AL-Mustaqbal University
College of Pharmacy

Hospital Training 5nd Stage

Gynecology

Obstetrics part (OB-GYN)

Session 2

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B- Diabetes mellitus in pregnancy

The pregnancy may be complicated by maternal diabetes mellitus where:

A- Women with pre-existing diabetes (and are classified as either IDDM or NIDDM)

B- Those developing carbohydrate intolerance during pregnancy (usually during third trimester) and are classified as Gestational Diabetes Mellitus (GDM) (1).

Diagnosis:

The American Diabetes Association suggests the following targets for women who develop gestational diabetes during pregnancy. More or less stringent glycemic goals may be appropriate for each patient.

Before meal (preprandial): 95mg/dl or less.

1 h after meal (postprandial): 140mg/dl or less.

2 h after meal (postprandial): 120mg/dl or less.

Complications of GDM

1- Fetal: Medical problems encountered in infants born to diabetic mothers (whether GDM or pre-existing g DM) are shown in the following table 1 : Medical Problems Encountered in Infants Born to Diabetic Mothers

1- Macrosomia (large babies: greater than 4 kg)

2- Hypoglycemia

3- Intrauterine growth retardation

4- Late fetal death

5- Cardiomyopathy (asymmetric septal hypertrophy)

6- Pulmonary hypertension

7- Idiopathic respiratory distress syndrome (IRDS)

8- Hyperbilirubinemia

9- Hypocalcemia and hypomagnesemia

10-Thrombosis and abnormal clotting

2-Maternal:

A- Complications of GDM to pregnant women include:

1- Pre-eclampsia and gestational hypertension.

2- Preterm labor.

3- Recurrent vulvo-vaginal infection (thrush, UTI …..).

4- Long-term development of diabetes mellitus.

5- Increased incidence of operative delivery (like Caesarean section).

B- Complications of preexisting diabetes to pregnant women include:

1- Pre-eclampsia and gestational hypertension.

2- Preterm labor.

3- Recurrent vulvo-vaginal infection (thrush, UTI …..).

4- Increased incidence of operative delivery (like Caesarean section).

5- Exacerbation of pre-existing disease (retinopathy, nephropathy, and cardiac disease).

Management

A- Pregnant woman with preexisting diabetes:

1- The aim is to maintain glucose level within these ranges and to avoid hypoglycemia and hyperglycemia.

2- Most patents with pre-pregnancy diabetes are taking insulin, and this therapy must be maintained during pregnancy

3- For those on oral antidiabetic agents, it is advisable to convert them on insulin , because of the possible teratogenic effects and insulin facilitates a more effective manipulation of requirements as pregnancy progress.

4- In addition to insulin therapy, dietary advice is essential as it make glycemic control with insulin easier.

B-Pregnant woman with GDM

1- The aim is to maintain fasting glucose level below 100 mg/dL (about 5.5 mmol/dL) , below 125 mg/dL (about 7 mmol/dL) for 2 hours post-prandial glucose level, and to avoid hypoglycemia and hyperglycemia.

2- Glucose control can be achieved through:

1- Dietary control.

2- Insulin Therapy: If dietary control does not reduce hyperglycemia sufficiently to reach the recommended glucose levels, insulin therapy is needed.

The initial starting insulin dose should be based on existing weight. And a total daily insulin dose of 0.5 to 0.7 units/kg is given. Two thirds of this dose is usually given in the morning and one third in the evening. Also, one third of each dose is given as rapid-acting insulin and the remaining dose as intermediate. The second dose may be divided so that rapid-acting insulin is given at suppertime and intermediate at bedtime.

C-Delivery:

The most common risk with GDM is macrosomia (large babies), which can lead to birth injuries. Clinical judgment often becomes the determinant on whether a Cesarean delivery is appropriate

C- Pre-eclampsia

Definitions:

1-Pre-eclampsia (sometimes called toxemia of pregnancy) is a disorder of pregnancy characterized by hypertension (blood pressure (BP) >140/90 mmHg) and clinically significant proteinuria (protein in urine >300 mg/24 h) developing after 20 weeks of gestation.

2-Eclampsia: is a convulsion occurring in women with established Pre-eclampsia, in the absence of other neurological or metabolic causes.

3-Chronic hypertension is defined as BP elevation (BP >140/90 mmHg) that has persisted since before conception or 20 weeks of gestation.

4-Gestational hypertension refers to hypertension that develops in previously normotensive women after 20 weeks of gestation without other symptoms of pre-eclampsia

Etiology:

Although the primary events leading to pre-eclampsia are still unclear,there are cascade of events leads to the clinical syndrome

Sign and Symptoms of Pre-eclampsia:

Symptoms: may be asymptomatic, headache, visual disturbance, and epigastric pain.

