Learning Objectives:
At the conclusion of this knowledge-based activity, the pharmacist will be able to:

1. Define the recommended screening method(s) for diabetes and prediabetes in pregnancy, and apply these screening methods in practice.

2. Review and extrapolate information from the current treatment guidelines from the American College of Obstetricians and Gynecologists (ACOG), American Diabetes Association (ADA), American Thyroid Association (ATA), and Endocrine Society for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum for pregnant women with diabetes and thyroid disorders to guide their treatment of these patients in practice. Pharmacists and technicians will be able to identify measures in place to curb the opioid epidemic.

3. Design an appropriate and individualized treatment plan for a pregnant woman diagnosed with prediabetes, gestational diabetes mellitus, pregestational type 1 diabetes and type 2 diabetes, and thyroid disorders. Pharmacists will be able to apply opioid conversion factors to attain morphine milliequivalents from a prescription.

At the conclusion of this knowledge-based activity, the pharmacist and pharmacy technician will be able to:

1. Compare hyperglycemic agents in regard to efficacy, safety, and ease of use.

2. Identify the maternal-fetal risks associated with thyroid disorders in pregnancy.

Abstract
Objective/Goal: The purpose of this article is to review current screening methods, diagnostic testing, treatment guidelines and maternal-fetal risks associated with the two most common endocrine disorders in pregnancy – diabetes mellitus and thyroid dysfunction.

Summary: Endocrine disorders, such as diabetes mellitus and thyroid disease, are two of the most common comorbidities in pregnancy. The preexistence of these conditions, if controlled, poses minimal adverse risks for maternal-fetal outcomes. However, poorly controlled pre-existing conditions and newly diagnosed conditions, have been associated with adverse maternal-fetal outcomes. Additionally, the presence of thyroid antibodies increases
the risk of adverse pregnancy outcomes such as fetal loss, preterm delivery, perinatal mortality, and large-for-gestational age. The initial diagnosis of these conditions is often delayed by the overlap of normal physiologic changes associated with pregnancy and laboratory capabilities, including trimester-specific reference ranges for biochemical markers.

**Conclusion:** The recommendations in this article for screening, diagnostic methods, and management are in accordance with the ACOG, ADA, ATA, Endocrine Society for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum, and United States Preventive Services Task Force (USPSTF). The screening for gestational diabetes mellitus (GDM) in asymptomatic pregnant women should occur after 24 weeks gestational age. The two-step screening process is the most commonly used screening tool. The diagnosis of GDM is characterized by two or more abnormal 3-hour oral glucose tolerance tests (OGTT). The decision to incorporate pharmacotherapy is individualized; however, all plans should incorporate diet and physical activity. There is no recommendation for universal screening of thyroid dysfunction. Testing should be conducted in those with a personal history of thyroid disease or symptoms of thyroid disease. Thyroid stimulating hormone (TSH) and thyroxine (T4) are the diagnostic tests utilized to diagnose thyroid disease. Pharmacotherapeutic options are determined by the disease process and trimester of pregnancy.

**Keywords:** prediabetes, gestational diabetes mellitus, pregestational type 1 diabetes mellitus, pregestational type 2 diabetes mellitus, hypothyroidism, hyperthyroidism, pregnancy, levothyroxine, and thionamide.

**Introduction**

Endocrine disorders in pregnancy present a unique challenge to the clinician. In many instances, the clinical presentation of a pregnant patient with an endocrine disorder may be difficult to distinguish from normal pregnancy changes. The hypermetabolic state of pregnancy alters the function of most endocrine glands due to placental hormone production and an enhanced protein-binding state. At 10 weeks gestation, the placenta is able to produce large amounts of estrogen and progesterone to help sustain a pregnancy. Placental production of progesterone worsens insulin resistance and leads to increased insulin requirements. Insulin requirements may also be increased due to placental secretion of insulin antagonists, such as insulinase and cortisol. Pregnancy is also associated with changes in thyroid hormone metabolism. Within seven weeks gestational age, circulating thyroxine-binding globulin and total thyroxine concentrations are increased; and, peak by approximately 16 weeks gestational age. The increase in renal iodine excretion, thyroxine-binding proteins, thyroid hormone production, and thyroid stimulatory effects of human chorionic gonadotropin (hCG) contribute to altered thyroid function test values in the pregnant woman. The pituitary gland naturally increases in size and function during pregnancy resulting in a 10-fold increase of maternal plasma prolactin levels. Increased prolactin levels are associated with an increase in thyrotropin-releasing hormone production and lactation. In addition, enhanced pituitary production of melanocyte-stimulating hormone causes hyperpigmentation in late pregnancy. Hormonal changes play in an integral role in fertility, pregnancy, delivery, and breastfeeding. Early recognition of endocrine dysfunction and appropriate management is pivotal in achieving favorable perinatal outcomes. The purpose of this article is to review current screening, diagnostic, and treatment recommendations for common endocrine disorders in pregnancy.

