Diabetes Mellitus in Pregnancy

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October 2019

Objectives

- Define and classify DM in pregnancy
- Understand the pathophysiology, screening and diagnosis of GDM
- Describe the management of DM in pregnancy-

  essays written like this
  - Preconception
  - Antenatal
  - Intrapartum including newborn care
  - Postpartum including contraception and subsequent preconception care
- Briefly outline complications of DM in pregnancy and their management

Diabetes mellitus

- DM
  - Chronic metabolic condition characterized by absolute or relative insulin deficiency resulting in increased glucose concentration *etiology + outcome*
- *Type 1 :* characterized by absolute insulin deficiency
- Type 2: characterized by defective insulin secretion, insulin resistance, or increased glucose production

DM in pregnancy-classification

Pregestational diabetes	Gestational diabetes (GDM)
Pregnancy in pre-existing DM • Type 1 diabetes • Type 2 diabetes	DM diagnosed in pregnancy

- About 4.2 % of American women have DM in pregnancy
- **GDM**
  - Carbohydrate intolerance of varying severity with onset or first recognition during pregnancy. *From hx it maybe preexisting but dx at pregnancy*
  - Comprises 90% of pregnancies complicated by DM
  - Affects 1% to 14% of pregnancies
  - More than 50% of GDM result in Type 2 diabetes in 20 years

DM in pregnancy: White classification

Plasma Glucose Level				
Class	Onset	Fasting	2-Hour Postprandial	Therapy
A_1	Gestational	< 105 mg/dL	< 120 mg/dL	Diet
A_2	Gestational	> 105 mg/dL	> 120 mg/dL	Insulin
Class	Age of Onset (yr)	Duration (yr)	Vascular Disease	Therapy
B	Over 20	< 10	None	Insulin
C	10 to 19	10 to 19	None	Insulin
D	Before 10	> 20	Benign retinopathy	Insulin
F	Any	Any	Nephropathy[a]	Insulin
R	Any	Any	Proliferative retinopathy	Insulin
H	Any	Any	Heart	Insulin

[a]When diagnosed during pregnancy: proteinuria ≥ 500 mg/24 hr before 20 weeks' gestation.

DM in pregnancy-proposed classification

1. **Gestational**: diabetes diagnosed during pregnancy that is not clearly overt (type 1 or type 2) diabetes
2. **Type 1 : Diabetes resulting from β-cell destruction, usually leading to absolute insulin deficiency**
    1. Without vascular complications
    2. With vascular complications (specify which), *which one specify*
3. **Type 2: Diabetes from inadequate insulin secretion in the face of increased insulin resistance**
    1. Without vascular complications
    2. With vascular complications (specify which)
4. **Other types** : genetic in origin, associated with pancreatic disease, drug-induced, or chemically induced

American Diabetes Association

GDM-Pathophysiology

Glucose Metabolism

- Normal pregnancy is a "diabetogenic state" because of the progressive increase in postprandial glucose levels and associated increased insulin response in late gestation.
- *As pregnancy progresses increase on glucose levels*
- However in early gestation- *pts who are pregdm follow them*
  - anabolic state characterized by the increase in maternal fat stores and decrease in free fatty acid (FFA) concentration
  - decreases in maternal exogenous insulin requirements likely from
    - increased insulin sensitivity
    - decreased substrate availability secondary to factors such as nausea *and vomiting*
    - the fetus acting as a glucose sink - continuous fetal draw of glucose
    - enhanced maternal insulin secretion
    - increase in insulin clearance likely from insulinase
  - blood glucose levels are 10-20% lower

GDM-Pathophysiology

- **Glucose Metabolism**
  - Later in pregnancy, especially in third trimester
  - Decrease in maternal peripheral insulin sensitivity especially in women with decreased insulin sensitivity before conception (e.g. type 2 DM). Result from:
    - increased production of placental and maternal hormones e.g. hPL, progesterone, estrogen, cortisol, and prolactin
    - mediators of insulin resistance- eg tumor necrosis factor-α and leptin (both produced in the placenta) and resistin
  - 30% increase in maternal fasting hepatic glucose production with advancing gestation due to decrease in maternal hepatic glucose sensitivity

