SECONDARY FORMS OF DIABETES

Ildiko Lingvay, MD, MPS, MSCS Office: U9.134, Phone: 214-648-2779
Email: Ildiko.Lingvay@utsouthwestern.edu

LEARNING OBJECTIVES:

- Recognize the frequency of secondary forms of diabetes
- List pharmacological agents that are most commonly associated with hyperglycemia
- Identify the common features of Maturity Onset Diabetes of the Young
- Recognize the challenges related to treatment of Cystic Fibrosis Related Diabetes
- Identify the consequences and list treatment of gestational diabetes

Diabetes Mellitus is a heterogeneous disorder characterized by an elevated glucose level. While type 1 and type 2 diabetes are the most common forms, there are many other conditions that cause or predispose to diabetes. The table below summarizes the current classification of diabetes, illustrating the multitude of conditions or situations that are associated with elevations in glucose level.

This lecture will review in more detail Maturity Onset Diabetes of the Young (MODY), Cystic Fibrosis Related Diabetes (CFRD), drug-induced hyperglycemia, and Gestational Diabetes Mellitus (GDM).

1. Type 1 Diabetes Mellitus (beta-cell destruction leading to absolute insulin deficiency)
    A. Autoimmune (autoantibodies present)
    B. Idiopathic (same phenotype as 1A but absence of autoantibodies)
2. Type 2 Diabetes Mellitus (characterized by both insulin resistance and beta-cell dysfunction, contributions of each can be variable)
3. Other Specific Types of Diabetes
    A. Genetic defects of beta-cell function
        i. All MODYs
        ii. Mitochondrial DNA
        iii. Others
    B. Genetic defects in insulin action
        i. Type A insulin resistance
        ii. Leprechaunism
        iii. Rabson-Mendenhall syndrome
        iv. Lipoatophic diabetes
        v. Others
    C. Diseases of exocrine pancreas
        i. Pancreatitis (acute and chronic)
        ii. Trauma and pancreatectomy
        iii. Pancreatic cancer
        iv. Cystic fibrosis
        v. Hemochromatosis
        vi. Fibrocalculous pancreatopathy (tropical diabetes)
        vii. Others

D. Endocrinopathies
    i. Acromegaly
    ii. Cushing's syndrome
    iii. Glucagonoma
    iv. Pheochromocytoma
    v. Hyperthyroidism
    vi. Somatostatinoma
    vii. Aldosteronoma
    viii. Others
E. Drug or chemical induced (see separate table in section below)
F. Infections (congenital rubella, cytomegalovirus, etc)
G. Rare immune-mediated diabetes
    i. "Stiff man" syndrome
    ii. Anti-insulin receptor antibodies
    iii. Others
H. Other genetic syndromes sometimes associated with diabetes
    i. Down's syndrome
    ii. Klinefelter's syndrome
    iii. Turner's syndrome
    iv. Wolfram's syndrome
    v. Freiderich's ataxia
    vi. Huntington's chorea
    vii. Laurence-Moon-Biedl syndrome
    viii. Myotonic dystrophy
    ix. Porphyria
    x. Pater-Willi syndrome
    xi. Others

4. Gestational Diabetes Mellitus

Table 1: Classification of diabetes, showing the many other forms of diabetes besides type 1 and type 2. Adapted from American Diabetes Association (Diabetes Care, Vol 30, Supplement 1, 2007). Highlighted conditions are further detailed in this lecture.

Maturity-Onset Diabetes of the Young (MODY)

MODY describes a collection of monogenic diabetes disorders that are inherited in an autosomal dominant fashion. These disorders are characterized by nonketotic diabetes mellitus, onset before age 25, and a primary defect in ß-cell function. They also lack the antibodies usually associated with type 1 diabetes. To date 13 such genetic diseases have been reported (See Table), and the list continues to grow.

Most other MODY genes encode transcription factors that control pancreatic development and regulate the expression of genes such as insulin or those encoding proteins involved in glucose transport and metabolism and mitochondrial metabolism. As a whole, MODY accounts for as much as 5% of diabetes in populations of European descent. Clinically, the presentation of MODY shares features of both type 1 and type 2 diabetes, and unfortunately it is misclassified in as much as 80% of cases. As in type 1 diabetes, MODY patients present at a young age and are usually neither obese nor insulin resistant, but as in type 2 diabetes, MODY patients may be adequately controlled, at least early on, with oral antidiabetes drugs and are not prone to ketosis. All MODY patients thus far have a defect in glucose-stimulated release of insulin from the beta cell.