**Diabetes Mellitus in Pregnancy**

In 2017, the Centers for Disease Control and Prevention (CDC) reported more than 100 million Americans were diagnosed with diabetes or prediabetes. As the incidence of diabetes increases, the prevalence of diabetes in pregnancy continues to rise. Gestational diabetes mellitus comprises the majority of diabetes cases in pregnancy. Its prevalence runs parallel to that of type 2 diabetes mellitus; although, it may vary according to demographics, screening, and diagnostic methods. Increased mean maternal age and weight (specifically obesity) have been reported as likely reasons for the increasing prevalence. More than 36% of adults in the United States (US) are obese. The normal physiological changes of pregnancy confer a state of insulin resistance. Placental secretion of diabetogenic hormones (growth hormone, corticotropin-releasing hormone, placental lactogen, insulinase, progesterone) and metabolic changes promote fetal development, while maintaining adequate maternal nutrition. Impaired glycemic control has been associated with adverse maternal-fetal outcomes, such as preeclampsia, hydramnios, macrosomia, fetal organomegaly, maternal and infant birth trauma, operative delivery, perinatal mortality, respiratory problems, and metabolic complications. Currently, there is no guideline or recommendation to define patients at increased risk of adverse perinatal outcomes. However, there is a positive correlation between adverse outcomes
and maternal fasting plasma glucose levels above 75 milligram/deciliter [mg/dL].

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is one of the most common medical complications of pregnancy. Gestational diabetes mellitus is prevalent in 1.1% to 25.5% of pregnancies in the US. A systematic review and meta-analysis of several randomized controlled trials associated management of GDM to fewer cases of preeclampsia, shoulder dystocia, and macrosomia. Early identification of glucose intolerance during pregnancy is pivotal to minimizing adverse maternal-fetal outcomes. Controversy exists regarding the definition of GDM and screening methods. The American College of Obstetricians and Gynecologists (ACOG) published a February 2018 Interim Update “to reflect a limited, focused change to clarify and provide additional information on the pharmacologic treatment” of GDM.

The United States Preventative Services Task Force (USPSTF) recommends screening all pregnant women after 24 weeks gestational age for GDM. Women who are overweight or obese, and have a diabetic risk factor should be screened for prediabetes or early GDM at the onset of prenatal care (Table 1). The two-step approach is the most commonly used screening method in the US. The first-step entails the administration of a 50 gram oral glucose solution followed by a glucose level venous sample at 1-hour. If the woman meets or exceeds the laboratory screening threshold, the women will undergo a 3-hour oral glucose tolerance test of a 100 gram solution (second-step). There is variance and subsequent debate regarding the screening threshold for the 1-hour glucose challenge. However, many facilities range from 130 milligram/deciliter (mg/dL) to 140mg/dL, with varied sensitivities and specificities.

Upon diagnosis of GDM, women should receive nutrition and exercise counseling. The American Diabetes Association (ADA) recommends counseling by a registered dietician, including a personalized meal plan based upon the woman’s body mass index. The ultimate goal of fetal well-being is largely based upon medical nutritional therapy’s success in achieving normoglycemia, preventing ketosis, and providing adequate weight gain based on maternal body mass index (BMI). Future recommendations will likely include a low-glycemic index, carbohydrate diet based upon the known benefits demonstrated in the non-pregnant population. Physical activity and exercise play a pivotal role in glucose control among women with GDM. Additional benefits include improved cardiac health, increased pain control during labor, decreased risk of preterm birth, and improved fetal neurodevelopment. The ADA recommends 20-30 minutes of moderate intensity exercise every day for women diagnosed with GDM, or deemed at risk of disease development.

The inability to adequately control glycemic levels by diet is indicative of pharmacologic intervention to minimize adverse maternal and fetal outcomes. Insulin remains the first-line pharmacologic therapy to maintain glycemic control during pregnancy since insulin does not cross the placental barrier, and optimal glucose levels can be achieved with intensive management. The recommended initial dose of insulin is 0.7-1.0 units/kilogram daily, and should incorporate both a short and long acting insulin, tailored to the patient’s needs. If the patient is unable or not willing to initiate insulin therapy, both metformin and glyburide are supported by randomized controlled trials. While both appear to be safe in pregnancy, both drugs cross the placental barrier. Metformin may be preferred as it offers the additional benefit of minimal neonatal and maternal hypoglycemic episodes compared to glyburide. Metformin is initiated at 500 milligrams (mg) by mouth at bedtime. The dose may be increased by 500 mg weekly to a maximum dosage regimen of 2550 mg daily (850 mg three times daily). The most common maternal side effect of metformin therapy is gastrointestinal discomfort (cramping, gas, diarrhea). These side effects can be minimized with slow dose titration, administration with food, and use of an extended release formulation. Renal function is monitored to ensure the woman’s ability to adequately eliminate the drug and current US package insert data has been changed from a serum creatinine discontinuation marker (≥1.4mg/dl) to a glomerular filtration rate of less than 30ml/min. Glyburide is an effective oral anti-diabetic agent and an alternative to metformin. It lacks teratogenic risks; however, a 2015 systematic review associated glyburide with an increased incidence of neonatal hypoglycemia and macrosomia compared to insulin or metformin. The initial therapy is recommended at 2.5-10 mg daily in divided doses, although some patients may require up to 20 mg to obtain glycemic control. If metformin or glyburide fail to maintain glycemic control, they may be combined with each other or insulin.