GDM- Pathophysiology

- **Lipid metabolism**
  - Insulin produces excessive fetal growth particularly in fat, the most insulin-sensitive tissue
  - Increased lipolysis (preferential use of fat for fuel, in order to preserve glucose and protein)
  - Increased serum triglyceride (300%) and cholesterol (50%) levels
  - Spares glucose for fetus, since lipids do not cross the placenta
  - Provides building blocks for increased steroid hormone synthesis
  - Birthweight is positively correlated with TG and FFA concentration in late pregnancy
- **Amino acid metabolism**
  - 15% increase in protein synthesis during the second trimester and a further 25% increase in the third trimester

GDM-screening and diagnosis

- Universal vs risk factor-based screening?
- Criteria for mass screening *relate to diabetes*

1. The condition sought should be a health problem for the individual and community.
2. There should be an accepted treatment or useful intervention for patients with the disease.
3. The natural history of the disease should be adequately understood.
4. There should be a latent or early symptomatic stage.
5. There should be a suitable and acceptable screening test or examination.
6. Facilities for diagnosis and treatment should be available.
7. There should be an agreed policy on whom to treat as patients.
8. Treatment started at an early stage should be of more benefit than treatment started later.
9. The cost should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a once and for all project.

GDM-screening and diagnosis

- **Universal screening** @ 24-28 weeks GA *for all*
- **Screen earlier if risk factors for GDM:** if not diagnosed repeat @ 24-28 weeks/with symptoms

Previous GDM, impaired glucose metabolism, or glucosuria	BMI ≥30 kg/m^2
Prediabetes	Polycystic ovarian syndrome
High risk population (e.g. Hispanic, South Asian, Asian, African, Arborigin)	Current fetal macrosomia or polyhydramnios *fundal height greater than GA*
Age ≥35 years	History of macrosomic infant
Family history of DM	
Corticosteroid use	Acanthosis nigricans

GDM-other risk factors

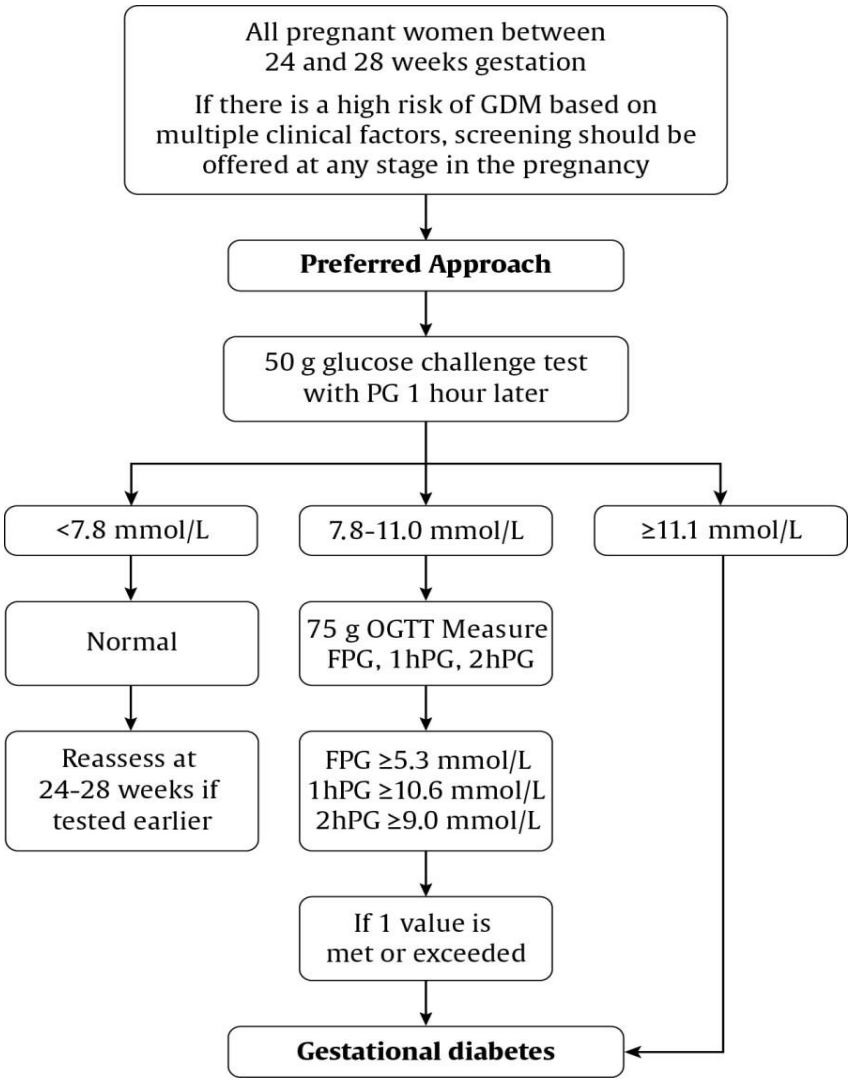
1. Recurrent fetal loss
2. Persistent glycosuria- ≥2+ on 1 occasion or ≥ 1+ on ≥ 2 occasions
3. Prior stillbirth, unexplained neonatal death, congenital malformations, prematurity.
4. History of pre-eclampsia or polyhydraminos
5. Chronic hypertension
6. Recurrent severe moniliasis or UTI -*candidiasis*
7. History of traumatic delivery with neurological disorder in the infant- *suspect macrosomia*

