utero has been shown to be associated with an absolute risk of autism of 2.95 % in children exposed to valproate in utero compared with 1.02 % in children not exposed to valproate [16]. Similarly, when looking at the absolute risk of autism spectrum disorder, which may include Asperger's syndrome and other pervasive developmental disorders, the risk is 4.15 % versus 2.44 % [16].

Seizure control in the context of pregnancy can be variable and can be difficult to assess. Most of the data reported on seizures in pregnancy come from large cohort studies, many of which are observational and lack control groups. While there are a number of pregnancy registries around the world, some collect data both retrospectively and prospectively, while others only enroll women when they are pregnant and collect data prospectively. The large, multinational EURAP registry collects data from over 30 countries worldwide, so is not a population-based study. Some studies collect patients from very specialized epilepsy centers, where patients may be more refractory and thus require the services of a tertiary referral program, whereas other studies may collect a broader representation of epilepsy patients. These methodological factors lead to the wide differences in reported rates of, for example, seizure freedom in pregnancy.

Broadly speaking, however, over half of women with epilepsy will remain seizure-free during pregnancy, and some may even experience an improvement in seizure control. Seizure freedom prepregnancy is a strong predictor of seizure freedom during pregnancy and should suggest that optimizing seizure control prior to conception should be a priority [1]. An anticonvulsant medication, preferably in monotherapy, that controls a woman's seizures prior to pregnancy is very likely to keep her seizure-free during pregnancy as long as it is maintained at prepregnancy serum concentrations throughout.

Unfortunately, perhaps one-third of women with epilepsy have an increase in seizure frequency during pregnancy [2, 17]. The causes for this can include nonadherence to the treatment regimen, a situation that may occur more often when preconceptual counseling and advice is not provided. Other physiologic interactions can include change in volume of distribution related to advancing states of pregnancy

and increases in creatinine clearance and hepatic metabolism that can lower serum concentrations of anticonvulsants. Regular monitoring of serum concentrations of anticonvulsant levels and appropriate adjustment of oral dosing should be performed regularly throughout pregnancy, with the rate and amount of adjustment determined by the specific anticonvulsant. With lamotrigine, for example, clearance is known to increase until 32 weeks' gestational age before declining; thus, checking levels and adjusting dosing monthly until the 7th or 8th month of pregnancy would be warranted [18].

As the need to increase medication during pregnancy may be difficult for patients to accept, considerable time should be spend in counseling and educating patients beforehand to increase the likelihood of adherence to the regimen.

There are additional risk factors that can increase the likelihood of seizure breakthroughs in pregnancy. These include having partial-onset or localization-related epilepsy and a requirement for multiple anticonvulsants to control seizures [19]. Patients with this latter risk factor should be monitored particularly closely as adjusting doses of each medication will be required.

When seizures occur in pregnancy, they may occur at any time, and in one study, some women developed convulsive or nonconvulsive status epilepticus during pregnancy [20]. The cases of status epilepticus were not seen more commonly in one trimester or another. A risk factor for seizures in delivery is the occurrence of seizures earlier in the pregnancy, suggesting that women who have breakthrough seizures during pregnancy perhaps should be watched more carefully at the time of delivery. For women who have seizures induced by hyperventilation, particular care should be taken to avoid deep or heavy breathing during labor. Seizures in pregnancy do not seem to be related to an increased risk of stillbirth or spontaneous abortion, however.

As a final, and perhaps more controversial point, there is some evidence that seizures occurring in pregnancy may be associated with an increased risk of epilepsy later in life for the infants. Yerby reports a 2.5 times increased risk of seizures in the offspring of mothers who had seizures during pregnancy [21].

It is important to consider the potential for pregnancy-related complications in women with epilepsy. A question frequently encountered in clinical practice is whether or not women with epilepsy should be scheduled for elective cesarean delivery or are at higher risk for other pregnancy-related complications. In a retrospective study where women with epilepsy were compared with a control population of women without medical problems, there were no increases in risk for preeclampsia, stillbirth, or preterm delivery [22]. A case–control study of pregnancies in women with epilepsy compared with women without epilepsy was similar in rates of pregnancy-induced hypertension, duration of labor, premature contractions, or cesarean section rates [23]. More recent data also support that women with epilepsy have no greater risk of intrauterine growth retardation, stillbirth, preeclampsia, or preterm delivery than women without epilepsy [24].

An update to the American Academy of Neurology/American Epilepsy Society's practice parameter on management issues for women with epilepsy found that women with epilepsy probably do not have a substantially increased risk (greater

than two times expected) of cesarean section [1]. The lack of substantial class I and class II evidence makes definitive statements about obstetrical complications challenging, but there does not seem to be significant evidence that common obstetrical complications such as late pregnancy bleeding, premature contractions, or premature labor and delivery occur with greater frequency in women with epilepsy [1].

The need for supplemental oral vitamin K prior to delivery is sometimes called into question for women with epilepsy taking particularly the enzyme-inducing older anticonvulsants. The potential risk is for development of hemorrhagic disease of the neonate in babies, despite the routine administration of intramuscular vitamin K to all babies postdelivery. Choulika et al. reviewed medical records for 204 newborns exposed in utero to anticonvulsants and compared them to 77 control newborns not exposed to anticonvulsants in utero [25]. No babies in either group were noted to have hemorrhagic disease; only one of the women in the study received prenatal vitamin K. More specific to the older anticonvulsants, which are specifically believed to interfere with the vitamin K-dependent clotting factors, Kaaja et al. found no increase in bleeding complications between pregnancies in women taking phenobarbital, carbamazepine, phenytoin, primidone, or oxcarbazepine compared with pregnancies in women without epilepsy and not taking anticonvulsants [26]. Rather, risk factors for bleeding complications were related to premature birth (less than 32 weeks' gestation) and alcohol abuse.

Breastfeeding in women with epilepsy is a controversial area, and proper consideration needs to balance the potential risks and benefits to the developing neonate against the risks and benefits to the postpartum mother. There are many potential benefits to the newborn from breast milk, including reduced risk for infections such as otitis media, for immune-mediated conditions for asthma and dermatitis, and for chronic disorders such as diabetes and obesity [27]. The most obvious risk to consider, however, is the risk of exposure to maternal anticonvulsants expelled in breast milk. This is particularly concerning since animal studies have shown a number of neuronal-specific effects on developing brain tissue, increasing the possibility that neonatal exposure could lead to long-term developmental effects. A number of research teams have developed long-term cohort-based studies to explore these concerns, and, so far, in at least one study looking at adjusted IQ in children exposed to monotherapy with anticonvulsants during gestation, then breastfed postdelivery, preliminary analysis "fails to demonstrate deleterious effects of breastfeeding during [antiepileptic drug] therapy on cognitive outcomes in children previously exposed in utero" [27].

Following delivery, doses of anticonvulsants need to be decreased, and significant counseling should be given with respect to the need for contraception and to continue adherence to folic acid throughout the childbearing years, regardless of a patient's stated desire to have additional children. There is a significant interaction between certain anticonvulsants and exogenously administered hormonal contraception, particularly when the anticonvulsant has an effect on the cytochrome P450 system. Enzyme-inducing anticonvulsants such as carbamazepine, phenytoin, phenobarbital, and topiramate can increase the risk of oral contraceptive failure. For women who prefer to use oral or implanted hormonal contraception, the use of enzyme neutral agents such as lamotrigine or levetiracetam would be recommended

[2]. However, as increased activity of the P-450 system can occur with administration of hormonal contraception, serum levels of anticonvulsants metabolized by this system must be checked and oral dosing adjusted to compensate for the lowered anticonvulsant levels.

Conclusion

Women with epilepsy can and do have uneventful pregnancies and normal, healthy babies. There are, however, additional risks that should be considered, some of which may be minimized through careful prenatal counseling and discussion. Optimizing seizure control prior to conception, preferably using an anticonvulsant in monotherapy at the lowest dose needed to control seizures may decrease the risk of breakthrough seizures during pregnancy, as will careful monitoring and adjustment of oral dosing throughout the pregnancy. Folic acid should be recommended to all women of childbearing age with epilepsy, and breastfeeding may be safely encouraged. Following delivery, additional counseling regarding adequate contraception should be offered.