MODY 2 is one of the most common forms of MODY and results from mutations in glucokinase, which supports the key role of this enzyme as a glucose sensor in ß-cells. The phenotype is that of mild, stable elevation in fasting glucose. It is important to recognize as this form of diabetes seldom needs any treatment due to lack of progression or associated complications.

MODY 3 is the second most common form of MODY, occurring most frequently in the European population (it is the first most common MODY type in Europe). It results from mutation in the HNF1alpha gene which encodes the transcription factor HNF1alpha. The clinical presentation of MODY 3 and 1 (due to HNF4alpha mutation) are very similar, both presenting with loss of insulin secretory capacity that is slowly progressive. Most patients, at least in the early stages of the disease, respond very well to sulfonylureas, but some eventually need insulin as insulin secretion declines over time. Patients with MODY 3 also have a lower threshold for renal glucose excretion and commonly have glucosuria, a feature not present in MODY 1.

Important:

Correctly identifying a patient with MODY can have important consequences:

- Patients with MODY 1 & 3 are readily responsive to treatment sulfonylureas (SU), yet if not correctly identified are most commonly treated with insulin.
- Diagnosis of certain MODYs can lead to investigations that identify other associated abnormalities (for example MODY 5 can be associated with renal cysts and genitourinary abnormalities).
- Appropriate genetic counselling can occur to help assess risk of transmission to offsprings.

	Affected Gene	**Affected Chromosome**	**Frequency Amongst MODYs**	**Clinical Features**
MODY 1	HNF4α	20q13	5-10%	Intrauterine and neonatal hyperinsulinemia; low TG; SU responsive (at least early on).
MODY 2	GCK	7p13	30-50%	Mild fasting hyperglycemia since birth. Generally no need for treatment.
MODY 3	HNF1α	12q24	30-50%	Renal glucosuria. SU responsive.
MODY 4	IPF1	13q12	≈1%	Trial of SU warranted.
MODY 5	HNF1β	17q12	≈5%	Cystic renal disease, genitourinary abnormalities, pancreatic atrophy, exocrine dysfunction. Insulin requiring.
MODY 6	Neuro-D1	2q31	Very rare	Obesity might facilitate diabetes in mutation carriers.
MODY 7	KLF11	2p25	Very rare	Phenotype similar to type 2 diabetes.
MODY 8	CEL	9q34	Very rare	Associated with exocrine pancreatic deficiency and lipid-soluble vitamin deficiency (i.e. vitamin E).
MODY 9	PAX4	7q32	Very rare	
MODY 10	INS	11p15.5	Very rare	Phenotype heterogeneous among mutation carriers.
MODY 11	BLK	8p23	Very rare	"Diabetogenic" in the setting of obesity and other risk factors.
MODY 12	ABCC8	11p15	Very rare	Phenotype similar to MODY 1& 3
MODY 13	KCNJ11	11p15	Very rare	So far only one mutation identified.

Table 2: The 13 types of MODYs identified to date. SU – sulfonylurea, TG - triglyceride

Cystic Fibrosis Related Diabetes

Cystic fibrosis-related diabetes (CFRD) is a distinct type of diabetes mellitus associated with the genetic condition Cystic Fibrosis (CF). CFRD shares features of both type 1 and type 2 diabetes as there is both insulin deficiency caused by pancreatic islet cell destruction and insulin resistance which is multifactorial in causation.

CFRD is the most common non-pulmonary comorbidity of CF, occurring in approximately 20% of adolescents and 40-50% of adults. The increase in prevalence is thought to be multifactorial and has to do with increased awareness, improvements in screening practices, and longer lifespans of CF patients.