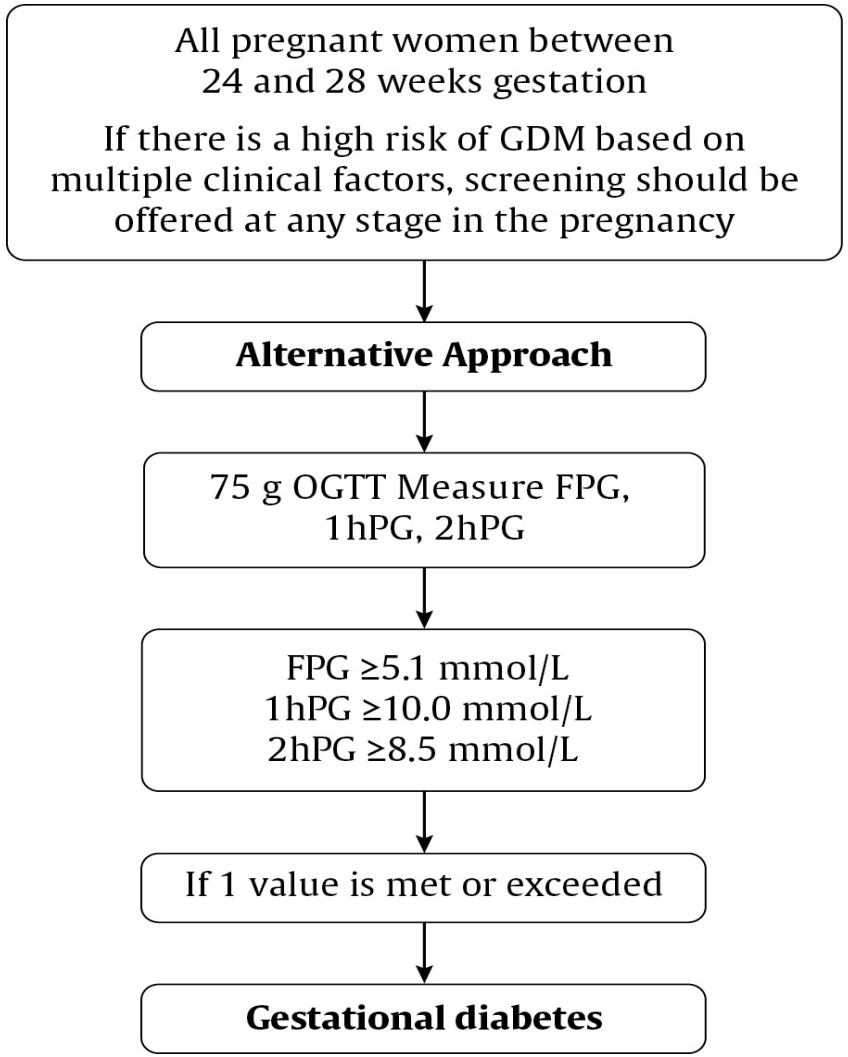
Forms basis for important +ves and –ves in Hx