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Pregnancy and Chronic Kidney Disease

Geena Joseph, Sarah L. Housman, and Melanie P. Hoenig

Abbreviations

ACR	Albumin-to-creatinine ratio
BP	Blood pressure
CNI	Calcineurin inhibitor
CKD	Chronic kidney disease
ESRD	End-stage renal disease
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
Urine PrCr	Urine protein-to-creatinine ratio

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Case 1

A 34-year-old nulliparous woman with a history of chronic kidney disease and hypertension presents for preconception counseling. Her reduced renal function was secondary to reflux nephropathy and a congenital single kidney (baseline creatinine 1.4–1.6 mg/dL). At the age of 12, the patient had surgical ureteral reimplantation. Her blood pressure is well controlled with lisinopril and hydrochlorothiazide. Discussions regarding pregnancy began when she transitioned to adult care, and more in-depth counseling regarding the risks and potential complications of pregnancy was addressed when she and her spouse began to consider pregnancy more seriously. The patient decides to proceed with pregnancy planning; she begins prenatal vitamins, and lisinopril was switched to labetalol with good blood pressure control.

Laboratory studies included a creatinine 1.4 mg/dL, uric acid 8.0 mg/dL, and urine protein-to-creatinine ratio (urine PrCr) = 0.4 mg/mg.

One year later, she becomes pregnant. She begins low-dose aspirin and a high-calcium diet. During pregnancy, she is monitored by both maternal fetal medicine and nephrology, and her creatinine remains stable at 1.4 mg/dL. While pregnant, she requires only labetalol 100 mg twice daily, and her average blood pressure is 130/80. Her blood pressure increases to 140/85 by 37-week gestation. Her pregnancy is complicated by intrauterine growth restriction (IUGR), and her urine protein-to-creatinine ratio increases from 0.4 to 0.8 g/g. Given the poor fetal growth over this period and the fact that the fetus is in the breech position, she has an elective cesarean section at 37 weeks and 5 days. She delivers a 2275 g baby girl (5–10th percentile). Apgar scores are 8 and 9. The infant requires care in the neonatal intensive care unit for 2 days due to hypoglycemia but then thrives and achieves age-appropriate milestones.

The mother is monitored closely postpartum. Her blood pressure is well controlled on labetalol and hydrochlorothiazide 6.25 mg while lactating. Her creatinine increases over the subsequent 8 months postpartum to 1.9 mg/dL, and her urine protein-to-creatinine ratio remains 0.8 mg/mg.

Renal Physiology in Normal Pregnancy

The physiology of normal pregnancy leads an increase in glomerular filtration rate (GFR) (Fig. 1). This increase is related to several factors, which include an increase in cardiac output, a decrease in peripheral vascular resistance, and an increase in total body water, which ultimately lead to an 80 % increase in renal plasma flow. These changes begin shortly after the first missed period and continue to midtrimester such that in 20 weeks, the GFR may be up to 50 % above baseline. The serum creatinine falls commensurate with the increase in the GFR. Normally, the GFR declines slightly during the third trimester and returns to prepregnancy levels with delivery or up to 3 months postpartum [2]. In the setting of chronic kidney disease (CKD), the physiologic increase in GFR (and fall in serum creatinine) may not occur.

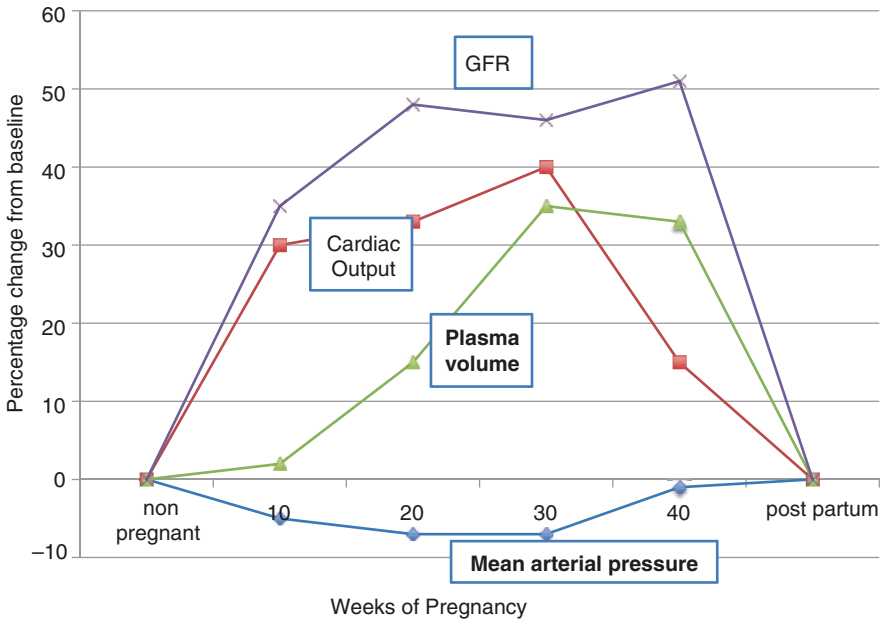

Fig. 1 Normal physiologic changes in pregnancy (Adapted using data from Ueland and Metcalfe [1], Davison and Dunlop [2], Hytten and Paintin [3])

Blood pressure typically decreases by 15–20 mmHg during the first 20 weeks of pregnancy. A decreased sensitivity to vasoconstrictive agents such as angiotensin II and an increased production of vasodilators such as nitric oxide appear to contribute to a significant reduction in systemic vascular resistance and enhance placental perfusion [4, 5]. The blood pressure then increases toward baseline during the third trimester.

Under normal circumstances, in the nonpregnant state, there is a small amount of proteinuria, and this is typically absorbed in the proximal tubules, which normally function at near maximum capacity for reabsorption of albumin, the predominant protein in blood. The net result under normal circumstances is that there is very little proteinuria. In the setting of a physiologic increase in renal blood flow and consequently GFR, as with normal pregnancy, there may be a small increase in proteinuria up to 200–300 mg/day by the third trimester. In twin pregnancies, there is a greater increase in cardiac output and often a greater increase in proteinuria; however, this increase would still result in very mild proteinuria normally under 0.5 g/day [6]. In patients with proteinuria at baseline, the physiologic changes from pregnancy can commonly cause an increase in proteinuria even without a decline in renal function or worsening of the underlying renal disorder.

Uric acid, a product of purine metabolism, is filtered and reabsorbed in the proximal tubule. It may be elevated in the setting of reduced renal function and in volume depletion when there is increased proximal sodium reabsorption. Serum uric acid levels are

also increased in preeclampsia; this finding is consistent with the likely pathogenesis of preeclampsia whereby ischemic injury to the kidney occurs in the setting of endothelial damage. In addition, some have postulated that the hyperuricemia can also contribute to endothelial damage [7]. Uric acid levels typically decrease during pregnancy by 25–30 % because of plasma volume expansion and the increase in GFR. Since uric acid can be elevated in CKD, this marker is harder to interpret in the setting of reduced renal function and is not recommended to predict which patients will develop preeclampsia; however, the trend in serum uric acid levels can be useful.

The Management of Hypertension in Pregnant Patients with CKD

Hypertension in the setting of pregnancy is classified as chronic hypertension, gestational hypertension, or preeclampsia (Table 1). This case highlights the management of chronic hypertension in pregnant patients with CKD. Hypertension guidelines for the general CKD, nonpregnant population recommend a target blood pressure of <140/90 mmHg and advocate for a lower target of <130/90 mmHg for patients with proteinuria [8, 9]. These guidelines are based on large randomized controlled studies in thousands of patients that addressed the risks of overall mortality, cardiovascular and renal morbidity, stroke, coronary interventions, and end-stage renal disease (ESRD). During pregnancy, the goals for blood pressure treatment differ from goals in the general population. Instead of long-term goals, the goals are short term and directed at avoiding immediate end-organ damage to the

Table 1 Classification of hypertension in pregnancy

Chronic hypertension	Gestational hypertension	Preeclampsia[a]
A diagnosis of hypertension before pregnancy	Hypertension in patients at >20-week gestation without a prior diagnosis of hypertension	New onset hypertension on two occasions after 20-week gestation (usually in third trimester after 37-week gestation)
Hypertension during the first 20 weeks of pregnancy	Absence of preeclampsia	Proteinuria (>0.3 g/24 h or urine protein/creatinine > 0.3 mg/mg)[b]
Hypertension that persists beyond 12 weeks postpartum	Hypertension resolves postpartum	End-organ damage[c]

Hypertension is defined as >140/90 mmHg

[a]As defined by the American College of Obstetricians and Gynecologists, 2013

[b]The urine protein-to-creatinine ratio (urine PrCr) on a random urine specimen approximates the amount of proteinuria in grams. Although this has not been rigorously tested in pregnancy, this test allows clinicians to follow proteinuria without regularly measuring 24-h urine collections

[c]End-organ damage is defined as platelet count <100,000/μl, serum creatinine >1.1 mg/dL or doubling of the serum creatinine, AST/ALT to twice-normal concentrations, pulmonary edema, new cerebral or visual symptoms

mother and fetus while limiting the risks of altered uteroplacental perfusion which might ultimately affect fetal growth and development [10].