The development of CFRD appears to be related to several risk factors: increased age, female gender, exocrine pancreatic insufficiency, severe CF genotype, lung function, poor nutritional status, and liver disease. For example, the δ F508 homozygous CF genotype is known to be associated with pancreatic insufficiency in nearly all CF patients and patients with this genotype have a higher prevalence of CFRD as compared to compound heterozygotes and other genotype groups. The prevalence of CFRD is also higher in patients with more severe pulmonary disease, worse pulmonary function measured by FEV_1 percent, more pulmonary exacerbations treated with antibiotics and glucocorticoids, and higher prevalence of *Pseudomonas aeruginosa, Burkhdderia cepacia, Stenotrophomonas maltophilia, Candida, and Aspergillus.*

Although CFRD shares features of both type 1 and type 2 diabetes, there are distinct differences which place this clinical entity in a separate category. The table below highlights some of these differences.

	CFRD	Type 1 diabetes	Type 2 diabetes
Prevalence in population	35% of CF patients	0.2% of general population	11% of general population
Peak age of onset	20–24 years	Childhood, adolescence	Mid to late adulthood
Usual body habitus	Normal to underweight	Normal	Obese
Insulin deficiency	Severe but not complete	Complete	Partial, variable
Insulin resistance	Usually modest, waxes and wanes with infection	Usually modest	Severe
Autoimmune etiology	No	Yes	No
Ketones	Rare	Yes	Rare
Hemoglobin A1C	Unpredictable relation to mean blood glucose	Related to mean blood glucose	Related to mean blood glucose
Usual treatment	Insulin	Insulin	Oral agents, insulin
Microvascular complications	Yes	Yes	Yes
Macrovascular complications	No	Yes	Yes
Metabolic syndrome features	No	No	Yes
Cause of death	Lung disease	Cardiovascular	Cardiovascular

Table 3: CFRD compared with type 1 and type 2 diabetes

Although the hallmark feature of CFRD is a reduction in beta cell mass due to islet cell destruction leading to insulin deficiency, the etiology of CFRD is intricate and the mechanisms leading to the development of CFRD have not been fully elucidated at present. It is believed that pancreatic damage arises from changes in the composition of pancreatic secretions secondary to the mutation in the cystic fibrosis transmembrane regulator (CFTR) protein with resulting thick, viscous secretions blocking the pancreatic ducts, causing interstitial edema, impairing blood flow, and thus leading to both pancreatic endocrine and exocrine damage. The initial stage of insulin deficiency is later followed by a component of insulin resistance thought to be related to increased counter-regulatory hormones and inflammatory cytokines during acute CF exacerbations as well as the use of exogenous glucocorticoids and other immunosuppressant therapies used to treat certain pulmonary infections and following lung transplantation.