Overt diabetes: diagnosis

Measure	Threshold
Fasting plasma glucose	≥7.0 mmol/L (126 mg/dL)- *stop doing other tests no need for other tests*
Hemoglobin A1c	≥ 6.5%
Random plasma glucose	≥11.1 mmol/L (200 mg/dL) plus Confirmation *Basically no need for multiple test just one is need for diagnosis… just know cut offs*

GDM Diagnosis: Two Approaches





- **Unrestricted diet and unlimited physical activity at least 3 days prior to the OGTT**
- **The patient should fast for 8 hours before the OGTT, no fasting before the GCT**

- *Preferred approach adv is that no requirement for fasting required… something osulivan????*
- *Alternative is gold standard but requires fasting and may be lost to follow up.*

Effect of DM on pregnancy

- **Pre-eclampsia:** 10-25% of all pregnant women with GDM
- **Infections:** chorioamnionitis and postpartum endometritis, wound infection, vaginal candidiasis, UTI – *due to low immunity so consequence is that higher dose of antibiotics*
- **PPH:** from uterine distension/polyhydramnios etc
- **Cesarean section and vaginal operative deliveries, birth injuries :** fetal macrosmia and CPD
- Weight gain
- Hypertension
- Miscarriages
- Long term risk of type-2 diabetes mellitus, metabolic syndrome and CVD

Effect of DM on pregnancy

- Perinatal Morbidity and Mortality
  - Fetal Death/Stillbirth
    - Due to chronic intrauterine hypoxia:
      - from altered oxygen release from RBC or altered uterine and placental blood flow
      - Fetal hyperinsulinemia increase fetal metabolic rate and oxygen requirement
      - Maternal hyperglycemia, ketoacidosis, preeclampsia, and vasculopathy, can also reduce placental blood flow and fetal oxygenation

Congenital Malformations

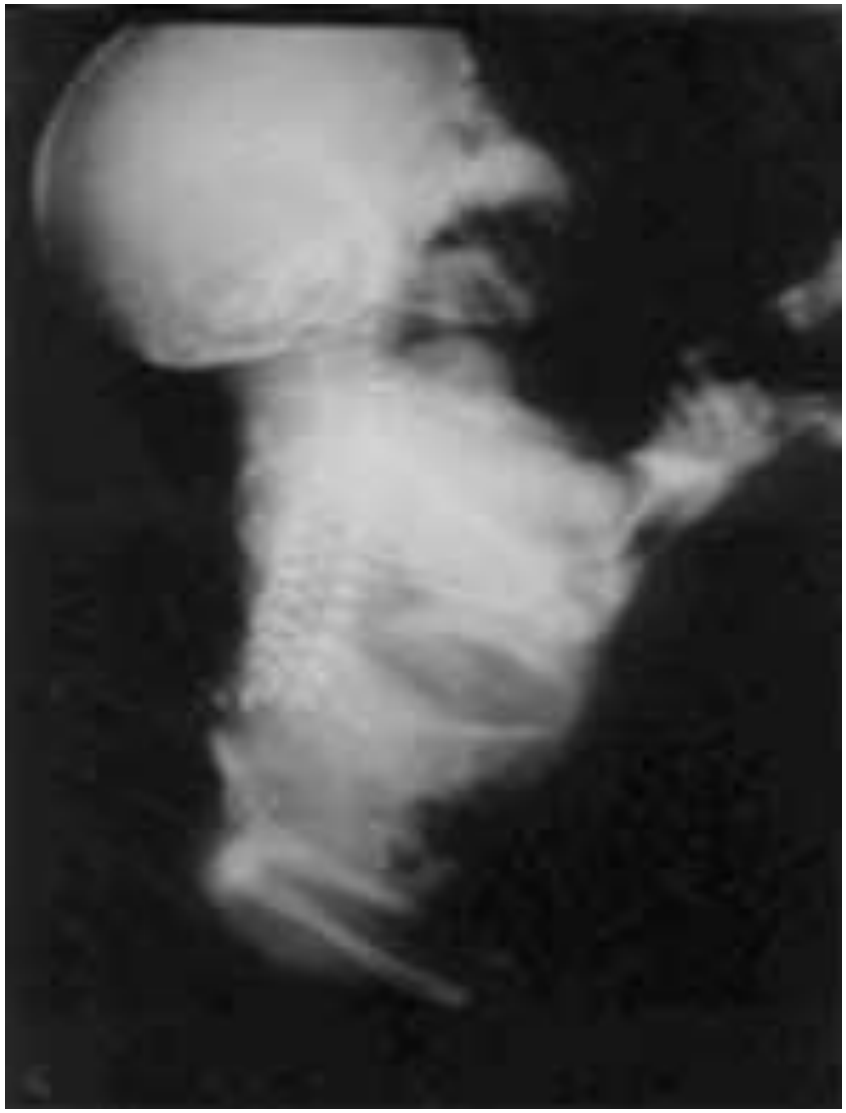
- Increased 6-10-fold
- Affects most organ systems and must act before week seven of gestation especially in type 1 DM
- Due to
  - Hyperglycemia
  - Ketone body excess
  - Somatomedin inhibition
  - Arachidonic acid deficiency
  - Free oxygen radical excess