Counseling women to monitor fasting and postprandial values using an at-home glucose monitor is an important component to GDM management. The cost, education, and compliance required to appropriately maintain an insulin regimen can pose challenges for many women; and, may preclude it as a viable option for women with GDM. Women with a history of GDM are at increased risk for developing cardiovascular disease,
metabolic syndrome, and Type 2 Diabetes Mellitus (T2DM). The seven-fold increased risk associated with the progression to T2DM requires screening at six to 12 weeks postpartum to ensure fasting glucose levels are within normal levels. Additional screenings should be conducted every one to three years.

Pregestational diabetes mellitus Type I

Type 1 Diabetes Mellitus (T1DM) accounts for 5% to 10% of diagnosed diabetes cases in the US, and approximately 0.2% to 0.5% of all diabetes cases in pregnancies. Aggressive maternal-fetal management, advances in insulin therapy, and improvements in neonatal care have significantly contributed to a decrease in T1DM associated infertility rates, fetal and neonatal mortality. There is a positive correlation between glycemic control and perinatal outcomes. The changing hormone levels in pregnancy lead to fluctuations of insulin sensitivity and insulin requirements, thereby highlighting the importance of individualized plans and education.

The National Institute for Health and Clinical Excellence (NICE) recommends preconception counseling for all patients with diabetes. Early diabetic consultation and good glycemic control (before and throughout pregnancy) play an integral role in minimizing adverse maternal and fetal outcomes. Clinicians may also offer or identify a structured education program for pregestational diabetes mellitus type 1 (PDM 1) to address diabetes education and self-management strategies.

Nutrition therapy for the management of diabetes is not a one-size-fits-all. The ADA emphasizes the importance of a knowledgeable health care team to provide diabetes nutrition therapy and support. The guideline recommends a referral for any newly diagnosed diabetic patient or individual seeking self-management strategies to a Registered Dietician for nutrition therapy. Emphasis is placed upon carbohydrate counting and bedtime snacks to aid in the prevention of nocturnal hypoglycemia and glycemic control (Table 2).

The hemoglobin A1c (A1C) target in a pregnant woman is 6-6.5%; however, the optimal target is less than 6% if achievable without significant hypoglycemia. The A1C levels are monitored monthly or until glycemic control is achieved.

Feldman et al. recommend “women with T1DM should begin a basal-bolus regimen preconception, if they are not already on one with either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) therapy with a goal of achieving target fasting and pre-meal blood glucose and reducing peak postprandial glucose.” There have been no studies to demonstrate superiority of CSII versus MDI in pregnancy.

A variety of insulins are thought to be safe in pregnancy as long as proper dosing is provided to maintain tight control with limited hypoglycemic excursions. Basal insulins include intermediate-acting NPH and the long-acting insulin analogs - glargine, detemir, and degludec. Prandial insulins include short-acting regular insulin and rapid-acting insulin analogs - aspart and lispro. Pollex et al. conducted a systematic review and meta-analysis to compare the safety of insulin glargine to NPH during pregnancy. There were no adverse outcomes associated with glargine use in pregnancy; however, long term effects are unknown. Mathieson et al. conducted the first randomized, controlled clinical trial evaluating maternal efficacy and safety outcomes of insulin detemir and NPH in pregnant women with T1DM. Study authors concluded detemir was noninferior to NPH when used as a basal insulin in a basal-bolus regimen for pregnant women with T1DM. Most noteworthy, was the potential clinical benefit of detemir in regard to fasting blood glucose control. Detemir achieved lower fasting blood glucose levels with no increased incidence of hypoglycemic events, including nocturnal hypoglycemia.

Detemir and NPH are rated as a pregnancy category B by the US Food and Drug Administration (US FDA). The prandial insulins are also considered safe and are rated as pregnancy category B. Degludec is rated as pregnancy category C and glargine has no human pregnancy data to reference safety in pregnancy. On June 30, 2015, the US FDA transitioned from using pregnancy categories to the Pregnancy and Lactation Labeling Rule in an effort to support health care providers in determining risks, benefits, and counseling of pregnant women and nursing mothers. The implementation will be phased over three to five years; thereby, prompting the need to conduct individualized risk assessments. Table 3 depicts the onset, peak, duration of action, and pregnancy category for the insulin discussed above.

Education regarding the most common complication of PDM 1, hypoglycemia, must be reinforced to patients and family members throughout the pre-/intra-/postpartum periods. Patients with PDM 1 have an increased risk of hypoglycemia in the first trimester and immediately postpartum. A rapid decline in insulin resistance at delivery of the placenta may significantly decrease insulin requirements. Patient education encompasses prevention, recognition, and treatment of hypoglycemia. Prevention focuses heavily on the recognition of symptoms and understanding the disease process. The increased risk of hypoglycemic
events during pregnancy for women with PDM 1 highlights the importance of glucose monitoring, and its role in the prevention and treatment of hypoglycemia. Self-monitoring of blood glucose is a fundamental component of glycemic control and health outcomes. The participatory role of self-monitoring is believed to improve the control of blood glucose levels and health outcomes, and has been shown to significantly decrease an individual’s A1C. Most importantly, healthcare providers may incorporate records of blood glucose levels to guide medical nutrition therapy and physical activity, prevent hypoglycemia, and medication adjustments. The identification of hypoglycemia via associated signs and symptoms or blood glucose monitoring will minimize treatment delay and subsequent complications for the pregnant woman and fetus.