Strict blood pressure targets in pregnancy have been extensively studied as a potential strategy to lower the risk of preeclampsia and pregnancy complications, but results have been disappointing. Several meta-analyses including a 2014 Cochrane review showed that treatment of mild to moderate hypertension during pregnancy does not decrease the risk of preeclampsia, neonatal death, preterm birth, or small-for-gestational-age babies [11].

Given the lack of definitive evidence, guidelines differ on the appropriate blood pressure target in pregnancy. The National Institute for Health and Clinical Excellence guidelines recommend a target blood pressure of <150/100 mmHg during pregnancy, whereas the American College of Obstetricians and Gynecologists recommends a target of <160/110 mmHg [12, 13]. There is strong evidence to suggest that severe hypertension ≥160/110 mmHg is associated with severe complications of maternal stroke and fetal abruption; therefore, severe hypertension should always be treated. Care of patients with hypertension and CKD adds a layer of complexity, and some advocate for slightly lower target of <140/90 mmHg although there is no data to support this recommendation [14].

In the largest study to date, 987 pregnant women with hypertension were randomized to either strict blood pressure control with a target diastolic blood pressure (DBP) of <85 mmHg vs. a target DBP <100 mmHg. Both groups had the same rates of pregnancy loss, need for high-level neonatal care, and maternal complications. The group randomized to less tight control had higher rates of severe maternal hypertension. Overall, this study showed no significant difference in the rates of serious maternal complications and major adverse perinatal outcomes with less tight versus tight control of blood pressure in pregnancy [15]. Of note, none of the patients enrolled in the study had CKD.

Ideally, hypertension management should begin before conception. Many women with CKD take angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs) as they are recommended for patients with proteinuric CKD to decrease proteinuria and slow progression of kidney disease [16, 17].

In pregnancy, however, ACE inhibitors cross the placenta in pharmacologically significant amounts and have a well-documented pattern of fetal risks with second- and third-trimester exposure. These fetotoxic effects include renal tubule dysplasia, renal agenesis, and other fetal abnormalities including oligohydramnios, hypoplastic lungs, hypocalvaria, and neonatal hypotension, likely stemming from a decrease in fetal angiotensin or an increase in fetal bradykinin [18]. It is generally assumed that ARBs will lead to similar complications, although published data is limited [19, 20]. The Food and Drug Administration (FDA) has labeled ACE inhibitors as contraindicated in the second and third trimesters since 1986; however, first-trimester exposure has been controversial, making prepregnancy counseling and management of young women with chronic kidney disease less straightforward. The evidence for first-trimester risk of congenital abnormalities with ACE inhibitor exposure is conflicting: a retrospective study linked first-trimester prescriptions for ACE inhibitors to a significantly greater

risk of serious fetal abnormalities [21], whereas a large cohort study and systematic review did not show an increase in risk [20, 22]. It is possible that this discrepancy is related to characteristics of the hypertensive pregnant population such as undiagnosed diabetes, maternal obesity, or hypertension itself. In the general population, the decision to stop ACE inhibitors prior to conception and control blood pressures with pregnancy-safe medications is obvious. In chronic kidney disease patients, especially with significant proteinuria, the decision is more difficult since ACE inhibitors appear to slow the progression of disease in those with significant proteinuria. Increasingly, experts in the field recommend a more tailored approach to the use of ACE inhibitors in women who are considering pregnancy [23, 24]. In the patient who is able to work closely with her care team and is at high risk for progression without an ACE inhibitor, such as those with proteinuria of >1 g/day, it may be reasonable to continue the ACE inhibitor until pregnancy is confirmed in the first trimester, particularly when conception may take months to years. Yet, the decision to conceive on an ACE inhibitor requires a careful discussion with the patient regarding potential risks and benefits. If a woman chooses to conceive on an ACE inhibitor, she is instructed to discontinue the drug when she obtains a positive pregnancy test to limit exposure and arrange to be seen promptly to confirm pregnancy. At that time, if necessary, pregnancy-safe antihypertensive agents can be used and be prescribed. In patients who are less likely to identify pregnancy early or those whose blood pressure may not be readily controlled without ACE inhibitors, a preconception change in regimen is more appropriate.

Methyldopa, labetalol, and nifedipine are considered first-line agents in pregnant patients or patients with hypertension who are trying to conceive as they have been studied in pregnancy and appear to be the safest [25–27], though methyldopa is used less often because it commonly causes nausea and fatigue and may increase liver enzymes. Thiazide diuretics are considered second-line treatment but are likely to be safe [28]. Patients with chronic hypertension should be seen in the office every 2–4 weeks in the first two trimesters, and visit frequency should be increased as needed, depending on the clinical course. Some suggest that women with chronic hypertension also monitor their blood pressure at home. In patients whose measurements correlate with office measurements, this can be a helpful adjunct to care but would not replace office evaluation of blood pressure. During office visits, urine protein should also be measured.

In this vignette, blood pressure variations mirrored the normal trends in blood pressure during pregnancy. The patient's blood pressure medication requirement decreased during the first half of pregnancy, and then her blood pressure increased toward her baseline during the third trimester. This normal trend is worth noting so that it is not mistaken for the onset of preeclampsia.

Classification of CKD in Pregnancy

The classification of CKD in pregnancy has traditionally differed from the classification of CKD in the general population. This is a reflection of the fact that these considerations preceded the newer "stages" of CKD that have been embraced by the

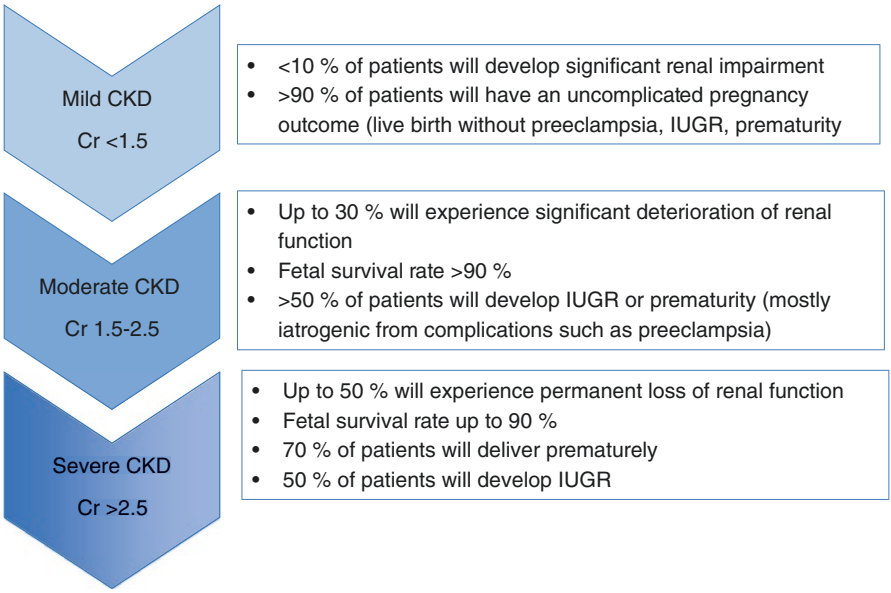

Fig. 2 Risks of maternal and fetal complications during pregnancy in CKD (For references, see associated text)

National Kidney Foundation. The latter uses estimated GFR (eGFR) rather than the serum creatinine, whereas, in pregnancy, risk is separated into three categories: mild, moderate, and severe based solely on the value of the serum creatinine prior to conception. These categories are also defined slightly differently in various publications, which make it more difficult to counsel patients. More recent publications have begun to consider pregnancy risk in the context of the estimated GFR and also consider proteinuria [29]. See Fig. 2 for a summary of risks by classification.

