DIABETES IN PREGNANCY

Learning Objectives:

By the end of this lecture, the student needs to:

1- Evaluate the pathophysiology of diabetes in pregnancy and carbohydrate metabolism.
2- Describe the types of diabetes.
3- Recognize screening for diabetes during pregnancy.
4- Identify maternal, fetal & neonatal complications.
5- Outline the proper management of pregnancy complicated by diabetes in regard to: pre-conception, antenatal, intrapartum & postpartum care.
6- Select suitable family planning for such patients.

Introduction:

Diabetes complicates approximately 3-4% of pregnancies.

Prior to the introduction of insulin in 1921, 40% of pregnant women died mainly of ketoacidosis, while fetal loss reached more than 50% due to miscarriage, premature labor, late intrauterine and neonatal deaths.

Diabetes may complicate a pregnancy either because a woman has pre-existing insulin-dependent (IDDM) or non- insulin dependent (NIDDM) before pregnancy or she develops transient impaired glucose tolerance or diabetes during her pregnancy (gestational diabetes). Women who develop GDM have chronic insulin resistance and that GDM is a "stress test" for the development of diabetes later in life, it usually arises in the late second trimester.

Pathophysiology:

Diabetes mellitus is a syndrome in which hereditary and environmental factors interact leading to inadequate insulin action.

Pregnancy is potentially diabetogenic condition:

1. Significant hormones affect carbohydrate (CHO) metabolism during pregnancy especially progesterone, human placental lactogen, prolactin, tumor necrosis factor and cortisol which are all insulin antagonists causing relative insulin resistance especially in the third trimester.
2. Other factor also is the progesterone-induced increased appetite, food intake and fat deposition.

Normal pregnant women demonstrate increased pancreatic ß-cells response and hyperinsulinemia which facilitates the supply of glucose to the fetus by altering maternal energy metabolism from CHO to lipids.

This increased amount of insulin secreted by maternal pancreas during normal pregnancy will result in a fall in the fasting and pre-prandial level of glucose; while in contrast, following a CHO challenge, the level of glucose is higher than non-pregnant state.

Women with GDM have exaggeration of this insulin resistance possibly due to limited pancreatic ß-cells ability to increase insulin secretion; this will result in increase in blood glucose level in response to glucose load in the third trimester.

Diabetes leads to increase of all metabolic substrates that are available to the fetus. Glucose crosses the placenta by facilitated diffusion and fetal blood glucose level closely follows the maternal level. Free fatty acids cross by simple diffusion. Some amino acids cross by active transfer and their concentration may be higher in the fetus than the mother.

Insulin does not cross the placenta and as a result the elevated concentrations of glucose and amino acids in the fetal circulation stimulate the ß-cells of the fetal pancreas leading to ß-cells hyperplasia and hyperinsulinemia, which is teratogenic during the period of embryogenesis. Since insulin is a major fetal growth factor, this hyperinsulinemia will cause selective fetal macrosomia.

Screening for gestational diabetes:

It is to diagnose previously unrecognized cases of pre-existing diabetes and identify those at risk of developing NIDDM later in life.

No single screening method has been shown to be perfect in terms of sensitivity and specificity for GDM

Screening for gestational diabetes is targeted for high risk group and performed between 24-28wks of gestation using oral glucose challenge test (OGTT).

The risk factors for development of diabetes in pregnancy:

1. Obesity (BMI >30 kg/m^2).
2. First degree relative with diabetes.
3. Previous gestational diabetes.
4. Previous baby >4.5kg.
5. Ethnic origin: South Asia and Middle East (Saudi Arabia, United Arad Emirates, Iraq, Jordan, Syria, Lebanon and Egypt).
6. Previous unexplained stillbirth or poor obstetric history and congenital anomaly.

The National Institute for Health and Care Excellence (NICE) guidelines (2015) OGTT involves checking fasting venous plasma glucose after an overnight fast, then ingesting a 75gm load and check venous plasma glucose at 2 hours for women with one or more risk factors.

ORAL GLUCOSE TOLERANCE TEST (NICE)

Test	venous plasma glucose mmol/L (mg/dl)
fasting	≥5.6 (100.8)
2 hr	≥7.8 (140.4)

The WHO and International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommend two hours OGTT with three readings, recommended universally for all women without risk factors.