**Pregestational diabetes mellitus Type II**

Approximately 90% to 95% of adult diabetic cases are categorized as Type II diabetes mellitus (T2DM). It is characterized by hyperglycemia due to the progressive deterioration of insulin secretion, resistance to insulin, and inadequate suppression of glucagon production. The etiology of T2DM is a combination of genetic components and environmental factors, such as obesity. The management is further complicated with pregnancy. Women with T2DM prior to pregnancy is known as pregestational diabetes mellitus Type II (PDM II). PDM II affects eight percent of all pregnant women with diabetes. Treatment regimens include diet management, insulin administration, oral anti-diabetic agents, or a combination of all three. The pre-pregnancy regimen prescribed to this population remains effective to treat hyperglycemia during pregnancy while protecting the growth of the fetus and preventing teratogenicity. The following are recommended medications for the treatment of PDM II.

**Insulin**

If nonpharmacologic interventions (diet and physical activity) do not maintain glycemic control, insulin therapy is the recommended pharmacologic intervention. Insulin is advantageous because it does not cross the placenta and results in sustained glucose control when used as prescribed. The use of insulin is limited by the duration of action, which necessitates a strict schedule and, in some cases, more than one type of insulin. Insulin is classified as short acting and long acting and is prescribed based on the level of glucose control required by the PDM II pregnant woman. Short and rapid acting insulins are regular, lispro, and aspart. Intermediate and long acting insulins are isophane (NPH), detemir, glargine, and degludec. Table 3 depicts the onset, peak, duration of action, and pregnancy category for the insulin products discussed above.

**Oral anti-diabetic agents**

Oral anti-diabetic agents are utilized when glycemic control cannot be achieved through diet management and/or a combination of insulin. There are many advantages of oral anti-diabetic agents that may increase compliance – easy to incorporate into a daily routine; provide an alternative to individuals with needle phobias; do not require refrigeration; cost effective; and, a simplified dosing regimen compared to insulin therapy. Limited research evaluating the safety and efficacy of oral anti-diabetic agents in pregnant women yields three treatment options for T1DM – metformin and acarbose (pregnancy category B) and glyburide (pregnancy category C).

Metformin is a second generation biguanide that reduces insulin resistance by increasing insulin sensitivity. Additionally, it reduces hepatic glucose production, hepatic glycogenolysis, and decrease intestinal glucose absorption. The dosing range of metformin begins at 500 mg once daily, but can range up to 2550 mg per day with an expected decrease in A1C of 1-2 %. Although metformin crosses the placenta, it is rated a pregnancy category B drug that is not associated with fetal anomalies. In many instances, metformin is the first line oral anti-diabetic agent used when diet management and insulin use are not effective.

Glyburide is a second-generation sulfonylurea that stimulates the secretion of insulin from the pancreatic beta cells, and is beneficial in PDM II patients because it crosses the placenta in minimal amounts and is highly protein bond. The dosing of glyburide ranges from 2.5 mg to a maximum of 20 mg per day. Glyburide can reduce A1C by 1-2%. About 10% of women tolerate the side effects of glyburide, which include hypoglycemia and weight gain. The disadvantage of using acarbose is mild to moderate gastrointestinal effects. The side effects can be mitigated by instructing the patient to take with the first bite of each meal (breakfast, lunch, and dinner) and gradually increasing the dosage at four to eight week intervals.

The management of PDM II prior to and throughout pregnancy plays a critical role in the prevention of maternal and fetal complications. As
mentioned previously, the first line management of diabetes in pregnant women is the incorporation of medical nutritional therapy and physical activity. If nonpharmacologic interventions alone are not effective, the use of insulin and oral anti-diabetic agents may be required. The goal is to maintain glycemic control in the pregnant diabetic patient.

**Thyroid Disease**

Thyroid disease is the second most common endocrine disorder in women of childbearing age. In the absence of diagnosis and treatment during pregnancy, a woman may be at an increased risk of miscarriage, placenta abruption, hypertensive disorders in pregnancy and fetal growth restrictions. A guideline update was published regarding routine screening and subclinical hypothyroidism based upon current, consistent scientific evidence.

The physiological requirements of the thyroid hormone may increase by 20-40% within the fourth week of pregnancy. The cross-reactivity of the alpha subunit of hCG with the thyroid-stimulating hormone (TSH) receptor results in lower TSH reference ranges during pregnancy. Fluctuating levels of serum-binding protein can affect free thyroxine (FT4) values that rely on estimates rather than direct measurements, resulting in inaccurate reported values. It is imperative for clinicians to be knowledgeable of laboratory capabilities for thyroid assays. Table 4 indicates trimester-specific reference ranges for common thyroid tests.

There is insufficient evidence to recommend universal screening for thyroid disorders, however, screening is recommended for “high-risk” women planning pregnancy. Table 5 identifies the recommended screening criteria for any woman over the age of 30.