For the general population, formulas such as the Cockroft-Gault or the Modification of Diet in Renal Disease (MDRD) equation are used to estimate GFR. These formulas are used when the renal function is stable and include the serum creatinine and additional factors such as age, weight, gender, ethnicity, blood urea nitrogen, and serum albumin. None of these formulas perform well when the renal function is close to normal or when there is acute kidney injury. Importantly, these formulas also have not been validated for pregnant women [30]. The performance of MDRD equation in pregnancy may substantially underestimate GFR in pregnancy compared to GFR measured by inulin clearance [31]. Reliance on the MDRD formula during pregnancy is not recommended because of this discrepancy. Nevertheless, these estimates have become the standard for measurement of eGFR in the nonpregnant population and therefore are readily available and can be useful in preconception counseling. For comparison, a 30-year-old nonpregnant woman whose serum creatinine is 1.4 mg/dL would have an eGFR of approximately 50 ml/min/1.73 m^2 using several different formulas.

The degree of proteinuria plays a very important role in determining renal prognosis for patients with CKD who are not pregnant. In fact, this characteristic is so

important that the Kidney Disease: Improving Global Outcomes guidelines recommend classifying patients based on both eGFR and level of albuminuria [32]. Those with the most albuminuria are the most likely to have a further decline in renal function. It is likely that significant proteinuria also increases the risk of adverse pregnancy outcomes for women [29, 33]. The gold standard for measuring proteinuria remains the 24-h urine collection (with measurement of the urinary creatinine to assure a complete collection). Significant proteinuria in pregnancy is defined as proteinuria ≥0.3 g/day. Yet this test is difficult to do repeatedly because the sample sometimes requires refrigeration and its collection is cumbersome and time consuming. Instead, a random urine specimen that measures protein and creatinine can be used to calculate the urine protein-to-creatinine (urine PrCr) ratio. This value approximates the number of grams per day of urinary protein. Normal urine PrCr is < 0.2 mg/mg (20 mg/mmol) so a ratio of >0.3 mg/mg (0.30 mg/mmol) represents significant proteinuria in singleton pregnancy [34]; a threshold up to 0.4 mg/mg (40 mg/mmol) may be more appropriate in multiple pregnancy [35, 36].

A urinary albumin-to-creatinine ratio (ACR) can also be used since albumin is the major protein in blood and, therefore, the major protein in urine when there is proteinuria from altered glomerular hemodynamics or glomerular disease. The ACR was initially popularized to detect minute amounts of urinary albumin, too small to be detected by the urinary dipstick, and the units of measurement are three orders of magnitude smaller than the urine protein-to-creatinine ratio. Normal ACR is <30 mcg/mg creatinine. The urinary dipstick typically turns positive at approximately 300 mcg/mg creatinine. The sensitivity and specificity for both the ACR and urine PrCr are excellent when the urinary protein is very low [37]. Although the urinary ACR test has not been validated in pregnancy, it is recommended for screening nonpregnant diabetic patients and routinely used instead of 24-h urine collections to assess proteinuria in patients with CKD. Thus, either the urine PrCr or the urinary ACR can be used to follow patients who have CKD and are pregnant. Although these "spot" tests are less accurate than the 24-h collection, they are clearly more accurate than the urinary dipstick alone since the latter is dependent on the concentration of the urine.

CKD in Pregnancy: Complications

All women with underlying kidney disease are at increased risk of both maternal and fetal complications in pregnancy [38]. A systematic review of pregnancy outcomes in chronic kidney disease revealed that women with CKD appear to have at least a twofold higher risk of developing adverse maternal outcomes (gestational hypertension, preeclampsia, eclampsia, and maternal mortality) compared with women without CKD. Similarly, premature births occurred at least twice as often in women with CKD compared with women without CKD. Other fetal outcomes such as IUGR, SGA, neonatal mortality, stillbirths, and low birth weight were all higher in women with CKD compared to women without CKD; however, the rates vary depending on the study [39].

The risk of complications in pregnancy depends on many factors including baseline kidney function, proteinuria, type of renal disease, disease activity, scarring on kidney biopsy, and hypertension. The literature suggests that the strongest predictors of complications are baseline kidney function and severity of hypertension.

Mild CKD

Mild CKD has traditionally been classified as a prepregnancy serum creatinine less than 1.5 mg/dL(133umol/l), which would represent an estimated GFR of 50 ml/min/1.73 m^2 or greater for women over 21 years of age. These patients typically do relatively well during pregnancy. Most of the available studies suggest that renal function is generally preserved among patients with mild CKD. Less than 10% of women with mild CKD who also have minimal proteinuria (<1 g/24 h) and well-controlled blood pressure will develop permanent, significant renal impairment, and greater than 90% of patients will have successful pregnancy outcomes defined as having a live birth in the absence of preeclampsia, premature delivery, and IUGR [40, 41]. Hypertension appears to be the main predictor of pregnancy outcome for patients with mild CKD, as uncontrolled hypertension (defined as MAP >105 mmHg) in this population carries a higher risk for pregnancy complications [41].

Moderate CKD

Moderate CKD is traditionally classified as a prepregnancy serum creatinine range of 1.5–2.5 mg/dL (132–221umol/L). This includes a wide range of renal function that would reflect a preconception range of estimated GFR from 25 to 50 ml/min/1.73 $m^{2.}$.

In patients with moderate CKD, up to 30% will experience significant deterioration of renal function that will persist postpartum [42, 43]. In addition, there is a 10% risk of progression to ESRD by 12 months postpartum; this risk is likely to be greater with higher preconception creatinine values and significant proteinuria [42, 44]. Among patients with moderate CKD, although the fetal survival rate exceeds 90%, greater than 50% of fetuses will experience IUGR or prematurity (often related to preeclampsia) [33, 42, 43]. Furthermore, a longitudinal multicenter cohort study of 49 pregnant patients with moderate-to-severe kidney disease showed that the combination of prepregnant proteinuria (>1 g/day) and Cr>2.0 mg/dL predicted postpartum renal decline and worse fetal outcomes more than reduced GFR or proteinuria alone [33].

Severe CKD

The preconception serum creatinine that characterizes severe CKD in pregnancy varies somewhat in the literature, and this is related to the limited number of patients in this category who conceive. Certainly, a serum creatinine greater than or equal to

2.5 mg/dL would be considered severe CKD by most. This value is likely to correlate with an eGFR below 25 mL/min/1.73 m^2. Since preparations for dialysis or evaluation for renal transplant are appropriate for patients with eGFR below 25 ml/min/1.73 m^2, the prospect of pregnancy in this setting complicates care considerably. These patients tend to have a difficult time conceiving, and they have the highest risk of maternal and fetal complications. Indeed, combined data from several sources suggest that nearly all women with severely reduced renal function will have a complication during pregnancy and half will experience permanent loss of renal function and may need to start dialysis during pregnancy or postpartum [29]. The risk of prematurity is significant and estimated to be as high as 70–90 % in some studies and IUGR risk of up to 50–65 % [29, 45, 46]. Despite the high risk of complications, approximately 75–90 % of patients will have a live birth. Patients must be counseled about the potential long-term consequences associated with prematurity and the additional stress of potentially caring for a sick child while addressing their own health issues such as initiation of dialysis. Counseling patients about these complex issues is important so that patients can make educated decisions.

Primary Renal Disease and Pregnancy

Although much of the literature on CKD in pregnancy categorizes the clinical course by the preconception creatinine, the underlying renal disease and the disease activity prior to conception can greatly affect outcome. For example, in patients with systemic lupus erythematosus or systemic sclerosis, adverse maternal and fetal outcomes are more likely than in women who have a history of reflux nephropathy. Patients with a history of nephrolithiasis or recurrent pyelonephritis may have specific challenges but tend to do well with pregnancy. Similarly, women who have previously donated a kidney and therefore have reduced renal mass tend to have favorable outcomes during pregnancy but may have a greater risk of gestational hypertension and preeclampsia compared to the general population [47]. In general, renal disease should be treated and well controlled prior to pregnancy to improve outcomes; this is particularly true for lupus nephritis, diabetic nephropathy, and glomerulonephritis.