ORAL GLUCOSE TOLERANCE TEST (WHO)

Test	Maximal normal blood glucose mmol/L (mg/dl)
fasting	≥5.1 (91.8)
1 hr	≥10 (180)
2 hr	≥8.5 (153)

Due to high risk of recurrence, women who have had GDM in a previous pregnancy should be offered either early self monitoring of blood glucose or a 2 hour OGTT as soon as possible after booking (16 weeks), repeated at 24-28weeks if GTT was normal.

Fasting or random blood glucose, HBA1c or urinalysis should not be used for screening.

Effects of pregnancy on diabetes:

-Nausea and vomiting particularly at early pregnancy.
-Greater importance of tight glycemic control.
-Increased insulin requirements in second half of pregnancy.
-Increased risk of severe hypoglycemia.
-Increased deterioration of retinopathy and nephropathy.

Effects of diabetes on pregnancy:

Fetal and neonatal complications of diabetic pregnancy:

1. Miscarriage and congenital fetal abnormality:

Miscarriage may be higher in poorly controlled diabetes which may be related to the increased fetal anomalies which are 2-4 times more than normal pregnancy.

Good diabetic control, especially prior to pregnancy, reduces these risks; this is assessed by measurement of glycosylated hemoglobin which gives a retrospective assessment of control where high levels in early pregnancy are associated with: neural tube defects, congenital heart disease (transposition of the great vessels, dextrocardia and ventricular septal defect) , central nervous system anomalies (anencephaly, hydrocephaly and spina bifida) and caudal regression syndrome (agenesis of sacrum and hypoplasia of lower limbs).
All women should have detailed fetal anomaly scan at 20 weeks (include four-chamber cardiac view).
Women with GDM have no excess risk of congenital malformations since their blood glucose would be expected to be normal during organogenesis.

2. Macrosomia:

Fetal macrosomia defined by either a birth weight greater than 4kg or a birth weight centile greater than 90. Maternal glucose stimulates fetal insulin production and causes hyperplasia of insulin sensitive tissues, also it enhances the production of human placental growth hormone, fetal insulin-like growth factor which also cause organomegaly and macrosomia.

A major problem associated with prolonged labor, traumatic birth, shoulder dystocia, Erb's palsy and possible hypoxic damage. It is suspected clinically or on ultrasound examination by accelerated growth pattern in the late second and third trimester.

3. Sudden unexplained late stillbirths (10-30%):

It is a risk in poorly controlled patients with vascular disease and pregnancy complicated by polyhydramnios or macrosomia. It occurs less with good diabetic control. The cause is not fully understood but may be attributed to hypotension from osmotic diuresis, chronic hypoxia from defect in placental maturation and increased metabolism and fetal acidosis.

4. Neonatal respiratory distress syndrome (RDS) and transient tachypnea:

In vitro studies showed that insulin antagonizes the action of cortisol on lecithin synthesis which may delay maturation of surfactant production systems. Incidence decreased with better diabetic control and delayed delivery.

5. Neonatal polycythemia:

Fetal hyperinsulinemia causes increased metabolism and increased O2 consumption (hypoxia) which may stimulate fetal erythropoeisis and cause polycythemia. The baby may appear plethoric. For this reason; it is unwise to strip the umbilical cord of blood into the baby at delivery since this may worsen the condition. Exchange transfusion is indicated if haematocrite is >65%.

6. Neonatal Hypoglycemia:

It occurs because the infant continues to produce large amount of insulin in the immediate neonatal period due to recent fetal hyperglycemia.
Low blood glucose is common 60 minutes after birth and gradually rises over the next 6 hours. All infants should be checked at 2, 4, 6 and 12 hours, if capillary blood glucose 1.4mmol/l or less by 4 hours of age, intravenous infusion of 10% dextrose should be given.

7. Neonatal hyperbilirubinemia:

Bruising, polycythemia, RDS and prematurity all predispose to jaundice.
Early feeding, vitamin K 1mg at birth i.m, phototherapy and exchange transfusion all used to manage hyperbilirubinemia.