**Hypothyroidism**

Hypothyroidism may be classified as overt or subclinical. Overt hypothyroidism is characterized by elevated TSH and low FT4 levels, whereas subclinical hypothyroidism is a mild form of hypothyroidism defined by an elevated TSH and normal FT4 levels. Overt hypothyroidism occurs in 0.3-0.5% of women screened. It is associated with an increased risk of preclampsia and gestational hypertension, placenta abruption, preterm delivery and low birth weight, increased rate of cesarean section, postpartum hemorrhage, and perinatal morbidity and mortality. Subclinical hypothyroidism is more common; prevalent in approximately 2-2.5% of women screened in the US. The indications, treatment, and outcomes of pregnant women with overt hypothyroidism is clear. However, there is debate regarding treatment versus no treatment of subclinical hypothyroidism, and associated outcomes. Maraka et al. demonstrated a relationship between treatment of subclinical hypothyroidism and a lower risk of pregnancy loss; specifically noting a lower risk among women with TSH values 4.1 to 10 mU/L (pre-treatment). In several other studies, women with subclinical hypothyroidism were reported to be at increased risk for severe pre eclampsia, preterm delivery, placental abruption, and/or pregnancy loss compared with eutrophic women. The increased risk for women with subclinical hypothyroidism highlights the importance of antibody status. Women with subclinical hypothyroidism and positive anti-thyroid peroxidase antibodies are at greater risk of adverse pregnancy outcomes, such as spontaneous miscarriage and preterm birth.

Treatment is consistent with recommendations by the American Thyroid Association (ATA) and the Endocrine Society for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum.2,3,5 Levothyroxine (LT4), a synthetic form of thyroxine, is the recommended treatment for hypothyroidism. The conversion of LT4 to the active thyroid hormone, triiodothyronine (T3), facilitates normal metabolism, growth and development. The goal of LT4 therapy in pregnancy is to restore eutrophism in a timely manner and decrease the risk for adverse perinatal outcomes. Recommended dosing is based upon TSH levels, using assay method and trimester-specific reference ranges (Figure 1). Pregnant women with a TSH greater than 4 mU/L, with low FT4 (overt hypothyroidism) should receive close to the full replacement dose - approximately 1.6 micrograms/kilogram (mcg/kg) body weight per day. A TSH greater than 4mU/L, with normal FT4 (subclinical hypothyroidism) should receive approximately 1 mcg/kg per day. A pregnant woman with a TSH 2.6 to 4 milliunits/Liter (mu/L) requires additional diagnostic testing for the presence of thyroid peroxidase (TPO) antibodies, consideration of prior history of spontaneous abortion(s), and patient preferences. If the decision was made to treat, the recommendation is to begin with 50 mcg daily.

The increased demand for LT4 during pregnancy and associated complications reinforces the criticality of preconception counseling among women with preexisting hypothyroidism. “Serum TSH should be evaluated preconception, and LT4 dose adjusted to achieve a TSH value between the lower reference limit and 2.5 mU/L.” Abalovich et al. concluded approximately 50-85% of women with preexisting hypothyroidism require an increased dose of levothyroxine during pregnancy.
Instruct women with preexisting hypothyroidism with a suspected or confirmed pregnancy to urgently notify their health care provider for evaluation to mitigate risk of early prenatal loss. The ATA recommend women who manage their preexisting hypothyroidism with LT4 to increase their dose of LT4 by ~20%-30%, if pregnancy is confirmed by a home pregnancy test. Most importantly, these women should urgently notify their health care provider for further evaluation. Another approach is to measure serum TSH levels upon pregnancy confirmation and a repeat serum TSH in four weeks. The physiological changes of pregnancy may cause a variation of TSH requirements from 10% to 80%. It is recommended to obtain serum TSH levels four weeks after any change in the dose of T4, and at least once each trimester.

Hyperthyroidism

Hyperthyroidism is rare in pregnancy, occurring in 0.1% to 0.4% of pregnancies. Very often, the condition does not present for the first time until pregnancy. Additionally, the signs and symptoms of hyperthyroidism often overlap with symptoms in normal pregnancy – tachycardia, palpitations, systolic murmur, bowel disturbance, emotional upset, and heat intolerance. The presence of a goiter in conjunction with common signs of thyroid disease (weight loss, eye signs, tremor or pretibial myxedema) are indicative of hyperthyroidism.

The diagnosis of hyperthyroidism in a pregnant woman is aligned with that of a nonpregnant man or women. Treatment is a two-prong approach – (1) decrease thyroid hormone synthesis and (2) control symptoms. The goal is to maintain TSH at 0.1 to 0.3 mU/L (mild hypothyroidism) with the lowest possible dose of medication. Maternal serum free thyroxine (FT4) concentration should be maintained at the trimester-specific normal range for pregnancy. The maternal total thyroxine (TT4) and triiodothyronine (T3) should be maintained at 1.5 times above the nonpregnant reference range. Trimester-specific reference ranges for common thyroid tests is available in Table 4. The ATA and ACOG recommend monitoring thyroid function every four weeks for the review and adjustment of medication.