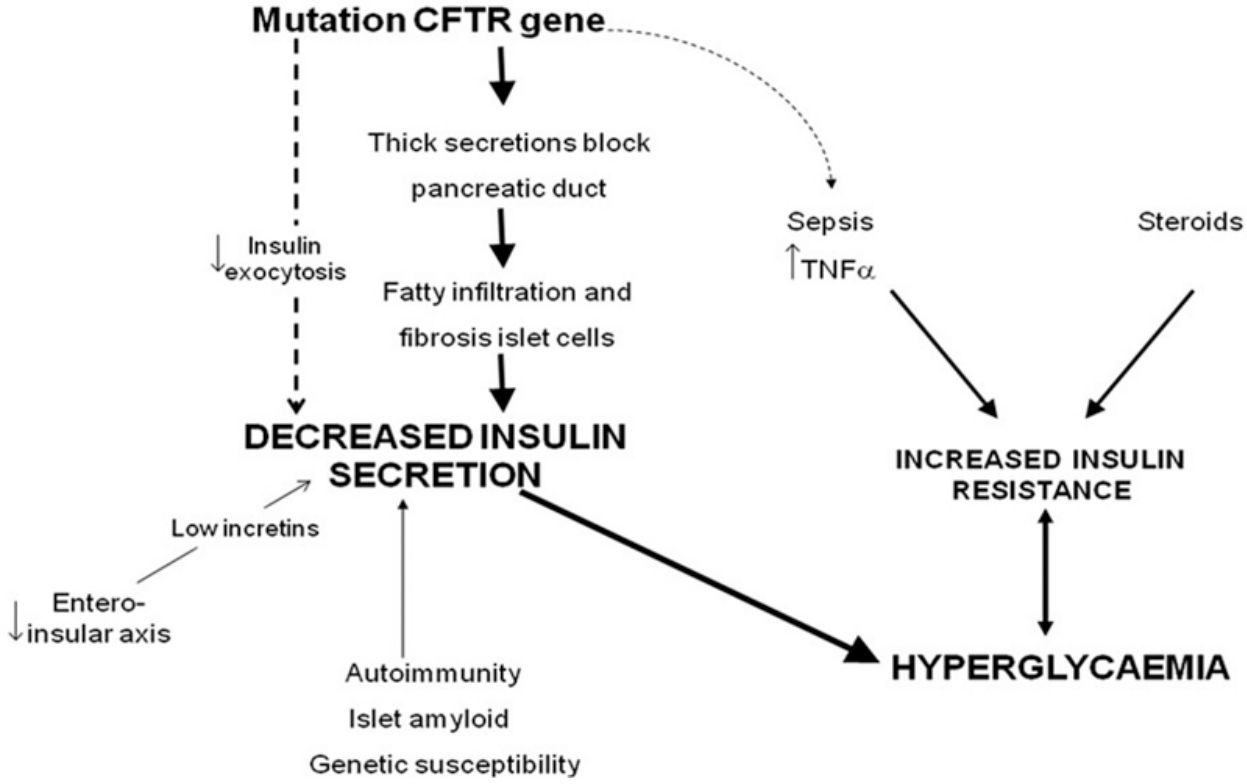

Figure 1: Pathophysiology of CFRD. From: https://www.thieme-connect.de/media/srccm/201502/10-1055-s-0035-1547319-i01108-2.jpg

There are several complications of CFRD that may directly impact morbidity and/or mortality. Microvascular complications including diabetic polyneuropathy, nephropathy, and retinopathy can occur just like in other forms of diabetes, and are related to the duration of CFRD and the overall glycemic control. On the other hand, CFRD patients appear to be immune to macrovascular complications as there are no reports yet of death from atherosclerotic cardiovascular disease. Most important though is the impact of diabetes on survival in CF as patients with CFRD, particularly females, have a significantly higher mortality rate (greater than six fold) than patients with CF without diabetes. The presence of CFRD (both insulin deficiency and hyperglycemia) negatively impact CF pulmonary disease.

CFRD is frequently clinically silent, therefore annual screening for CFRD is recommended by age 10 years in all CF patients. The current gold standard for screening in this population is the 2

hour 75 gram oral glucose tolerance test (OGTT). Other screening tests (like Hemoglobin A1c, fructosamine, urine glucose, and random glucose) have been shown to have low sensitivity and poor predictive ability in detecting diabetes in the CF population.

Patients with CFRD should preferably be managed by a specialized multidisciplinary team with expertise in diabetes and CF. The mainstay of therapy is insulin as it has been shown to improve not only glucose levels, but its anabolic effect is also beneficial for the nutritional and metabolic derangements associated with CF.

Blood glucose goals, Hemoglobin A1c goals, and screening for both microvascular and macrovascular complications for CFRD patients are the same as for all patients with diabetes. However, nutritional goals and guidelines for CFRD patients are very different as adequate caloric intake to maintain BMI is critical to their health and survival.

	Type 1 & Type 2 Diabetes	**CFRD**
Calories	Calculated for maintenance, growth, or reduction diets	120-150% RDA Calories never restricted
Carbohydrate	Individualized	Total intake unrestricted
Fat	Individualized <10% calorie intake from saturated fats Dietary cholesterol intake <300 mg/d	High fat intake (35-40% of total calories)
Protein	Protein reduction in presence of diabetic nephropathy (0.8 g/kg)	Protein reduction may not be appropriate
Sodium	Salt restriction to reduce macrovascular complications (<2,400 mg/d)	High sodium diet essential (>4,000 mg/d)

Table 4: Comparison between nutrition recommendations of Type1 & Type 2 Diabetes and CFRD.

Drug Induced Diabetes

Several pharmacologic agents can induce or contribute to hyperglycemia, especially in patients with preexistent risk factors. The table below illustrates the classes and specific agents that have been implicated, along with the mechanism of action. In clinical practice the most commonly encountered situation is the hyperglycemia due to the use of systemic glucocorticoids, followed by that of certain antipsychotics, both of which can have a significant effect on glycemia, especially in patients at high risk of diabetes or who already have pre-diabetes.