Poor glycemic control at time of conception: risk factor

Congenital malformations

- Cardiac (most common): transposition of great vessels, Ventricular septal defect, Atrial septal defect
- Central nervous system
  - NTD-spina bifida, Anencephaly, hydrocephalus
  - sacral agenesis/caudal dysplasia-characteristic
- Genitourinary tract: ureteric duplication
- Gastrointestinal: anorectal atresia
- Renal agenesis, Duplex ureters, Cystic Kidney
- Situs inversus

Caudal regression syndrome
(abnormal development of lower spine)



Macrosomia

- Pedersen hypothesis
  - maternal hyperglycemia → fetal hyperglycemia → Increased fetal β-cell mass → hyperinsulinemia → excessive fetal growth
- GDM results in elevated lipids and amino acids which stimulates the fetal pancreatic β cells and placenta to release insulin and other growth factors hence excessive fetal growth
- Characterized by increased fat mass compared with fat-free mass.
- Disproportionate, larger chest-to-head and shoulder-to-head ratios compared with normoglycemic

Risk for shoulder dystocia

Two Extremes Of Growth Abnormalities

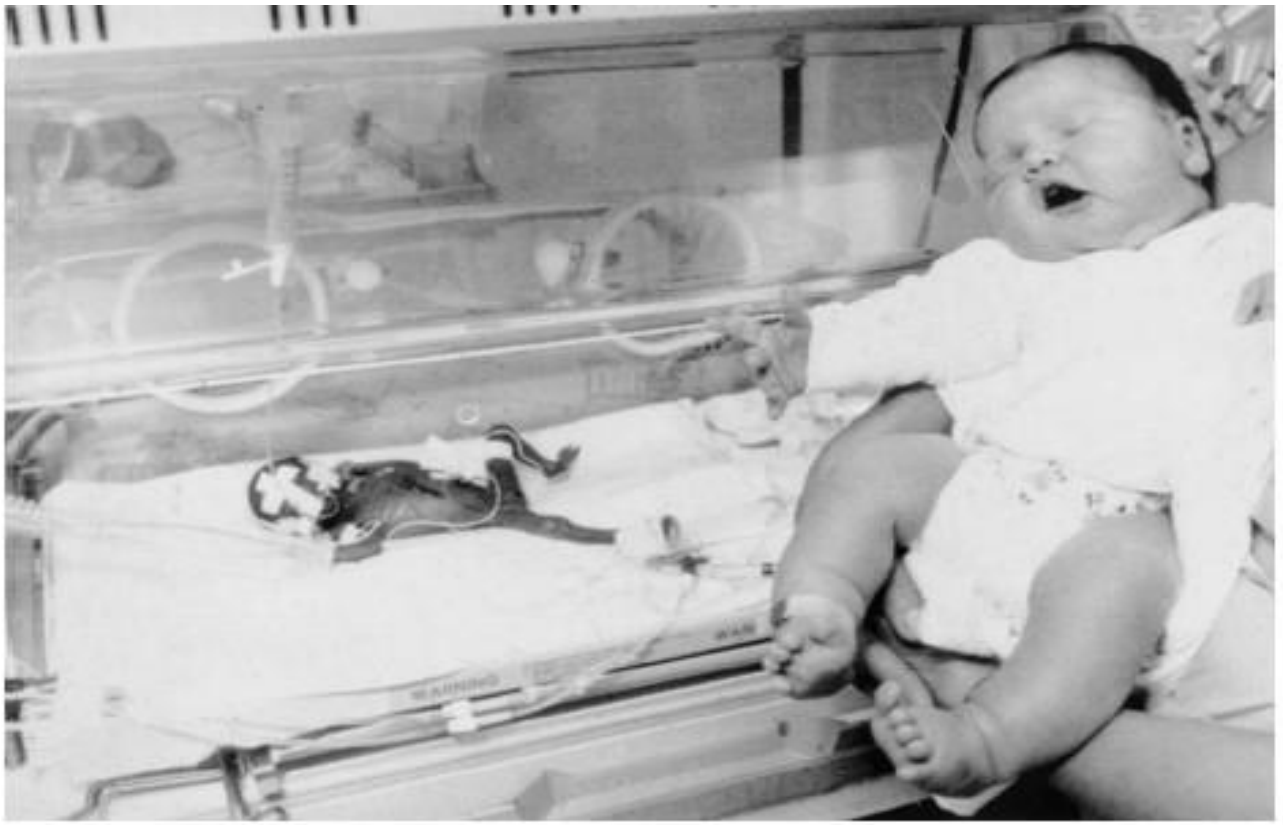


Figure 1. Two extremes of growth abnormalities seen in infants of diabetic mothers. The small growth-restricted infant or the left weighed 470 g and is the offspring of a woman with nephropathy, hypertension, and severe preeclampsia