Treatment is indicated for women with symptomatic, moderate-to-severe, and overt hyperthyroidism. Grave’s disease, toxic adenoma, toxic multinodular goiter and gestational trophoblastic disease are all likely causes of thyroid level fluctuations in pregnant women. These diseases may result in TSH values below 0.05 mU/L as well as elevations in trimester specific FT4 and/or T3 and T4 concentrations, that exceed 1.5 times the upper limit of normal in nonpregnant women. Treatment is not required if the maternal hyperthyroidism is mild, such as cases of transient, subclinical hyperthyroidism; hCG-mediated, overt hyperthyroidism; hyperemesis gravidarum-associated hyperthyroidism; and, subclinical hyperthyroidism.

Therapeutic options are limited due to the potential of adverse fetal effects. The primary treatment of hyperthyroidism is thionamides (Table 8). Thionamides impede the synthesis of the thyroid hormones, T3 and T4. Selection is dependent upon the trimester the drug is being initiated. Propylthiouracil (PTU) is preferred during the first trimester of pregnancy due to embryopathy during organogenesis associated with methimazole. Methimazole (MMI) is preferred during the second and third trimesters due to hepatotoxicity associated with PTU. The highest risk of congenital anomalies is associated with thionamide exposure between six and 10 weeks gestational age. Reports have associated methimazole exposure to choanal and esophageal atresia, scalp defects, minor facial anomalies, and psychomotor delays. Additionally, reports of severe hepatic failure, liver transplantation and death raised concerns regarding utilization of PTU beyond the first trimester and during lactation. Further review of thionamides during lactation prompted a recommendation of moderate use; specifically, recommending PTU as a second-line therapy (no more than 300 mg/day) due to severe hepatotoxicity concerns. Severe cases of hyperthyroidism may require the full initial dose of PTU, 100 mg three times per day, or methimazole, 5 to 30 mg daily.

Beta blockers may be prescribed to control symptoms, such as tachycardia and tremor. Several clinical trials have associated maternal use of beta blockers with fetal growth restriction, hypoglycemia, respiratory depression, and bradycardia. Atenolol prescribed greater than two to six weeks was specifically noted to be a concern. Clinicians are encouraged to begin weaning the patient from the beta blocker as soon as the hyperthyroidism is controlled (Table 6).

A preexisting history of hyperthyroidism prior to pregnancy prompts a discussion regarding treatment options. Women may elect to undergo surgical intervention, radioiodine therapy, switch from MMI to PTU before trying to conceive, or switch to PTU upon a confirmed pregnancy test. If the woman has been treated with methimazole for 1 to 1.5 years, has a normal TSH level on low-dose therapy, and is thyrotropin receptor antibody (TRAb) negative, she may choose to discontinue MMI with careful monthly monitoring of
thyroid function tests. The risk of hepatotoxicity and identification as third on a list of drugs leading to liver transplantation prompted the ATA Advisory Committee to limit PTU use to the first trimester of pregnancy. This does not apply to patients with a MMI allergy or with thyroid storm. Currently, routine monitoring of hepatic enzymes during PTU-administration is not recommended due to the rare occurrence of liver dysfunction associated with anti-thyroid therapy.2,41

Discussion

Early recognition and treatment of endocrine dysfunction improves perinatal outcomes. Successful disease management for most preexisting endocrine disorders has posed little impact on maternal-fetal morbidity. The increased risk of adverse pregnancy outcomes associated with fetoplacental transfer of maternal antibodies has also been demonstrated among women undergoing in vitro fertilization, during pregnancy and postpartum. Clinical and technological advancement in the treatment of endocrine disorders has played a significant role in fertility.

Conclusion

Diabetes mellitus and thyroid dysfunction are two of the most common endocrine disorders in pregnancy. Other endocrine disorders, such as pituitary dysfunction and adrenal and parathyroid disease are far less common or associated with infertility and rarely occur. This review of pregnancy-related changes, pathogenesis, and current recommendations for disease management are essential to antenatal recognition and treatment.

References


Tables, Graphs, and Illustrations

Table 1. Screening for diabetes and prediabetes.

<table>
<thead>
<tr>
<th>Screen early in pregnancy if patient is overweight with body mass index (BMI) of 25 (23 in Asian Americans, and one of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical inactivity</td>
</tr>
<tr>
<td>First-degree relative with diabetes</td>
</tr>
<tr>
<td>High-risk race or ethnicity, i.e. African American, Latino, Native American, Asian American, Pacific Islander.</td>
</tr>
<tr>
<td>Previously gave birth to an infant weighing 4,000 grams or more</td>
</tr>
<tr>
<td>Diagnosed with hypertension</td>
</tr>
<tr>
<td>High-density lipoprotein &lt; 35 mg/dL; Triglycerides &gt; 250 mg/dL</td>
</tr>
<tr>
<td>Polycystic ovarian syndrome</td>
</tr>
<tr>
<td>HgbA1C &gt; 5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing.</td>
</tr>
<tr>
<td>Other clinical conditions associated with insulin resistance.</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
</tr>
</tbody>
</table>

Table 2. Glycemic targets in pregnancy.

| Fasting < 95 mg/dL and either | One-hour postprandial < 140 mg/dL OR Two-hours postprandial < 120 mg/dL |
Table 3. Insulin Pharmacodynamics and Pregnancy Categories.\textsuperscript{22}