Steroid drugs (i.e. prednisone) can induce a form of iatrogenic Cushing's syndrome. One study estimated that glucocorticoid-induced hyperglycemia occurs in 32% and overt diabetes in 18% of patients treated with this class of medication. These numbers are even higher (>50%) in the inpatient setting, when high doses of steroids are used. Administration of steroid by other routes (inhaled, topic, intra-articular) carries a much lower risk compared with oral administration.

The association between anti-psychotic agents and diabetes is complex as patients with schizophrenia have a 2-3 fold elevated risk of diabetes compared with the general population, likely due lifestyle factors but also family history. The addition of anti-psychotic drugs is associated with a further increase in the risk of diabetes, and carries with it an unexplained feature: diabetic ketoacidosis is a relatively common occurrence despite the general phenotype resembling that of type 2 diabetes. While weight gain is common with these drugs, this in itself does not provide sufficient explanation for the development of diabetes. The full mechanistic explanation is still being investigated.

It is important to assess the risk of hyperglycemia in patients whom agents known to increase the risk of diabetes are initiated, and to monitor periodically their glycemic status. If hyperglycemia occurs it is preferable – if possible - to stop the offending agent, or at least substitute with another agent with less/no effect on glycemia. If hyperglycemia persists, close monitoring and treatment should be initiated.

It is noteworthy that several cardiovascular agents commonly used in patients with high cardiovascular risk, metabolic syndrome, and diabetes (beta-blockers, niacin, statins, thiazide diuretics) can potentially increase glucose levels. The overall effect of these agents on glycemia is relatively small, and in general it is considered that their benefit in lowering cardiovascular morbidity outweighs the risk in this situation.

Table 5: Drugs associated with increased glucose levels or overt diabetes. Bolded agents/classes are most commonly associated with hyperglycemia. Adapted from UpToDate graphic 67257 version 9.0.

Class	**Drug**	**Mechanism**
Anti-infectives		
Fluoroquinolones	**Gatifloxacin**, moxiflocacin	↓insulin secretion
HIV antiretrovirals	Protease inhibitors Nucleaoside reverse transcriptase inhibitors (NRTIs)	↑peripheral insulin resistance
Other	Pentamidine	Initial hypoglycemia, followed by beta-cell destruction
Antipsychotics		
1st generation	**Chlorpromazine**, perphenaxine	↑peripheral insulin resistance & ↓insulin secretion
2nd generation	**Clozapine**, iloperidone, **olanzapine**, paliperidone, quetiapine, risperidone	↑peripheral insulin resistance & ↓insulin secretion
Cardiovascular		
Beta-blockers	Atenolol, metoprolol, propranolol	↑peripheral insulin resistance
Lipid lowering	**Niacin**	Altered hepatic glucose metabolism
	Statin	Risk very low
Thiazide diuretics	Hydrochlorothiazide, chlorthalidone, chlorthiazide, indapamide	↑peripheral insulin resistance & ↓insulin secretion
Vasodilators	Diazoxide	↑peripheral insulin resistance & ↓insulin secretion & ↑hepatic glucose production
Vasopressors	**Epinephrine**, norepinephrine	↑ glycogenolysis, ↑ hepatic glucose production, ↑ glucagon and cortisol & ↓insulin secretion
Gonadotropin-releasing hormone agonists	When used in men for androgen deprivation therapy for metastatic prostate cancer	
Glucocorticoids, systemic	Class effect	↑peripheral insulin resistance & ↑hepatic glucose production & ↑ expression of PPAR-gamma
Sex hormones		
	Progesterone/progestin containing oral contraceptives Megestrol acetate	↑peripheral insulin resistance & ↑hepatic glucose production
Growth hormones	Somatotropin, tesamorelin	↑ counter-regulatory responses
Immunosuppressants	Cyclosporine, sirolimus, tacrolimus	↓insulin secretion & release

Gestational Diabetes Mellitus

The normal physiology of pregnancy includes insulin resistance that develops as pregnancy progresses. This is thought to result from rising levels of specific hormones, cytokines, and metabolites, such as human placental lactogen, glucocorticoids, progesterone, tumor necrosis factor alpha, and free fatty acids. In response to increasing insulin resistance, β-cell compensation by the pregnant woman allows her to maintain normal fasting and postprandial glucose levels. However, if there this inadequate β-cell compensation, for example in a woman who has risk factors for future type 2 DM, then she may develop gestational diabetes mellitus (GDM), which is defined as glucose intolerance that is first diagnosed in pregnancy.