8. Neonatal hypocalcemia:

Maternal hyperglycemia alters placental expression of calbindin mRNA that affects calcium status at birth resulting in neonatal hypocalcaemia. It is more common in infants who are hypoglycemic and acidotic, and may cause neuromuscular excitability, apnoeic spells and fits.

9. Neonatal hypomagnesaemia.

10.Neonatal cardiomyopathy:
Fetal hyperinsulinemia predisposes to hypertrophic cardiomyopathy.

11. Development of diabetes in the baby:
Maternal hyperglycemia, via fetal programming, can cause changes in gene expression that increase fetal future susceptibility to obesity, diabetes and other health problems.
Both type I & type II diabetes in the mother increase the risk of childhood obesity, metabolic disturbances and the risk of developing diabetes, the risk is higher among children of mothers whose glycemic control was poor in pregnancy.

Obstetric complications:
The longer the duration of diabetes; the higher chance of pre-existing vasculopathy, renal dysfunction and retinopathy, these complications increase the risk of pre-eclampsia and IUGR.

1. Pre-eclampsia:
Is twice as frequent than non-diabetic. Perinatal mortality is doubled due to the need of preterm delivery and IUGR. It may be difficult to be diagnosed since edema may occur due to large baby and polyhydramnios, proteinuria due to UTI or diabetic nephropathy and high blood pressure common in quarter early diabetic pregnancies.
All women with diabetes should be offered low-dose aspirin from 12 weeks to reduce the risk of pre-eclampsia.

2. Polyhydramnios:
It could be due to fetal osmotic diuresis induced by maternofetal hyperglycemia and it is one of the characteristic features of the poorly controlled diabetes.

3. Premature labor (20%):
Premature labor is mostly associated with polyhydramnios.
Drugs that are used for premature labor treatment as ß-sympathomimetic and glucocorticoid are potentially hazardous in diabetic pregnant women since ß-sympathomimetic cause hepatic glycogenolysis and insulin resistance, glucocorticoid have synergistic effect, so that they may cause severe hyperglycemia and ketoacidosis. They should be avoided or to be used with great care monitoring blood glucose levels and to increase the dose of insulin and intravenous insulin and glucose infusion. Alternative use of other tocolytics should be considered.

4. Diabetic nephropathy:
Diabetic nephropathy is a continuous spectrum from microalbuminuria, proteinurea and impaired renal function to end-stage renal disease (increasing serum urea and creatinine).
Evaluation of renal function should be performed in all pregnant diabetic patients. A 24hour urine specimen for albumin and creatinine clearance should be done.
Diabetic nephropathy is associated with increased fetal risks: IUGR, stillbirth and preterm delivery, requiring increased fetal surveillance. Maternal risks are: super-imposed pre-eclampsia, placental insufficiency, renal failure and morbidity or death from macrovascular disease.
Consequences depend on blood pressure, low-dose aspirin, glycemic control and protein intake. Although renal condition may worsen during pregnancy, this is rarely permanent and tends to improve after delivery.

5. Retinopathy:
Pregnancy is associated with progression of pre-existing retinopathy. It is therefore recommended postponed pregnancy if significant retinopathy is present pre-conception, to allow for laser treatment.

All pregnant diabetic patients should have retinal examination in early pregnancy so that any lesion requiring laser photocoagulation can be treated since pregnancy may cause progression of the disease.

Rapidly improving glycemic control during pre-conception and pregnancy can worsen retinopathy.

6. Neuropathy:

Diabetic neuropathy can manifest as peripheral sensory or autonomic neuropathy, the latter can affect cardiovascular, gastrointestinal and urogenital systems.

Gastrointestinal involvement is a cause of gastroparesis which can cause erratic absorption of meals resulting in episodes of hyper and hypoglycemia.

7. Infections:

a- Urinary tract infection is more common in diabetic women and asymptomatic bacteriuria should be checked at 28, 32 and 36 weeks. Infections should be treated with parenteral antibiotics since pyelonephritis seriously affect pregnancy outcome.

b- Monilial vaginitis and vulvitis is more due to the high glucose content of vaginal epithelium and presence of glycosuria.