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspart</td>
<td>10-15 minutes</td>
<td>40-50 minutes</td>
<td>3-5 hours</td>
<td>B</td>
</tr>
<tr>
<td>Lispro</td>
<td>10-15 minutes</td>
<td>30-90 minutes</td>
<td>3-5 hours</td>
<td>B</td>
</tr>
<tr>
<td>Regular U-100</td>
<td>30 minutes</td>
<td>3 hours</td>
<td>8 hours</td>
<td>B</td>
</tr>
<tr>
<td>Regular U-500</td>
<td>30 minutes</td>
<td>3 hours</td>
<td>Up to 24 hours</td>
<td>B</td>
</tr>
<tr>
<td>Isophane (NPH)</td>
<td>1-2 hours</td>
<td>4-8 hours</td>
<td>10-20 hours</td>
<td>B</td>
</tr>
<tr>
<td>Detemir</td>
<td>1-2 hours</td>
<td>none</td>
<td>24 hours</td>
<td>B</td>
</tr>
<tr>
<td>Glargine</td>
<td>1-2 hours</td>
<td>none</td>
<td>24 hours</td>
<td>No human pregnancy data</td>
</tr>
<tr>
<td>Degludec</td>
<td>1 hour</td>
<td>none</td>
<td>42 hours (at steady state)</td>
<td>C</td>
</tr>
</tbody>
</table>

Table 4. Trimester-specific reference ranges for common thyroid tests.\textsuperscript{31}

<table>
<thead>
<tr>
<th>Test</th>
<th>Nonpregnant</th>
<th>First Trimester</th>
<th>Second Trimester</th>
<th>Third Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid-stimulating hormone</td>
<td>0.3 to 4.3</td>
<td>0.1 to 2.5</td>
<td>0.2 to 3.0</td>
<td>0.3 to 3.0</td>
</tr>
<tr>
<td>Thyroxine-binding globulin</td>
<td>1.3 to 3.0</td>
<td>1.8 to 3.2</td>
<td>2.8 to 4.0</td>
<td>2.6 to 4.2</td>
</tr>
<tr>
<td>Thyroxine, free</td>
<td>0.8 to 1.7</td>
<td>0.8 to 1.2</td>
<td>0.6 to 1.0</td>
<td>0.5 to 0.8</td>
</tr>
<tr>
<td>Thyroxine, total</td>
<td>5.4 to 11.7</td>
<td>6.5 to 10.1</td>
<td>7.5 to 10.3</td>
<td>6.3 to 9.7</td>
</tr>
<tr>
<td>Triiodothyronine</td>
<td>2.4 to 4.2</td>
<td>4.1 to 4.4</td>
<td>4.0 to 4.2</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Table 5. High risk factors for thyroid screening in pregnancy.\textsuperscript{2}

Any woman > 30 years old, with:

- A family history or autoimmune thyroid disease or hypothyroidism
- With goiter
- With known thyroid antibodies
- With Type 1 diabetes mellitus
- With fertility
- With a prior history of preterm delivery
- With prior therapeutic head or neck irradiation or prior thyroid surgery
- Currently receiving levothyroxine replacement
### Table 6. Management of hyperthyroidism.\(^{36,37}\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Dosage</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thionamides</td>
<td>Decrease thyroid hormone</td>
<td>Initial: Propylthiouracil (PTU) 5 to 10 mg daily&lt;br&gt;Methimazole 5 to 10 mg daily</td>
<td>Risk of fetal abnormalities associated with methimazole.</td>
</tr>
<tr>
<td></td>
<td>synthesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>Control of symptoms</td>
<td>Initial: Metoprolol 25 to 50 mg daily&lt;br&gt;Alternate: Propranolol 20 mg every six to eight hours</td>
<td>Adverse fetal effects; recommend weaning as soon as hyperthyroidism is controlled.</td>
</tr>
</tbody>
</table>
Management of Diabetes in Pregnancy.10,11,15

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Recommendation</th>
<th>Professional Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Diabetes Mellitus</td>
<td>Screen asymptomatic pregnant women after 24 weeks of gestation.</td>
<td>ACOG, USPSTF</td>
</tr>
<tr>
<td></td>
<td>Lifestyle management - Nutrition therapy, physical exercise, weight management (depending upon pregestational weight), and glucose monitoring (aiming for recommended targets).</td>
<td>American Diabetes Association</td>
</tr>
<tr>
<td></td>
<td>If unable to maintain glycemic control, pharmacology therapy is recommended.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin is the first-line agent recommended for the treatment of GDM.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral anti-diabetic agents - (metformin, glyburide).</td>
<td></td>
</tr>
<tr>
<td>Pregestational diabetes mellitus, Types 1 and 2</td>
<td>Insulin is the preferred agent; does not cross the placenta.</td>
<td>American Diabetes Association</td>
</tr>
<tr>
<td></td>
<td>Oral anti-diabetic agents are generally ineffective.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prescribe low-dose aspirin 60-150 mg/day from end of 1st trimester to delivery to lower risk of preeclampsia.</td>
<td></td>
</tr>
</tbody>
</table>
Endocrine Disease in Pregnancy: Current Recommendations
Corresponding Course Program Number: 0171-9999-19-019-H01-P & T

1. Complete and mail entire page. SCPHA members can take journal CE for free; $15 for non-members. Check must accompany test. You may also complete the test and submit payment online at www.scrx.org.
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3. Continuing Education statements of credit will be issued within six weeks from the date of the quiz, evaluation form and payment are received. Notification will be sent via email if you have not successfully completed the quiz. Participants scoring 70% or greater and completing the program evaluation form will be issued CE credit. Participants receiving a failing grade on any examination will have the examination returned. The participant will be permitted to retake the examination one time at no extra charge.