CKD and Preeclampsia

In the first case, the urine protein-to-creatinine ratio increased during pregnancy from 0.4 mg/mg prepartum to 0.8 mg/mg at delivery. Many patients with CKD have proteinuria and hypertension at baseline, and during pregnancy the proteinuria often increases. This can make it challenging to differentiate between chronic kidney disease and preeclampsia particularly since hypertension and proteinuria are two of the criteria used to make the diagnosis of preeclampsia. If hypertension and proteinuria are preexisting, other clinical signs should be used to diagnose preeclampsia such as placental

dysfunction, elevated liver enzymes, low platelets, or clinical symptoms. It is critical that the distinction between CKD and preeclampsia is made since an incorrect diagnosis of preeclampsia could lead to iatrogenic prematurity. To complicate matters, patients with CKD have up to four times higher risk of developing preeclampsia, compared to those without CKD [38]. An evolving understanding of the pathogenesis of preeclampsia may lead to the identification of serum biomarkers to help distinguish between the two entities. Biomarkers such as soluble fms-like tyrosine kinase 1 (sFlt1), an anti-angiogenic factor, are elevated in patients with preeclampsia and lead to a reduction in placental growth factor (PIGF) and vascular endothelial growth factor (VEGF). The dysregulation of these growth factors appears to result in placental endothelial dysfunction and the subsequent clinical manifestations of preeclampsia [48]. Patients with preeclampsia have marked elevations in sFlt1, reductions in PIGF, and a higher sFlt1/PIGF ratio compared to those who do not have preeclampsia but have CKD [49, 50]. Although prospective and longitudinal studies are still needed to define the role of these markers in clinical management, in the future, some combination of measurements of angiogenic factors may provide unique tools for caregivers to predict preeclampsia and differentiate preeclampsia from a change in renal function among pregnant patients with CKD.

Prevention of Preeclampsia

There are no treatments that can reliably prevent the development of preeclampsia. In several large randomized, multicenter trials and meta-analyses, low-dose aspirin appeared to confer some benefit in the general pregnant population though these benefits have not been confirmed in subgroup analyses of high-risk patients or those with CKD [51]. Nevertheless, low-dose aspirin at doses of 75–120 mg taken at bedtime and begun by the 16th week of gestation is broadly recommended by major relevant societies including the International Society of Hypertension in Pregnancy, the United Kingdom's National Institute of Health Care Excellence (NICE), and the American Congress of Obstetricians and Gynecologists (ACOG) [52, 53].

In addition, the World Health Organization endorses calcium supplementation before 20-week gestation in populations where calcium intake is low with a goal of 1.5–2 g of elemental calcium intake daily. This recommendation stems from randomized controlled trials that demonstrated a decreased risk of preeclampsia and preterm delivery with calcium supplementation, particularly in those women who had low-calcium diets [54, 55].

Case 2

A 39-year-old nulliparous woman with polycystic kidney disease (PKD) complicated by hypertension presents for prepregnancy evaluation. She is otherwise healthy. She has never had visible hematuria, kidney stones, or urinary tract

infections. Her father had PKD and developed ESRD in his late 40s and then died of a heart attack at the age of 61. Her blood pressure has been well controlled on metoprolol sustained release 100 mg daily for several years. Her menstrual cycles are normal, and she is using condoms for contraception. Her blood pressure was 132/87 mmHg. Abdominal examination was notable for palpable kidneys bilaterally. Her creatinine is 2.6 mg/dL (eGFR 22 mL/min/1.73 m^2). Old records reveal a creatinine of 1.9 mg/dL 3 years prior and 2.1 mg/dL the year prior to referral.

Despite minimal proteinuria and good blood pressure control, her renal function has declined relatively rapidly. She is counseled about the high risk of pregnancy complications and decides against pregnancy. She has no suitable donors for transplantation and is counseled regarding options for dialysis. She begins oral contraception to prevent an unplanned pregnancy and decides to pursue adoption.

The following year, she begins dialysis for symptoms of nausea and vomiting when her creatinine reaches 5.6 mg/dL, but the symptoms persist. Abdominal ultrasound reveals that she is pregnant, and the approximate age of the fetus is 21-week gestation. Her hemodialysis regimen is intensified and she receives 4 h, 6 days per week (total 24 h per week). Her residual urine output is 1.5 L/day so minimal fluid removal is required with dialysis. Her blood pressures remain normal throughout pregnancy without medication. The fetus has mild fetal growth restriction, but ultrasounds demonstrate normal uterine Doppler flow and amniotic fluid throughout pregnancy. At 35-week gestation, spontaneous labor begins and she delivers a 2619 g baby boy (50–70th percentile). Apgar scores are 8 and 9. The infant is monitored in the neonatal intensive care unit for 1 day given prematurity, but is then discharged and achieves age-appropriate milestones.

Preconception Counseling

Caregivers have variable training and experience giving "sad" and "bad news" to patients, and antenatal counseling in the setting of advanced chronic kidney disease provides a particular challenge. First, the statistics available to help patients make an informed decision are limited and of variable quality. Furthermore, since outcomes relate both to the health of the mother and the chance of normal development and survival of the fetus, counseling is typically emotionally charged. In addition to providing data, it is useful to consider a multistep approach not unlike the steps used for counseling regarding a cancer diagnosis or recognition of advanced kidney disease and impending need for renal replacement therapy. These approaches include the creation of a relationship, identification of the patient's understanding of her health, sharing information regarding the risks, shared decision-making, a response to her emotions, and a thoughtful planning [56, 57].

Preconception counseling is an essential component of the care of women who are of childbearing age with chronic kidney disease. This counseling should begin at entry to care. All women with kidney disease are at increased risk of pregnancy complications; however, the risk varies based on the kidney disease stage, and therefore thoughtful planning in this population is necessary. For example, women with PKD who begin to lose kidney function should be encouraged to consider pregnancy earlier, when kidney function is still relatively preserved. Although it is fortunate that patients with reduced

renal function generally feel well until the GFR is so reduced that renal replacement therapy is imminent, (typically when the eGFR is below 10 ml/min/1.73 m^2), this also means that women may have difficulty believing that they are at higher risk of complications. In this situation, since women are usually asymptomatic, the risks of pregnancy outlined by caregivers may seem exaggerated. However, if counseling begins early, appropriate preparations can also begin. For patients with advanced CKD who understand the risks and decide against pregnancy, the spectrum of contraceptive options is available with the same risks and concerns as in the general population [58]. For women who decide to proceed with pregnancy, it is important for caregivers to suspend judgment and provide care with the help of a multidisciplinary team.

Advocate for Patients Who Would Like to Parent

In patients who have severely reduced renal function, it is important to remember that counseling against pregnancy is not the same as counseling against motherhood. Individuals with reduced renal function typically feel well (unless comorbid conditions impact their health). In this situation, caregivers should be advocates for parenthood if patients desire this. Women with chronic kidney disease can utilize the help of a gestational surrogate; although this strategy requires navigation of complex issues that range from contractual and financial issues to cultural pressures and ethical dilemmas [59], it allows a couple to have their own genetically related child. Adoption is an additional option for women who choose to forgo pregnancy because of the attendant risks. Women who choose this route may need support from caregivers to confirm that their health is sufficiently stable to ensure the safety, well-being, and permanence of the placement for an adopted child (Child Welfare Information Gateway) [60].

An additional option is for women to wait until they have a renal transplant to become pregnant. This option can be frustrating for women who are older and have a limited number of potential childbearing years or for women whose renal function is deteriorating slowly, and the time that lapses before progression, transplantation, and the requisite posttransplantation wait is daunting.

Although data is limited, a small series that looked at outcomes for children born to mothers with CKD did not find differences in maternal bonding, additional stress in the parent-child relationship, or other difficulties in parenting that might relate to the stress of maternal renal disease and treatment [61]. Additionally, egg or embryo harvesting can preserve fertility for longer.