delivered at 28 weeks' gestation. The neonate on the right is the 5100-g baby of a woman with suboptimally controlled diabetes Reprinted from Landon MB, Catalano PM, Gabbe SG. Diabetes mellitus. In: Gabbe SG, Niebyl JR, Simpson JL, eds Obstetrics: Normal and problem pregnancies. Philadelphia: Churchill Livingstone, 2002:1099–100, with permission from Elsevier, Inc.

Gabbe. Diabetes Mellitus in Pregnancy. Obstet Gynecol 2003.

17 pound/ 7.7 KG baby born to Brazilian diabetic mother

MSNBC News Services
Jan. 24, 2005

Neonate

- Hypoglycemia
  - < 35 to 40 mg/dL in first 12 hours of life is a byproduct of hyperinsulinemia, in up to 50% of macrosomic newborns
- Respiratory Distress Syndrome
  - hyperglycemia and hyperinsulinemia
  - insulin blocks cortisol action at the level of the fibroblast by reducing the production of fibroblast-pneumocyte factor which acts on type II cells to stimulate phospholipid synthesis
- Others: Neonatal hypocalcemia *apparently due to hyperglycemia???*, hypomagnesia, hyperbilirubinemia, polycythemia, cardiomyopathy

Effects of pregnancy on diabetes

- More insulin required to achieve metabolic control- *common in 3rd trimester*
- Progression of maternal complications
  - Retinopathy: esp. severe proliferative retinopathy
  - Nephropathy: especially if renal failure
  - High risk of maternal death in post MI patients