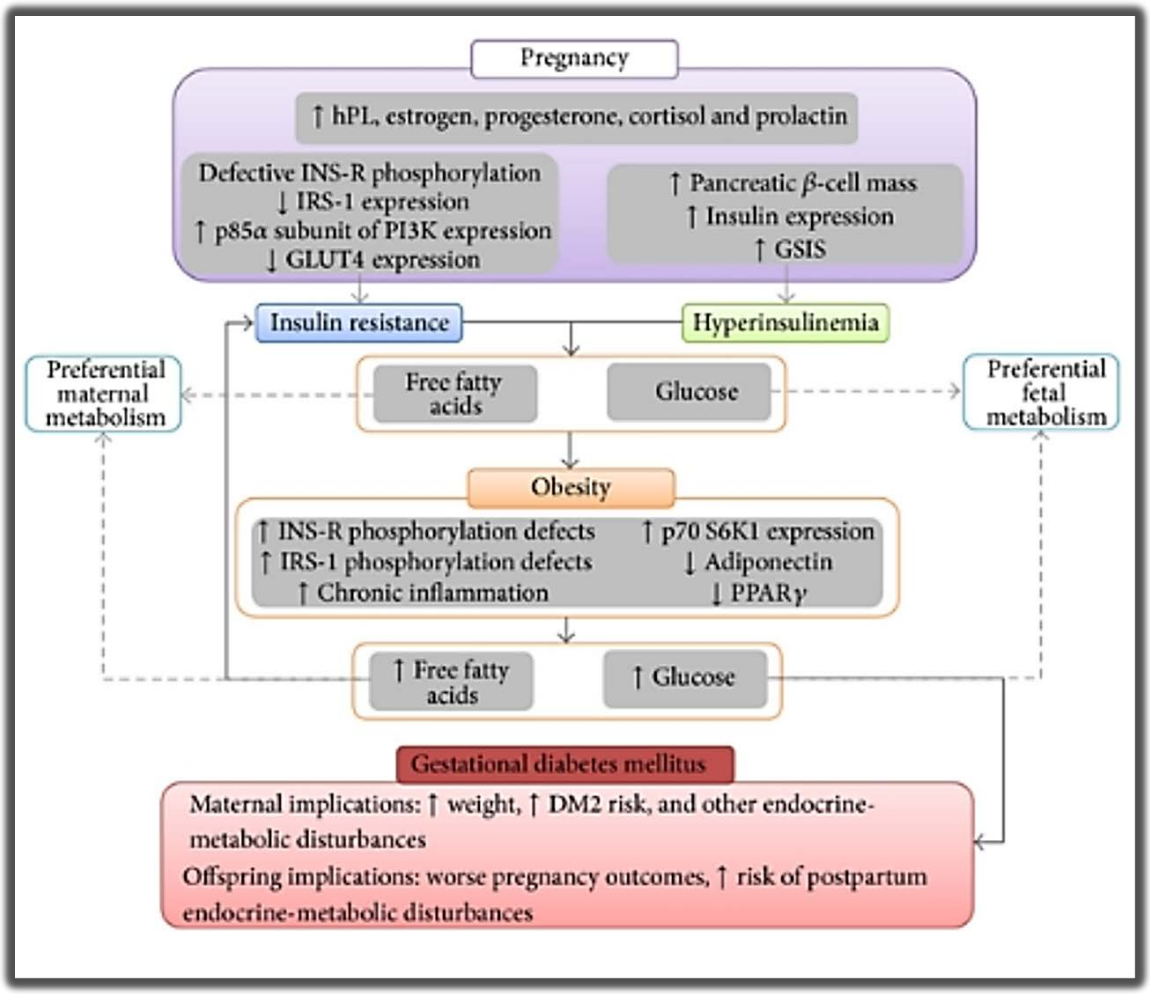

Figure 2: The pathophysiology and consequences of gestational diabetes. GSIS: glucose-stimulated insulin secretion; hPL: human placental lactogen; INS-R: insulin receptor; IRS-1: insulin receptor substrate-1; PPARγ: peroxisome proliferator-activated receptor γ