Care for Patients Who Become Pregnant While on Dialysis or Require Dialysis While Pregnant

Pregnancy is uncommon in ESRD patients on dialysis. There are several reasons for this observation. Many patients with ESRD feel poorly either from comorbid conditions or dialysis treatments and have reduced libido. In addition, irregular and

anovulatory cycles are common and felt to be related to a lack of estradiol-stimulated cyclic luteinizing hormone secretion and elevated prolactin levels [62]. Since most ESRD patients have irregular menstrual cycles, in the event that a woman does become pregnant, there may be a delay in the recognition of the pregnancy. ESRD patients who conceive have usually been on dialysis for less than a year. They usually have higher residual renal function and often conception occurs before the initiation of dialysis. The chance of successful pregnancy in women who conceived prior to initiation of dialysis is close to 90%, much higher than those who conceive on dialysis [63]. There are well-described strategies, for dialysis of a pregnant patient, albeit from a handful of small, published series, that can guide treatment. Intensification of dialysis is the cornerstone of care for successful pregnancy on dialysis. The best outcomes have been observed in centers where the dialysis prescription was more than doubled compared to usual care. In a series from Toronto, Canada, that described six pregnancies in five women, the dialysis time was increased using nocturnal hemodialysis to deliver a mean dose of 48 h weekly. In this series, there were no cases of preeclampsia or severe hypertension and only two babies developed IUGR though 50% required preterm delivery (defined as delivery before 37 weeks, though only one delivered before 32 weeks) [64]. Buoyed by this positive experience, the same group has now published a larger series of 22 patients who received intensive dialysis and compared these to a series of 77 patients who received less intensive dialysis. In this series, women who received more than 36 h of dialysis weekly had an 85% chance of a live birth, whereas those who received less than 20 h of dialysis weekly had a live birthrate of only 48%. Furthermore, women who had more intensive dialysis achieved longer gestational age and greater birth weights [65]. The authors conclude that pregnancy can be safe and feasible for a woman with ESRD who does hemodialysis. Pregnancy is also possible in patients who perform peritoneal dialysis; however, the ability to intensify the amount of dialysis is limited. The growing uterus limits surface area in the peritoneum and the volume that can be instilled. In order to increase dialysis, women who perform peritoneal dialysis with the cycler by night may need to add frequent exchanges to the daytime period or add hemodialysis to her peritoneal dialysis regimen [66].

The patient in the vignette was in optimal condition prior to pregnancy and although her pregnancy was unplanned and the diagnosis delayed, she maintained good residual renal function and with intensified hemodialysis, she had a good outcome.

Case 3

A 36-year-old woman is seen for preconception counseling. She has ESRD secondary to focal and segmental glomerulosclerosis and required dialysis for 1 year before she had a living-related kidney transplant from her brother. Her medications include an extended release formulation of tacrolimus 7 mg daily, prednisone 5 mg daily, and mycophenolate mofetil (MMF) 1000 mg twice daily. She has had stable renal function, since her transplant with a creatinine of 1.0 mg/dL (88 umol/L), a hemoglobin of 11.1 g/dL, and no proteinuria. She has had no complications, rejections, or infections. She never had hypertension.

She is counseled about the risks of pregnancy. She and her partner accept the risks and proceeded with preparation. Her mycophenolate mofetil is switched to azathioprine 125 mg daily and she begins prenatal vitamins. Her renal function remains stable and after 3 months, they try to conceive. Six months later, she conceives spontaneously and begins aspirin 81 mg daily; a high-calcium diet or calcium supplementation 1500 mg daily is also recommended.

She is followed jointly with a high-risk obstetrician and nephrologist. She is seen monthly with regular blood work, and during this time, her serum creatinine and blood pressure decrease with a nadir at 24 weeks. Her hemoglobin and iron studies decrease and she takes iron supplements as recommended. At 30 weeks, her blood pressure increases to 148/98 mmHg consistently, and she begins a long-acting formulation of nifedipine at 30 mg daily. Fetal ultrasound reveals mild fetal growth restriction, but normal umbilical artery Doppler studies were normal throughout the pregnancy. At 38 weeks, spontaneous labor begins, and she vaginally delivers a healthy baby girl who weighs 2922 g (70–90th percentile). Immediately postpartum the creatinine is noted to be higher at 1.29 mg/dL (114 umol/L), maternal blood pressure is normal, and she starts breastfeeding without difficulty. At 3 days postpartum, her blood pressure rises to 150/100 mmHg, and the nifedipine is increased. Eight weeks postpartum, her blood pressure returns to normal, and she no longer requires antihypertensive medication. At 1 year postpartum, the blood pressure is normal, and the creatinine remains stable at 1.2 mg/dL (106umol/L), without proteinuria.

Renal Transplant and Fertility

The first reported successful pregnancy with a renal allograft was in 1958, and since then over 14,000 pregnancies in renal allograft recipients have been documented [67–69]. Patients with advanced renal failure have impaired reproductive function, related to hypothalamic-pituitary-gonadal axis dysfunction [70]. Sexual function and fertility usually improve within months of renal transplantation, though the return of fertility is not guaranteed [69]. In one series, only two-thirds of renal transplant recipients had regular menstrual cycles, and slightly less had ovulation documented by rising progesterone and ultrasound visualization of follicle growth [71]. Pregnancy is estimated to occur in 5–12 % of women who are of childbearing age with a renal transplant, and approximately 50 % of these pregnancies are unplanned [72, 73]. In vitro fertilization has been used successfully in renal transplants; however data is limited [74].

Pregnancy Counseling and Preparation

Discussions regarding pregnancy should begin when women of childbearing age are seen for pretransplant evaluation and continue after transplantation. Emphasis should be placed on the need to continue immunosuppressive therapy during

Table 2 Guidelines for pregnancy in renal transplant recipients

Timing of pregnancy	No rejection in the past year (AST) Good health for about 2 years (EDTA)
Adequate and stable graft function	Creatinine <1.5 mg/dL (AST) Creatinine < 2 mg/dL (177 umol/L) but preferably <1.5 mg/dL (<133 umol/L) (EDTA)
Proteinuria	<0.5 g/day (EDTA)
Maintenance immunosuppression Dosing is stable	Prednisone <15 mg/day CSA and tacrolimus at therapeutic levels MMF and sirolimus are contraindicated (stop 6 weeks before conception)
Additional concerns	Maternal age, rejection within the first year, established noncompliance, comorbid factors

Adapted from both the American Society of Transplantation (AST) Consensus Statements, 2005, and European Dialysis and Transplantation Association (EDTA) Guidelines, 2002

pregnancy. Some women stop medications for fear of adverse effects on baby without understanding that loss of graft function carries a higher risk for the baby than the medications themselves. Pregnancies should be planned in order to decrease the risk of complications and increase the chance of successful pregnancy outcome. Recipients' care should be optimized prior to conception, and this may include a change in medications to those that are pregnancy safe, good blood pressure control, and a thorough discussion about the risks.

Two major groups, the European Dialysis and Transplantation Association (EDTA) and the American Society of Transplantation (AST), have published guidelines that are used for advising transplant recipients about pregnancy (Table 2) [75, 76]. The general consensus is that pregnancy can be considered in renal transplant recipients who are in good health posttransplant for a minimum of 1 year. Other favorable prognostic factors include creatinine <1.5 mg/dl (133umol/l), proteinuria <500 mg/day, no recent rejection, good blood pressure control, and stable pregnancy-safe immunosuppression. There is growing evidence that recipients may be able to conceive safely within <1 year, recognizing that the window of fertility may be narrow for some women [76, 77].

Pregnancy Outcomes in Patients with Kidney Transplant

Various studies have been published in regard to pregnancy outcomes in renal transplant recipients, and the chance of successful pregnancy ranges from 70 to 80 %. A systematic review and meta-analysis published in 2011, which included publications between 2000 and 2010, reported an average live birthrate of 73.5 %, miscarriage rate 14 %, abortion 9.5 %, stillbirth 2.5 %, and ectopic pregnancy 0.6 % [78]. The National Transplantation Pregnancy Registry (NTPR) is a voluntary registry initiated in 1991 in the United States. As of December 31, 2013, they have collected data on 1,687 pregnancies (1,744 outcomes) in 960 kidney transplant recipients. The live birthrate among

women treated with the different immunosuppression regimens was 75.5% (819 pregnancies) cyclosporine based, 71.5% (385 pregnancies) tacrolimus based, and 83.4% (377 pregnancies) azathioprine and/or prednisone [79].