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2. Overall evaluation of the article? (Poor) 1 2 3 4 5 (Excellent)
3. Was the information relevant to your practice? (No) 1 2 3 4 5 (Yes)

4. How long did it take you to read the article and complete the exam? ________________

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SELF-ASSESSMENT QUESTIONS

1. The recommended “two-step” approach to GDM screening involves the administration of ___ oral glucose solution followed by a venous glucose sample after ___ hour(s). If the measured blood glucose level meets or exceeds the laboratory threshold, the test is repeated. ___ of oral glucose solution is administered followed by a venous glucose sample after ___ hours.
   a. 100 grams, 1 hour; 200 grams, 2 hours
   b. 100 grams, 2 hours; 50 grams, 1 hour
   c. 50 grams, 3 hours; 100 grams, 1 hour
   d. 50 grams, 1 hour; 100 grams, 3 hours

2. The current ATA Guidelines provide which of the following recommendations regarding levothyroxine use in pregnant women?
   a. Levothyroxine should be discontinued upon laboratory confirmation of pregnancy due to congenital anomalies.
   b. Dosing of levothyroxine is based upon TSG levels using assay method and trimester-specific reference ranges.
   c. Levothyroxine should be dose at 1.6 mcg/kg in pregnant women diagnosed with subclinical hypothyroidism and at 1 mcg/kg in pregnant women diagnosed with overt hypothyroidism.
   d. Doses of levothyroxine may need to be decreased in pregnancy by 20-50% to mitigate the risk of early miscarriage.
3. Which of the following is true regarding the recommended therapeutic regimen for pregnant women diagnosed with overt hyperthyroidism?
   a. PTU is preferred to MMI throughout pregnancy due to lessened congenital abnormalities.
   b. PTU should be utilized only during the first trimester due to hepatotoxicity. MMI should be initiated in the second trimester and continue throughout pregnancy.
   c. MMI may be continued throughout pregnancy, if the patient meets specific preconception criteria and is monitored monthly.
   d. The therapeutic goal of PTU and MMI is to maintain maternal euthyroidism in an effort to mitigate fetal risk.

4. The most appropriate initial approach to treatment for a woman at risk for pregestational diabetes is:
   a. initiation of pharmacist-recommended dietary changes, an exercise regimen and education regarding carbohydrate counting.
   b. initiation of continuous subcutaneous insulin infusion therapy, as it is preferred over multiple daily injection insulin therapy.
   c. preconception counseling, including education for self-management as well as excellent glycemic control with an established pharmacotherapeutic regimen.
   d. Based on a recent meta-analysis, the patient's current regimen should be discontinued and insulins (detemir and aspart) should be initiated.

5. A patient calls the pharmacy regarding her levothyroxine medication. She informs you that she has just confirmed that she is pregnant by using a home pregnancy test. Her doctor has instructed her to increase her dose of levothyroxine by 30% independently until she can be seen to have labs drawn. Due to this increase in dose, the patient is worried that she may run out of her medication early, and her insurance will not cover an early refill of the medication. What is the primary reason that this increase in dose is medically necessary?
   a. Levothyroxine must be increased throughout pregnancy due to an increase in maternal blood volume.
   b. Levothyroxine must be increased in early pregnancy to decrease the risk of miscarriage.
   c. Levothyroxine must be increased in early pregnancy so that the fetus does not experience thyroid storm.
   d. Levothyroxine must be adjusted in early pregnancy, but the patient needs to have labs drawn by her prescriber first.

6. The goal of pharmacotherapeutic treatment of hyperthyroidism in pregnancy is:
   a. to target maternal TSH levels within the range of 0.1-0.3 mU/L by utilizing the lowest possible dose of medication.
   b. to maintain maternal euthyroidism in order to prevent fetal hypothyroidism.
   c. to maintain maternal euthyroidism in order to reduce the risk of maternal hepatotoxicity.
   d. to maintain maternal hyperthyroidism in order to prevent fetal hepatotoxicity.

7. Which of the following pharmacologic interventions specifically recommended for the management of PDM II requires an auxiliary label to “take with food”?
   a. Actos
   b. Canagliflozin
   c. Saxagliptin
   d. Acarbose

8. Which of the following is true regarding oral anti-diabetic agents?
   a. Metformin is the only oral anti-diabetic that causes gastrointestinal side effects.
   b. All oral anti-diabetic medications used to treat GDM, PDM I and PDM II are prescribed three times daily.
   c. Metformin, an oral anti-diabetic, is often preferred because it is associated with fewer neonatal and maternal hypoglycemic events than glyburide.
   d. Metformin produces a more significant decrease in maternal A1C than glyburide.