Women with GDM have increased risk for pregnancy related complications, including preeclampsia, polyhydramnios, asymptomatic bacteria and infections of the urinary tract. Also, there is increased risk to the fetus for stillbirth, macrosomia (birth weight >4000 grams), neonatal hypoglycemia, and other complications.

Current practice is for pregnant women not previously known to have diabetes to be screened for GDM with a two-step protocol between 24 and 28 weeks of gestation. First, a 50-gram glucose challenge test is administered. If the blood glucose at 1 hour post-challenge is ≥140 mg/dl, then a 100-gram oral glucose tolerance test (OGTT) is conducted over 3 hours.

The screening practices and cut-off values used for the diagnosis of GDM are not uniform and many different practices and guidelines are currently in use. Using the protocol described above, it is estimated that up to 6% of pregnancy are affected by GDM. The incidence is higher in high risk ethnicities (African American, Hispanic, native American, pacific islander and south Asian women) and has increased in the past 2 decades in line with the increase in maternal age and the obesity epidemic.

The first line treatment of GDM is a program of medical nutrition therapy and exercise. The goal of treatment is to normalize glucose levels as close as possible to those of pregnant women without diabetes. Each society has a different guideline regarding glucose goals, below is an example most commonly followed by our group. Of note, postprandial glucose levels are closely followed in patients with GDM, having been associated with maternal and fetal complications. On the other hand, HbA1c is not a commonly used measure, primarily as its half-life is too long to be helpful in GDM, but also because it tends to be lower in pregnant women.

Plasma glucose	**Fifth International Workshop-Conference on GDM**
Fasting	≤95 mg/dL (5.3 mmol/L)
1-hr postprandial	≤140 mg/dL (7.8 mmol/L)
2-hr postprandial	≤120 mg/dL (6.7 mmol/L)

If lifestyle modifications are not sufficient to achieve these glucose targets, insulin therapy is generally speaking the most favored second line therapy. Insulin is used because it is fast acting, easily titratable, and has the longest safety data. Treatment with metformin or glyburide, two oral antidiabetes drugs, is less common but may be considered; however, both glyburide and metformin cross the placenta, and long-term safety data are not available.

Immediately after delivery, many women revert to normal glucose tolerance; they nonetheless remain at risk of progressing to type 2 DM. Thus, gestational diabetes reveals a predisposition to type 2 DM; risk of progression to type 2 DM is correlated with the relative impairment of insulin secretion. Women with a history of GDM who still have impaired glucose tolerance on an oral glucose tolerance test performed 6-12 weeks postpartum are more likely to progress to type 2 DM than are those who have a normal postpartum OGT.

Note: for women who already have diabetes prepregnancy, it is important for glycemia to be well-controlled at the time of conception in order to minimize risk for congenital anomalies and spontaneous abortion. This means that pregnancies of women with diabetes mellitus must be planned, so that glucose control can be optimized prior to conception. Hyperglycemia at the time of conception and during the first trimester can lead to major fetal malformations, as opposed to hyperglycemia due to GDM which occurs later during pregnancy which is most commonly associated with fetal macrosomia.

Practice Questions:

1. Gestational Diabetes is often diagnosed in the first trimester of pregnancy. TRUE/FALSE

2. The following is true about Maturity Onset Diabetes of the Youth (MODY):
    a. There are at least 13 distinct named MODYs
    b. Is characterized by a defect in insulin secretion
    c. Autosomal dominant transmission
    d. Up to 5-10% of all cases of diabetes are due to MODY
    e. All of the above are true

3. Cystic fibrosis related diabetes is:
    a. Most commonly treated with insulin
    b. A rare occurrence in patients with cystic fibrosis
    c. Characterized by significant insulin resistance
    d. Autosomal dominant

Answers
1. False
2. E
3. A