Pregnancy with a renal transplant is associated with an increased risk of complications compared to the general population [78, 80, 81]. Women are at increased risk for hypertension, preeclampsia, preterm delivery, fetal growth restriction, low birth weight, and neonatal complications.

Effect of Pregnancy on Kidney Graft Function

A prospective study of creatinine and inulin clearance in renal transplant recipients with preserved renal function (creatinine clearance >50 mL/min) compared to healthy controls demonstrated that renal allografts accommodate normally to pregnancy [82]. In addition, a study of 18 transplanted women who had 25 pregnancies did not find an adverse effect of pregnancy on graft survival compared to graft survival in 26 female controls and 23 male controls. After a mean follow-up of 11.8 years posttransplant and 6.9 years after pregnancy with similar periods of follow-up for the control groups, graft survival is not significantly different in women who had become pregnant compared to both the female and male controls [83]. Since then, several case-control studies comparing graft survival of pregnant renal transplant recipients to matched nonpregnant controls have shown similar results. The majority of recipients in these studies had a creatinine <1.5 mg/dL (133mmo/L) and met pregnancy guidelines. Furthermore, a study from the Australia and New Zealand Dialysis and Transplant Registry matched 120 women with their first live birth to 120 renal transplant controls who never became pregnant; this study demonstrated no difference in the 20-year risk for renal allograft loss based on pregnancy [84].

Management

Management of renal transplant recipients considering pregnancy begins prior conception. This population is considered high risk and requires follow-up by a dedicated team including high-risk obstetrics and transplant nephrology. Patients often require medication changes, and other medical problems should be optimized prior to conception.

Pregnant kidney transplant recipients have the same risk for acute kidney injury as other pregnant and nonpregnant transplant patients [85]. Yet there are a few issues that require special attention in the pregnant transplant population. Urinary obstruction related to growing uterus is a rare complication and easily identifiable by ultrasound if a first-trimester ultrasound is done at baseline for comparison. Calcineurin inhibitor (CNI) toxicity is also possible given dose changes and changes to other medications during pregnancy. Opinions differ on the need or frequency for dose

adjustment of immunosuppression [86]. In general, most recommend following CNI levels and adjusting the dose to avoid toxicity or extremely low values [76]. Acute rejection is uncommon after the first year of transplant, and, based on the NTPR, the incidence is only 1–4 % in pregnancy [79]. Renal biopsy should be performed to confirm rejection if suspected. Preeclampsia should be considered after 20-week gestational age and investigated with blood work and fetal surveillance. Hemolytic uremic syndrome can occur with pregnancy or CNI. In the vignette, causes for a decline in renal function were explored, but fortunately, the serum creatinine stabilized so a kidney biopsy was not required.

Hypertension commonly complicates the pregnancies of patients with kidney transplants, and similar to the pregnant CKD population, most suggest a target BP of <140/90 mmHg.

There is normally a mild physiologic fall in hemoglobin values during pregnancy, which is the net result of an increase in red cell mass along with a larger increase in plasma volume. Patients with CKD and those with renal transplants may have only marginal erythropoietin production and are more likely to develop significant anemia during pregnancy. Iron deficiency should be treated, and erythropoietin-stimulating agents may be required to maintain a hemoglobin >10 g/dL.

Immunosuppressive Medications

Potential effects of immunosuppressive medications on the fetus mandate that patients receive extensive counseling around pregnancy [87] (Table 3). Prednisone has been extensively used in pregnancy for many conditions. In the first trimester, <9-week gestation, one study showed an increased risk of cleft palate compared to the general population [88], but a more recent population study from Norway showed no increase risk of orofacial clefts with first-trimester prednisone exposure [89]. Overall, if there is an

Table 3 Maintenance immunosuppression in pregnancy

Medication	FDA class	Comments
Prednisone	B	Possible low first-trimester risk of cleft palate Rare cases of fetal adrenal suppression and thymic hypoplasia if dose > prednisolone 15 mg/day close to term
Calcineurin inhibitors		
Cyclosporine	C	Increased risk of miscarriage, IUGR, preterm delivery, hypertension
Tacrolimus	C	Increased risk of IUGR, preterm delivery, and diabetes
Antiproliferative agents		
Azathioprine	D	Safe based on large cohorts of patients with transplant, SLE, Crohn's Not converted by fetal liver to active form
Mycophenolate mofetil Mycophenolic acid	D	Teratogenic in first trimester in humans
Rapamycin, sirolimus	C	Limited evidence, mainly case reports of safety

increased risk, it is small compared to the high risk of adverse fetal outcomes with graft loss, so the benefits of maintenance immunosuppression outweigh the risks.

Azathioprine has also been used safely by thousands of pregnant women for various conditions, though it is still labeled category D by the Food and Drug Administration (FDA). This designation is mainly based on malformations seen in animals given parenteral azathioprine in higher doses than used in humans. Azathioprine is considered safe in pregnancy by physicians for many reasons: the lack of evidence of harm in many human case series, radioactive labeling studies in humans that have shown that the majority of azathioprine administered to mothers appears in fetal blood as the inactive metabolite thiouric acid, and the suggestion that fetus lacks the enzyme inosinate pyrophosphorylase needed for conversion of 6-mercaptopurine (MP) to its active form protecting the fetus from azathioprine's effects [74, 90].

Calcineurin inhibitors (cyclosporine and tacrolimus) are currently the most commonly used maintenance immunosuppressive agents. There has been no indication of congenital malformations; however, there is a risk for fetal growth restriction. These agents also appear to confer a higher risk of hypertension and serum creatinine >1.5 mg/dL. In comparison with cyclosporine, pregnant women taking tacrolimus have a lower incidence of hypertension and hyperlipidemia but higher incidence of developing posttransplant diabetes mellitus. Tacrolimus has also been associated with transient perinatal hyperkalemia in the newborn [74].

Mycophenolate mofetil (MMF) is associated with an increased risk of spontaneous abortions and congenital malformations with exposure between 4- and 9-week gestation. Evidence accumulated since it came into use, and a 2013 study confirmed that the rate of anomalies might be as high as 22–27%. Malformations seen with MMF include facial deformities (microtia, cleft lip and palate, auditory canal atresia, micrognathia) and limb anomalies (short fingers and hypoplastic nails) [74, 91].

The risk of congenital anomalies with mycophenolate products is serious enough that the FDA has placed a black box warning and the company has instituted a Mycophenolate Risk Evaluation and Mitigation Strategy that requires providers to be educated about the teratogenicity of MMF. Patients should be on birth control while using MMF and switch to azathioprine at least 6–12 weeks prior to conception.

Evidence for mammalian target of rapamycin inhibitors (sirolimus/everolimus) in pregnancy is very limited. Since there are immunosuppressive options with more evidence of safety during pregnancy, there is general reluctance to use this category of drugs during pregnancy. Yet, there are several case reports of successful pregnancies with sirolimus and everolimus [79].

Infections

Transplant patients are immunosuppressed, and pregnancy is also a period when patients may be more susceptible to infections. Urinary tract infections and urinary reflux are common in pregnant renal transplant recipients; therefore, screening for pyuria and treating positive cultures are important to prevent pyelonephritis. Current guidelines endorse monthly screening [75].

Another serious potential posttransplant infectious complication is cytomegalovirus (CMV). Both primary and reactivation CMV infection can be transmitted to the fetus. Congenital infections have been associated with microcephaly, intrauterine growth restriction, sensorineural hearing loss, visual impairment, and developmental disorders, as well as a high mortality rate [92]. Preexisting immunity to CMV appears to reduce the risk to the fetus. Baseline CMV serology should be performed, and then patients should be retested if they develop a mononucleosis-like illness or if a fetal anomaly is identified on prenatal ultrasound that is suggestive of congenital CMV [74]. Maternal infection can be detected by the presence of CMV immunoglobulin M antibodies in maternal blood. Once found, further evaluation is undertaken to assess for congenital CMV infection.