Signs: Elevation of BP, edema.

Investigations for Pre-eclampsia:

The diagnosis and severity of pre-eclampsia-eclampsia can be measured with reference to the six major sites in which it exerts its effects: the central nervous system, the kidneys, the liver, the hematologic and vascular systems, and the fetal placental unit. By evaluating each of these areas for the presence of mild to moderate versus severe pre-eclampsia, the degree of involvement can be assessed, and an appropriate management plan can be formulated.

Management

The only cure for pre-eclampsia is delivery of the fetus &while it is the best treatment for the mother, it is not always the best option for the fetus because prematurity is the leading cause of neonatal mortality & morbidity. Therefore, if the patient were > 34 week of gestation she would delivered of her fetus. While women with severe pre-eclampsia or eclampsia should be delivered after a period of stabilization, regardless of the gestation age of the fetus

A-Mild to moderate pre-eclampsia

1- For mild to moderate pre-eclampsia-eclampsia, bed rest is the cornerstone of therapy. This increases central blood flow to the kidneys, heart, brain, liver, and placenta and may stabilize or even improve the degree of pre-eclampsia-eclampsia for a period of time. Bed rest may be attempted at home or in the hospital.

2-Antihypertensive therapy should be use especially if diastolic BP reaches 100 mmHg

a- Methyldopa (aldomet ®) is centrally acting α2 agonist. It is the most commonly used antihypertensive for hypertension during pregnancy. Usual dose is 750mg /day i.e. (250mg q 8 h) increase to 2-3gm/day.

Adverse effect: Lethargy, somnolence, drowsiness & potential depression.

b- Labetalol (Trandate ®) which is α and β blocker. This agent has good safety record in pregnancy . Daily dose is 400-800mg.

c- Calcium channel blocker(CCB).

Administration of CCB nifedipine appears to be safe and is used commonly to treat hypertension during pregnancy particularly severe hypertension unresponsive to standard treatment but some adverse effect reported (flushing, headache & reflex tachycardia & ankle edema).

B-Severe Pre-eclampsia

Symptoms are more dramatic and persistent. The blood pressure is often quite high, with readings over 160/110 mm Hg. Thrombocytopenia (platelet counts < 100,000/mcL) may be present and progress to disseminated intravascular coagulation. Severe epigastric pain may be present from. The HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) is a form of severe Pre-eclampsia

Mean arterial pressure (MAP): calculated as diastolic blood pressure + [(systolic diastolic)/ 3] is used to guide management and most protocols recommend the use of IV antihypertensive therapy if the MAP is > 125 mmHg . IV labetalol or hydralazine are most common drugs used. If one agent is ineffective, or if the side effect occur (e.g. tachycardia with hydralazine), the other agent can be used .

1- Hydralazine: Hydralazine (given IV) is the most commonly used treatment of severe hypertension in pre-eclamptic women. Since it is a potent vasodilator, hydralazine may increase a patient's risk of decreased intervillous blood flow and thus may impair uteroplacental perfusion. Consequently, some clinicians pretreat patients with plasma volume expansion (colloids) in an effort to prevent hypotension and fetal distress.

Dosing regimen (many regional protocols) for example:

Bolus dose of 5 mg IV if the mean arterial pressure (MAP) remains > 125 mmHg, followed by a further boluses of 5 mg (every 20-30 minutes) up to a cumulative dose of 15 mg. Once the MAP is < 125 mmHg, an infusion of 10 mg /hour is commenced, doubling (if necessary) at 30 minutes intervals, until a satisfactory response or a dose of a 40 mg/hour is attained.

2-Labetalol (given IV) is currently recognized as a second-line antihypertensive agent for treatment of severe hypertension in pre-eclamptic women and is reserved for use when target blood pressure is not achieved with hydralazine. It should not be administered to patients with asthma or congestive heart failure, as it is a nonselective beta-receptor antagonist .

Dosing regimen (many regional protocols) for example :

Bolus dose of 20 mg IV if the mean arterial pressure (MAP) remains > 125 mmHg, followed at 10-minutes intervals by 40, 80, 80 mg boluses up to a cumulative dose of 220 mg. Once the MAP is < 125 mmHg, an infusion of 40 mg /hour is commenced, doubling (if necessary) at 30 minutes intervals, until a satisfactory response or a dose of a 160 mg /hour is attained.

3-Nifedipine (Adalat ®): is also common choice to treat severe hypertension during pregnancy. Nifedipine 10 mg cap is given orally every 30-60min until the diastolic BP decrease < 110mmHg.