8. Coronary artery disease.

Diabetes is associated with macrovascular disease and premature coronary artery disease and should be seen by cardiologist pre-pregnancy.

9. Hyperglycemia / ketoacidosis.

Diabetic ketoacidosis is associated with high fetal loss and develops more quickly in pregnancy at lower glucose levels.

It can be caused by failure to appreciate the increasing insulin requirements in pregnancy, missed insulin doses, concurrent illness (infection), steroid therapy and stress.

It is defined as plasma glucose >12mmol/L, arterial PH <7.3 with ketonuria and ketonaemia, and associated with poor maternal and fetal outcomes.

CTG abnormalities are typical in third trimester and resolve with hyperglycemia treatment.

Treatment should involve diabetic team, treatment of precipitating cause, intravenous insulin via sliding scale and continuous CTG monitoring and would be unsafe to perform c/s until the woman is metabolically and hemodynamically stable.

10. Hypoglycemia:

Hypoglycemia is not harmful to the fetus but life-threatening to the mother, hypoglycemia is blood glucose <3.5 mmol/L. It is more frequent during the first trimester (nausea, vomiting and 10% decrease demands for insulin).

Risk factors are: poor hypoglycemic awareness, renal impairment gastroparesis and sleeping alone.

Advice on timing of meals and snacks, awareness of family members to treat hypoglycemia, carry sweets, identification that she is using insulin and specific advice on driving.

If the patient is conscious, correct hypoglycemia by 10-15 g of glucose (4 teaspoons of sugar or half a can of juice), followed by slow release CHO (bread), if unconscious then we should give 0.5-1 mg glucagon i.m or 150ml of 10% dextrose i.v in hospital.

11. Thromboembolic disease.

12. Increase operative delivery rate

Management of pregnancy complicated by diabetes:

I-Pre-pregnancy counseling:
Diabetic women attending pre-conception clinic have better pregnancy outcome than those who do not.
-Multidisciplinary
-Optimize glycemic control (HbA1c 6.1% or less), if above 10% not to become pregnant
-Discuss hypoglycemia effects
-Optimum sugar control (FBS< 5.5mmol/L, 2-hours post meal glucose < 7.8mmol/L)
-Review diet and weight loss
- Discuss pregnancy complications
-Prescribe 5mg folic acid
-Review renal function and blood pressure
-Retinal assessment
-Smoking cessation
-Drugs reviewed (stop statins, angiotensin converting enzyme (ACE) inhibitors and continue metformin)

II- Antenatal management:
The principle management of all diabetic pregnancies from time of conception through to the time of delivery is to achieve maternal euglycemia.

1. Combined care:
Best results are obtained when the patient is managed in a joint clinic with an obstetrician and physician. Women should be booked early in pregnancy, preferably before 10 wks. Antenatal visits should be every 2 weeks until 32-34 weeks and then weekly thereafter as frequent changes in insulin doses is required especially in third trimester.

2. Medical care:
The pregnant diabetic should be seen as early as possible during the first trimester to facilitate guidance with her diabetic control.
* Retinal screening
* Nephropathy screening
* Screening for non-diabetic complications:
- Other autoimmune diseases: In type I diabetes, women are susceptible to autoimmune thyroid diseases.
- Co-morbidities associated with insulin resistance in type II diabetes (obesity, hypertension & dyslipidemia).
Obesity is risk factor for hypertension, stillbirth, cesarean section, birth trauma and postpartum complications while hypertriglyceridemia is a source of glycerol and fatty acids, both can contribute to accelerated fetal growth.
* Special dietary advice for obese, walking after meals can decrease postprandial blood glucose rise.

3. Glycemic control:
The aim of treatment is to maintain blood glucose level as near as normal as possible by combination of exercise, diet, oral hypoglycemic agents and insulin.

Targets for daily capillary plasma glucose are:
- Fasting less than 5.3 mmol/L(95.4mg/dl)
- 1 hour after meals less than 7.8 mmol/L(140.4mg/dl)
- 2 hour after meals less than 6.4 mmol/L(115.2mg/dl)

I. Exercise: Women should be advised for moderate exercise (30 minutes a day (walking after a meal) may help blood glucose control.