In the general pregnant population, primary infection with toxoplasmosis is reported to cause neonatal infection in 25–65 % of exposed infants [90]. Suspected infection in the fetus can be detected by a combination of testing amniotic fluid and fetal blood as well as the finding of brain ventricular enlargement by ultrasound at 20–24 weeks. Treatment with sulfadiazine and pyrimethamine or spiramycin reduces the likelihood of congenital infection by 60 %, so primary infections should be treated even if the mother is not seriously ill. In immunosuppressed patients, congenital infection can occur after reactivation of toxoplasmosis, and consideration should be given to treating seropositive women with rising antibody titers. Pregnant kidney transplant recipients should be screened for toxoplasmosis each trimester [74].

Herpes simplex infection can be serious for the fetus and neonate. Before 20 weeks of gestation, vertical (mother-to-fetus) transmission can lead to spontaneous abortion in up to 25 % of patients. Herpes simplex is usually transmitted during birth, and women are routinely examined during labor for lesions in the birth canal. Cesarean sections are performed if herpes lesions are identified and fetal exposure is likely. Suppression with acyclovir or valacyclovir during the last month of pregnancy may reduce the need for cesarean section because of herpes lesions [74].

Overall, successful pregnancy is possible in women with renal transplants, but is associated with increased risk of complications and requires close follow-up by a dedicated team.

Breastfeeding

Patients with CKD

While ACE inhibitors are contraindicated in pregnancy, short-acting ACE inhibitors (such as captopril and enalapril) are considered safe during lactation as minimal amounts of the medication are transmitted into breast milk [93, 94]. These agents can be used safely after the immediate postpartum period as long as renal function is stable, when babies are ready to leave the hospital. All antihypertensive agents that are safe in pregnancy are considered safe for breastfeeding. Specific data can be found at LactMed, an online database for medications used during lactation [95].

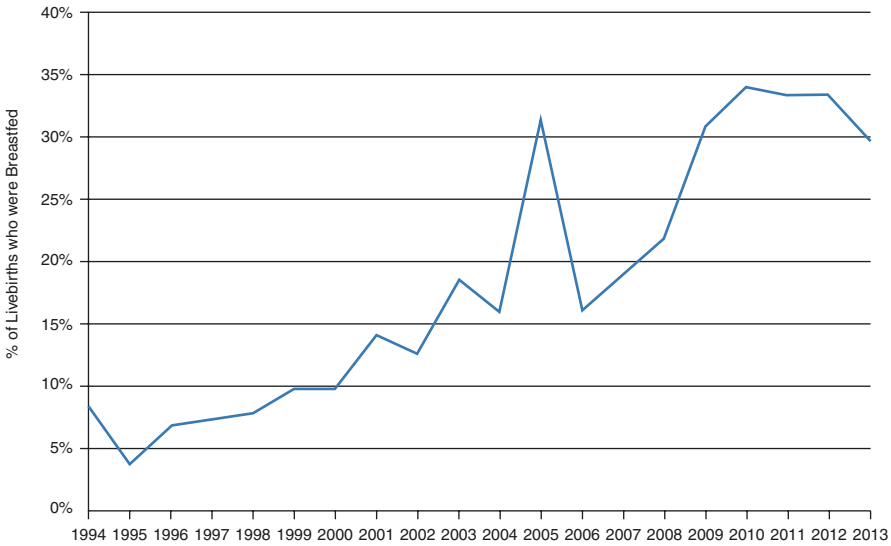

Fig. 3 NTPR trend in breastfeeding practices of transplant recipients (Published with permission from National Transplantation Pregnancy Registry (NTPR). 2013 Annual report: Gift of Life Institute. Philadelphia, PA: 2014. Available by request: NTPR@giftoflifeinstitute.org)

Patients with Renal Transplant

Breastfeeding in transplant recipients is controversial. Although breastfeeding is not recommended on the current labeling of most immunosuppressive medications and most transplant physicians advise against it, the NTPR has recorded an increasing trend in the number of recipients who choose to breastfeed their infants [79] Fig. 3.

Only small amounts of corticosteroids are present in breast milk, at most 0.1 % of the total prednisolone ingested by the mother. The American Academy of Pediatrics (AAP) considers corticosteroids safe for breastfeeding [96].

Cyclosporine and tacrolimus are excreted in breast milk in varying quantities. In a study of 14 transplant recipients using tacrolimus during pregnancy and breastfeeding, maternal blood, breast milk samples, and infant blood samples were studied for up to 72 days postpartum. The highest amount of tacrolimus excreted in breast milk was equivalent to 0.23 % of the maternal dose; this is comparable to other studies which suggest rates of 0.06–0.5 % of maternal dose. Eight of twelve breastfed infants showed the same rapid decline in serum tacrolimus levels after birth as bottle-fed infants, suggesting that patients who take tacrolimus need not be discouraged from breastfeeding [97].

Azathioprine is excreted into breast milk in varying amounts, but the majority of cases have undetectable amounts of azathioprine and 6-mercaptopurine, its active metabolite. Small amounts of 6-mercaptopurine can be detected in breast milk in samples taken within 4 h of administration of azathioprine [98]. Based on available data, an infant who is breastfed would receive 0.0075 mg/kg body weight, less than

1 % of the maternal dose and 1/1000th of the therapeutic dose of 1 mg/kg. Thus breastfeeding during treatment with azathioprine appears safe [96].

There is now long-term data from the NTPR on over 100 transplant recipients who chose to breastfeed their infants while taking immunosuppressive medications. The length of time the children were breastfed ranged from several days to 2 years. At last follow-up, which ranged from 3 weeks to 13 years, there were no specific problems reported in children attributed to breastfeeding [96]. The American Society of Transplantation consensus opinion is that breastfeeding need not be viewed as absolutely contraindicated [76].

Conclusion

When women with chronic kidney disease or a renal transplant consider pregnancy, a dedicated team is required to provide a tailored approach to counseling and care. Successful pregnancy in this patient population is challenging but rewarding. An overview of care is provided in Table 4.

Table 4 Approach to management of pregnancy in patients with CKD and renal transplant

Before pregnancy
Tests for antibodies to rubella, hepatitis B and C, and rubella vaccine if not immune
CBC, electrolytes, urea, creatinine, urine: UA, culture, PrCr, or ACR
24-h urine for protein and creatinine clearance for baseline
Review all medications for safety in pregnancy
Optimize all medical problems
Optimize blood pressure (BP < 140/90)
Consultation with high-risk obstetrician
During pregnancy
Low-dose aspirin (75–120 mg) at bedtime by 16-week gestation and high-calcium diet or calcium supplements (>1000 mg/day)
Ideally, daily home measurements of blood pressure by patient (BP <140/90)
Monitor – biweekly/monthly
Nephrologist and obstetrician visit
CBC, complete metabolic profile, urine: UA, culture, PrCr, or ACR monthly
Ultrasound assessment of fetal well-being from 26-week gestation
Monitor – each trimester
Consider 24-h urine for protein and creatinine clearance
Monitor – last trimester
Biweekly fetal surveillance
Examine for HSV lesion close to delivery and at labor
Peripartum and postpartum
C-section only for obstetric indications

(continued)

Continue BP monitoring for a minimum of 6–8 weeks postpartum (BP < 140/90)
Assess renal function and proteinuria 1 month and 6 months postpartum
Additional management for patients with renal transplant
Before pregnancy
Rh compatibility of patient and transplant
Tests for antibodies to HSV, CMV, and toxoplasmosis before pregnancy
PCR for CMV and toxoplasmosis before pregnancy
Switch immunosuppression to pregnancy safe (stop MMF, sirolimus, and everolimus 6 weeks before conception. May substitute with azathioprine, cyclosporine, tacrolimus, or prednisone)
During pregnancy
Kidney ultrasound during the first trimester
CNI levels (weekly to monthly)
Each trimester – CMV and toxoplasmosis PCR and/or IgM for seronegative women (optional)
Last trimester – check IgM to HSV for seronegative women

Abbreviations: CBC, complete blood count; PCR, polymerase chain reaction; CMV cytomegalovirus, BP, blood pressure; CNI, calcineurin inhibitor; UA, urinalysis; HSV, herpes simplex virus; MMF, mycophenolate mofetil

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