- Increased risk of coronary artery disease

- Cardiomyopathy

Treatment Type 1 or Type 2 DM

- **Goal**: prevent adverse pregnancy outcomes
- Multidisciplinary approach
  - Diet therapy: 40% to 60% carbohydrate, 20% protein, and 30% to 40% fat with < 10% saturated fats, up to 10% polyunsaturated fatty acids, and the remainder from monosaturated sources
  - Medications
    - Insulin-stimulate physiologic insulin requirements by providing basal and prandial insulin 2-4 daily injections or continuous insulin infusion (pump therapy) (CSII)
    - Metformin
  - Self-blood glucose monitoring

Treatment Type 1 or Type 2 DM

- **Screen and manage complications**
  - Retinopathy: Ophthalmologist consult- fundoscopy to evaluate for diabetic retinopathy at baseline and each trimester or more frequently if retinopathy is detected.
  - Nephropathy: Baseline renal function from a 24-hour urine creatinine clearance and protein. Refer *to nephrologist* if creatinine ≥ 120 micromol/litre, the urinary albumin:creatinine ratio > 30 mg/mmol or estimated GFR < 45 ml/min/1.73 m2
  - TSH-thyroid dysfunction in type 1 DM is as high as 40%
  - Vasculopathy- EKG, Echocardiogram
  - Urine culture

Treatment Type 1 or Type 2 DM

- **Preconception care**
  - Need for preconception care, education and advice at initiation of and before discontinuing contraception
  - HbA1c below 48 mmol/mol (6.5%), if >86 mmol/mol (10%) avoid conception
  - Self-monitoring of blood glucose
  - Test for ketonaemia
  - Metformin can be an adjunct or alternative to insulin if benefits outweigh the potential for harm
  - Stop: other OHAs, ACE inhibitors and angiotensin-II receptor antagonists, Statins

  - *Use methyldopa or nifedipine add hydralazine if the other 2 don't work.*

Management: GDM

- Counseling-education/monitoring
- Self-monitoring of blood glucose and targets
- Diet
- Exercise
- Medicines
  - metformin if targets not met using diet and exercise within 1–2 weeks
  - Insulin instead of metformin if metformin is contraindicated or unacceptable
  - Add insulin to diet, exercise and metformin if targets not met
  - Immediate insulin, with or without metformin and diet and exercise, if **FPG ≥ 7.0 mmol/litre at diagnosis OR FPG 6.0- 6.9** and have complications eg macrosomia or polyhydramnios
  - Glibenclamide: if targets are not achieved with metformin, decline insulin therapy or cannot tolerate metformin. *Prolonged hypoglycemia is a consequence*

Antenatal care

- Other aspects of routine care must continue
- Follow up-one to two weekly
- Test fasting, pre-meal, 1&2-hour post-meal and bedtime blood glucose levels
- Adhere to target blood levels for GDM
  - fasting: 5.3 mmol/l
  - 1 hour after meals: 7.8 mmol/litre or
  - 2 hours after meals: 6.4 mmol/litre
- Administer insulin preparations if indicated and watch for hypoglycemia esp 1st trimester
- Offer continuous glucose monitoring if poorly controlled

Antenatal care

- Evaluate for ketonemia if available, retinopathy, nephropathy-if proteinuria >5g/litre,
- Consider peripartum DVT prophylaxis
- Preeclampsia prevention - *low dose aspirin but stop at 36 weeks, calcium at 12 weeks that will low bp*
- Ultrasound- *indicate for what you need it for?*
  - Dating US scan
  - Anomaly scan CNS, fetal heart (4 chambers, outflow tracts and 3 vessels), at 18 to 20 weeks
  - Growth scan every 4 weeks from 28 to 36 weeks including AFV/EFW
  - Additional tests as indicated: NST, BPP, Doppler velocimetry