II- Diet comprises about 50% CHO, 20%protein and 20% fat with a generous amount of fiber, as 25% at breakfast, 30% at lunch, 30% at dinner and 15% at bedtime snack.

If after 1-2 weeks of diet and exercise, blood glucose is not within the target levels, additional therapy should be offered (oral hypoglycemic or insulin). This is for women with GDM.

III- Oral hypoglycemic agents have traditionally not been used in pregnancy because of the risks of neonatal hypoglycemia and teratogenesis.
Oral hypoglycemic agents are often used in patients with type II and gestational diabetes; they are cheaper, easier and convenient for pregnant women.
With the exception of metformin and glibenclamide, there are little available data about the safety of the other drugs in pregnancy, or whether they cross the placenta.

Metformin is increasingly used in patients with polycystic ovarian syndrome as it reduced the risks of first trimester miscarriage and the development of gestational diabetes. It crosses the placenta but not increase the risks of congenital malformations.
It improves insulin sensitivity, increases peripheral glucose intake and inhibits hepatic gluconeogenesis. It is well tolerated, easy to use, inexpensive with low risk of hypoglycemia.

IV- Insulin is required in pregnancy even for those who were controlled by diet alone before pregnancy. It is the gold standard to maintain euglycemia in pregnancy. The starting dose is calculated according to body weight in kg as 0.6 IU/kg in 1st trimester, 0.7 IU/kg in 2nd trimester and 0.8 IU/kg in 3rd trimester.

Insulin types are:

Type	Examples	Onset	Peak	Duration
Rapid acting	lispro (Humalog) Aspart (NovoRapid)	15 min	30-90 min	5 hours
Short acting	Regular	30 min	2-4 hours	4-8 hours
Intermediate acting	NPH lente	2-6 hours	4-14 hours	14-20 hours
Long acting	Ultralente	6-14 hours	Small or none 10-16 hours	20-24 hours
	Glargine	1-2 hours	None	24 hours

* Insulin regimens vary with the individual; the dose may be given as three pre-meal injections of short-acting insulin and a single intermediate or long-acting injection at bed time.
~Alternatively a twice-daily regimen of short and intermediate-acting insulin but it may be necessary to transfer the evening intermediate-acting injection to bed time to prevent nocturnal hypoglycemia. Those are called multiple daily injections (MDI).
The newer long-acting analogues may be associated with fewer hypoglycemic episodes (steady background without peaks).

Continuous subcutaneous insulin infusion (CSII) pumps using short-acting insulin
has less risks of hyper- and hypoglycemia and better compliance, the pump consists of a cannula inserted into the subcutaneous abdominal tissue, delivers continuous basal level of insulin, additional bolus doses are given for meal times.
CSII pumps are offered if MDI regimen does not achieve adequate control.

Insulin requirement rises progressively till term because of increased insulin resistance.

Monitoring for glucose levels:
* The adjustment of insulin dose is based on frequent daily blood glucose monitoring:
All women should test daily

-Type 1 DM and those with MDI:
Fasting level
Pre-meal
1-hour after every meal
Bedtime

Those on diet, oral treatment or single insulin dose:
Fasting
1-hour post meal
Bedtime (if take insulin)
-

This is done on daily basis when control of blood sugar is poor, but may be reduced to two-three times weekly with good control.
Insulin dose adjustment varies in individual patients, lifestyle, duration of diabetes and complications. There is no one formula that is applicable for all diabetic women.

*Glycosylated hemoglobin (HbA1c):
Glucose influences the slow glycosylation of hemoglobin during the red cell life cycle, so that the high HbA1c level reflects high plasma glucose concentration, in patients with HbA1c>8.5% in 1st antenatal visit, a careful ultrasound assessment for congenital anomalies should be done.
Glycosylated hemoglobin (HbA1c) provides an index of mean blood glucose concentrations in the preceding 4-12 weeks and does not reflect the subtle changes in blood glucose, in particular post-prandial level.
It falls in response to physiological changes in late pregnancy; therefore, current guidelines do not recommend its use routinely in second and third trimesters.