C-Eclampsia:

The occurrence of seizures defines eclampsia. The other abnormal findings of severe pre-eclampsia are also observed with eclampsia. It is associated with high mortality rate.

1- Magnesium sulphate is the drug of choice for the prevention of recurrent seizures in eclampsia. Regimens may vary between hospitals. Calcium gluconate injection is used for the management of magnesium toxicity . Prevention of seizure recurrence in eclampsia, initially by intravenous injection over 5-15 minutes, 4 g, followed by intravenous infusion,

1 g/hour for at least 24 hours after last seizure; if seizure recurs, additional dose by intravenous injection, 2 g (4 g if body-weight over 70 kg) Urinary output is checked hourly and the patient assessed for signs of possible magnesium toxicity such as loss of deep tendon reflexes or decrease in respiratory rate and depth, which can be reversed with calcium gluconate . 1g (10ml of 10% calcium gluconate) should given iv over 3 minutes.

2-Diazepam (valium®) 10 mg is suitable alternative.

3-Phenobarbital (luminal®) also can be use . If seizure does not resolved by medical intervention, termination of pregnancy is recommended

Caesarean Section

Definition: Caesarean section refers to an operation that is performed to deliver the baby via a transabdominal route.

Some of the indications for Caesarean section:

1-Patient has a previous history of Caesarean section.

2-Baby is too big to pass safely through the vagina.

3-The baby's buttock or feet enter the birth canal first instead of the head, this is called breech position.

4-The baby's shoulder enter the birth canal first instead of the head this is called shoulder or transverse position.

5-Labour is too slow or stops (no dilation of cervix after time is finish).

6-There are problems with the placenta (placenta praevia or abruption) which may cause dangerous bleeding during vaginal delivery.

7-Mother has infection like genital herpes

8-Twins, triplets or more.

9-Baby has problem during labor (such as a slow heart rate) this is called fetal distress.

10-Mother has DM or high BP

Ectopic Pregnancy

Ectopic pregnancy is derived from the Greek word ektopos, meaning out of place, and it refers to the implantation of a fertilized egg in a location outside of the uterine cavity, including the fallopian tubes (About 98% of ectopic pregnancies are tubal, cervix, ovary, cornual region of the uterus, and the abdominal cavity.This abnormally implanted gestation grows and draws its blood supply from the site of abnormal implantation. As the gestation enlarges, it creates the potential for organ rupture because only the uterine cavity is designed to expand and accommodate fetal development. Ectopic pregnancy can lead to massive hemorrahage , infertility, or death

Any condition that prevents or retards migration of the fertilized ovum to the uterus can predispose to an ectopic pregnancy, including a history of infertility,pelvic inflammatory disease, ruptured appendix, and prior tubal surgery. Combined intrauterine and extrauterine pregnancy (heterotopic) may occur rarely. The following risk factors have been linked with ectopic pregnancy:

1-Pelvic inflammatory disease (The most common cause is infection caused by Chlamydia trachomatis).

2-History of prior ectopic pregnancy.

3-History of tubal surgery and conception after tubal ligation.

4-Use of fertility drugs (clomiphene citrate or injectable gonadotropin) or assisted reproductive technology.

5-Use of an intrauterine device.

6-Increasing age, smoking, and others

Diagnosis and treatment

A-Clinical Findings

The classic clinical triad of ectopic pregnancy is pain (secondary to tubal distention or rupture), amenorrhea, and vaginal bleeding. Unfortunately, only 50% of patients present typically. Some patients may be collapsed and shocked from bleeding.

B-Laboratory Findings

Blood studies may show anemia. Quantitative serum pregnancy tests will show levels generally lower than expected for normal pregnancies of the same duration. If pregnancy tests are followed over a few days, there may be a slow rise or a plateau rather than the near doubling every 2 days associated with normal early intrauterine pregnancy or the falling levels that occur with spontaneous abortion(2).

C-Imaging

Ultrasonography can reliably demonstrate a gestational sac 6 weeks from the LMP and a fetal pole at 7 weeks if located in the uterus. An empty uterine cavity raises a strong suspicion of extrauterine pregnancy, which can occasionally be revealed by endovaginal ultrasound. Specified levels of serum hCG have been reliably correlated with ultrasound findings of an intrauterine pregnancy. For example, an hCG level of 6500 mU/mL with an empty uterine cavity by transabdominal ultrasound is virtually diagnostic of an ectopic pregnancy. Similarly, an hCG value of 2000 mU/mL or more can be indicative of an ectopic pregnancy if no products of conception are detected within the uterine cavity by transvaginal ultrasound.