Delivery

- Timing and mode individualized
- 37+0 weeks to 38+6 weeks
  - induction of labour, or CS if indicated due to complications for type 1 or 2 DM; otherwise await spontaneous labour.
- 38 weeks
  - Begin antepartum fetal testing if not delivered *as babies are lost commonly at this stage due to chronic fetal hypoxia*
- 39 weeks*- best time to deliver*
  - Tests of fetal wellbeing if not delivered
  - Deliver before 41 weeks
- Delivery before 37+0 weeks
  - If metabolic or any other maternal or fetal complication
- Anesthesia *for cs*
  - If GA-monitor blood glucose every 30 minutes from induction until delivery and consciousness

Intrapartum glucose monitoring

- Hourly blood sugars *while in labour*
  - maintained between 4 and 7 mmol/litre
- Intravenous dextrose and insulin infusion especially if plasma glucose is not maintained between 4 and 7 mmol/litre.

Newborn care

- Observation for > 24 hours
- Routine blood glucose 2–4 hours after birth.
- Evaluate and manage complications
  - polycythaemia *lead to jaundice*, hyperbilirubinaemia, hypocalcaemia and hypomagnesaemia etc
- Echocardiogram-*pick up cardiac lesions that may be missed*

Postnatal care

- Blood glucose control
  - Risk of hypoglycemia- *as placenta isn't there*
- Medicines
  - Stop all medications if GDM
  - Decreased insulin requirements
  - Administer one half of the pre-delivery dose before resuming regular food intake
- Breastfeeding
  - Early initiation *may help with glucose control*

Postnatal care

- Preexisting DM
  - Refer for medical care
  - Contraception and preconception advice
  - Avoid hormonal-DMPA, COC in long standing diabetes due to risk of thromboembolism and atherosclerosis- *avoid the pills*
  - Encourage LARC- *long acting reversible contraceptives*

- GDM
  - Counseling on hyperglycemia, future pregnancies, lifestyle-diet, exercise, weight- *comprehensive approach*
  - FPG 6–13 weeks / HbA1c after 13 weeks
    - FPG <6 or HbA1c <39 mmol/mol (5.7%):normal , moderate risk of type 2 DM
    - FPG 6.0-6.9 or HbA1c 39-47 mmol/mol (5.7% and 6.4%): high risk of type 2 DM
    - FPG ≥ 7 HbA1c ≥ 48 mmol/mol (6.5%)- have type 2 DM

Other key points

- Preterm labour in women with diabetes
  - Use steroids and give additional insulin
  - Do not use betamimetic medicines for tocolysis

Treatment blood glucose goals for Types 1 or 2 DM

TIME	**GLUCOSE LEVEL (mg/dL)**
Before breakfast	60-90 (3.3-5.0 mmol/L)
Before lunch, supper, bedtime snack	60-105 (3.3-5.8mmol/L)
Two hours after meals	≤120 (≤6.6 mmol/L)
2 am to 6 am	>60 (>3.3 mmol/L)

Objectives

Which one of the following is NOT a complication of gestational diabetes

A. Polyhydramnios
B. Fetal macrosomia
C. Fetal cardiomyopathy
D. Fetal growth restriction
E. None of the above

Objectives

- Which of these congenital malformation is characteristic of diabetes mellitus in pregnancy

A. Transposition of great vessels
B. Neural tube defect-spina bifida, anencephaly, hydrocephalus
C. Sacral agenesis
D. Anorectal atresia
E. All of the above

Objectives

- Which of the following is NOT diagnostic of GDM?

A. FBS 7.0 mmol/L

B. Hemoglobin A1c 7%

C. Random plasma glucose 12 mmol/L

D. 1 hour 50g Glucose Challenge test 7.9 mmol/L

E. None of the above

Which of these statements about insulin is not true?

A. It acts on liver, muscle, and fat
B. It inhibits hepatic glycogenolysis but stimulates gluconeogenesis
C. It is secreted by the B cells of the pancreas
D. It stimulates triglyceride storage in the liver
E. None of the above

- Findings in GDM which indicate a need for insulin therapy include:

A. Fasting plasma glucose levels >7.8 mmol/L
B. Postprandial plasma glucose levels >7 mmol/L
C. Fetal abdominal circumference >75th percentile
D. All the above (A—C)
E. None of the above (A—C)