4. Obstetric management:
*Early booking and dating of pregnancy are important.

*Blood for screening for neural tube defects at 16 weeks (α-feto protein).

*Ultrasound is used to measure fetal crown-rump length in early pregnancy and a biparietal diameter at about 16 weeks to determine duration of pregnancy, a detailed examination early and at 19-20 week and fetal echocardiography to exclude congenital abnormalities and serial measurements of fetal head and abdominal circumference to detect macrosomia.

*Doppler ultrasound and assessment of fetal wellbeing at weekly or twice weekly from 36 weeks of gestation, this eliminates the need to admit the patient and enables diabetic pregnancy to be continued near term.

Corticosteroids administration:
Corticosteroids given for lung maturity have adverse effects on glucose tolerance and they increase insulin requirements during pregnancy. This can be managed by increasing subcutaneous doses or intravenous insulin via sliding scale that often requires inpatient admission.
The peaks in blood glucose occur between 9-15 hours after the first dose and 8-15 hours after the second one

5. Timing of delivery:
For women with type 1 and type 2 pre-existing DM without complications, elective delivery between 37-38+6 weeks should be offered.

Women with optimal diabetic control, uncomplicated GDM should be allowed to progress between 38-40+6 weeks' gestation to reduce the likelihood of prematurity and improve the chances of spontaneous labor.

Poorly controlled cases with complications necessitate earlier delivery.

III- Intrapartum management:

*Normal vaginal delivery is the primary goal.

*Elective cesarean section may be indicated in malpresentation, fetal weight more than 4.5kg or history of previous cesarean section.

*Insulin during labor and delivery:
Most women are admitted electively.
Women admitted for planned induction should take their normal insulin dose the night before.
For elective cesarean section, normal bolus insulin with the evening meal and two-thirds of the usual basal insulin at night before admission is given.

Once in the ward, start insulin sliding scale with 5% glucose-insulin infusion during active labor and operative delivery and this is continued till the mother start taking meals.

*Intrapartum hyperglycemia predisposes to neonatal hypoglycemia, therefore it is vital to maintain euglycemia throughout labor and before cesarean section. This is best achieved by intravenous insulin via infusion pump. Maternal blood glucose should be measured hourly and blood glucose concentration kept between 4-7mmol/l.

*Pain stimulates the release of catecholamines causing glycogenolysis and hyperglycemia, therefore it is essential to use analgesia during labor (epidural anesthesia).

*Continuous monitoring of fetal heart rate because of increased incidence of fetal distress due to impaired oxygen release in utero-placental circulation.

*Partogram use to give early warning of the need for cesarean section thus minimizing the risk of shoulder dystocia.

IV- Postnatal care:

*Immediately after delivery the insulin infusion dose should be halved, as a rapid increase in insulin sensitivity occurs after placental separation, the pre-pregnancy insulin dose should be given as soon as normal diet is resumed. Women with GDM should stop oral hypoglycemic and insulin immediately after birth.

*Food intake should be adjusted by dietician.

*Diabetics are at increased risk of wound infection after surgery and prophylactic antibiotics are advised.

* Glycemic control is better in women who exclusively breastfeed than those who bottlefed. It may increase frequency of hypoglycemia in type1 DM, thus women should be advised to have a snack before or during breastfeeding.
Women with type 2 DM can safely take metformin or glibenclamide since only small amounts cross to breast milk.

*Women with GDM are at increased risk for developing type 2 diabetes, current guideline suggests performing FBS at 6-13 weeks and HbA1c at 13 weeks following delivery to ensure that diabetes has resolved. Lifestyle intervention that minimizes weight gain and encourage physical activity has been shown to reduce the progression rate the diabetes over the subsequent 4-5 years.

V- Contraception use:

- Progestogen-only pills have no effect on carbohydrate and lipid metabolism, and safe for diabetics who choose to breast feed their children.
- The modern low-dose oral contraceptive pills have little effect on high and low-density lipoprotein and can be used safely especially for young women.
- Injectable progestogenes may produce insulin resistance and insulin dose need to be increased, but not contra-indicated.
- Intra-uterine devices may also be used.
- Diabetic women who completed their families should be encouraged to consider sterilization.