D-Special Examinations

Laparoscopy is the surgical procedure of choice both to confirm an ectopic pregnancy and in most cases to permit pelviscopic removal of the ectopic pregnancy

Treatment

When a patient with an ectopic pregnancy is unstable or when surgical therapy is planned, the patient is hospitalized. Blood is typed and cross-matched. Surgical treatment is definitive.

In a stable patient, a single dose methotrexate IM (50 mg/m2 or approximately 1mg/kg)(4) is acceptable medical therapy for early ectopic pregnancy.

Iron therapy for anemia may be necessary during convalescence. Give Rho(D) immune globulin (300 mcg) to Rh-negative patients(2).

Prognosis

Repeat tubal pregnancy occurs in about 12% of cases. This should not be regarded as a contraindication to future pregnancy, but the patient requires careful observation and early ultrasound confirmation of an intrauterine pregnancy

Some Drugs that are Used in Obstetric and Gynecology

1-Clomifene (clomiphene) citrate (Clomid® citrate 50 mg tablet) Anti-oestrogens used in female infertility caused by anovulation (oligomenorrhoea or secondary amenorrhoea). Dose : 50 mg daily for 5 days, starting within about 5 days of onset of menstruation (preferably on 2nd day) or at any time if cycles have ceased; second course of 100 mg daily for 5 days may be given in absence of ovulation; 3 courses should constitute adequate therapeutic trial .

2-Dydrogesterone (Duphaston ® 10mg tablet)

Progesterone analogue used in: Endometriosis, dysfunctional uterine bleeding, dysmenorrhoea, amenorrhoea, and premenstrual syndrome . It may be used in the following but not recommended: Infertility, irregular cycles, and recurrent miscarriage (habitual abortion).

3-Norethisterone (Primolut N® 5 mg tablet): Progesterone analogue used in: Endometriosis, dysfunctional uterine bleeding, dysmenorrhoea, amenorrhoea, premenstrual syndrome and postponement of menstruation.

4-Medroxyprogesterone Acetate (Provera®: 2.5, 5 and 10 mg tablets, DepoProvera® 150 mg injection) Progesterone analogue used orally in: dysfunctional uterine bleeding , secondary amenorrhoea, endometriosis, progestogenic opposition of oestrogen HRT.

Depo-Provera® 150 mg injection used as a contraceptive for about three months.

5-Methyl ergometrine (methergin ®) tablet 125mcg, injection: 200 mcg /mL (1 mL ampoule). Use in the prevention and treatment of post partum hemorrhage.

6-Oxytocin (Pitocin®) 10 IU / mL (1 mL ampoule) use to induce or augment labour and the prevention and treatment of post partum hemorrhage.

7-Tamoxifen (10 and 20 mg tablet) used in breast cancer, and anovulatory infertility.

8-Human Chorionic Gonadotrophin; HCG (Pregnyl ® Injection, 500-unit amp, 1500-unit amp 5000-unit amp) is used in the treatment of infertility in women with proven hypopituitarism or who have not responded to clomifene.

9-Pergonal® injection contain 75 units of FSH, and 75 units of human LH) is used in the treatment of infertility in women with proven hypopituitarism or who have not responded to clomifene. lutropin alfa (Recombinant human LH) Injection, 75-unit Luveris®.use like pergonal®.

10-Conjugated oestrogens (Premarin® 652 mcg, and 1.25 mg tablets) use as a Hormone replacement therapy (HRT) for a alleviating menopausal symptoms.

11-Trisequens ® tablets: 12 blue tablets of estradiol 2 mg; 10 white tablets of estradiol 2 mg, norethisterone acetate 1 mg and 6 red tablets of estradiol 1 mg. use as a hormone replacement therapy (HRT) for a alleviating menopausal symptoms.

12-Danazol (Danol®100 mg, 200 mg cap). It is licensed for the treatment of endometriosis and for the relief of severe pain and tenderness in benign fibrocystic breast disease where other measures have proved unsatisfactory.

13-Bromocriptine (Parlodel® 2.5 mg tablet): is used for the prevention of lactation in galactorrhoea.

14-Cabergoline (Dostinex ® 0.5 mg tablet) has actions and uses similar to those of bromocriptine, but its duration of action is longer.

15-Goserelin (Zoladex® 3.6 mg injection): Gonadorelin analogues are used in the treatment of endometriosis, precocious puberty, infertility and breast cancer.

16-Buserelin, Leuprorelin acetate, Nafarelin, Triptorelin: Gonadorelin analogues are used in the treatment of endometriosis, precocious puberty, infertility and breast cancer. [

17-Tranexamic acid (Cyklokapron®, Exacyl® 500 mg tablet, and 500 mg /5 mL injection). It is used to stop vaginal bleeding.

18-Isoxsuprine (Duvadilan® 10 mg and 20 mg tablet): uterine relaxant

Thank you