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Recent Advances in the Management of Gestational Diabetes and Pre-Eclampsia

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***Abstract*: Gestational Diabetes is a highly prevalent condition, which has a great impact on maternal and fetal Health. It a condition triggered by metabolic adaption, which occurs during the second half of pregnancy. The aim of this review to discuss the advances in management of GDM, as well as their implications in the field, the issue of hyperglycemia in early pregnancy. Pre-eclampsia is a multisystemic disease characterized by the development of hypertension after 20 weeks of gestation, with the presence of proteinuria or, in its absence, of signs or symptoms indicative of target organ injury.**

***Keywords*: Gestational diabetes, fetal macrosomia, insulin, metformin, pregnancy, diagnosis, risk factors pre-eclampsia, management, Labetalol.**

1. Gestational diabetes

A. Introduction

Treatment of gestational diabetes mellitus (GDM) aims to reduce hyperglycaemia and in turn reduce the risk of adverse perinatal outcomes including large for gestational age (LGA), macrosomia, shoulder dystocia, neonatal hypoglycemia and the need for caesarean section [1]. Diet modification is often used as first-line treatment; pharmacological treatments (metformin, glibenclamide (glyburide) and/or insulin) are offered. Although results from these reviews generally indicate that treatment reduces the risk of adverse perinatal outcomes. Several trials have been published and recommended criteria for GDM diagnosis have changed.

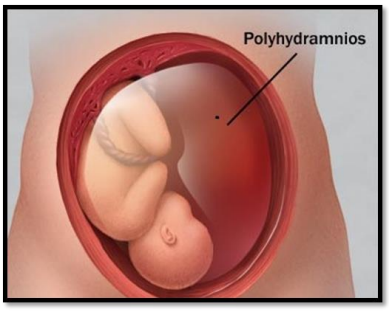

Fig. 1. Effects of diabetes on pregnancy

Diabetes mellitus (DM) is one of the most common medical complications of pregnancy; gestational diabetes mellitus (GDM) accounts for approximately 90-95% of all cases. [2] GDM is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. The prevalence of GDM varies from 1 to 14%, in direct proportion to the prevalence of Type 2 diabetes in a given population or ethnic group.

1) High risk patients

- GDM during previous pregnancy.
- High weight babies born from a previous pregnancy.
- A history of stillbirth or infants with congenital abnormalities.
- Poor obstetric history including recurrent fetal wastage, hypertension, eclampsia, hydramnios, etc.
- A history of repeated or persistent urinary tract infection.

2) Fetal complications

- Macrosomia
- Hypoglycemia
- Jaundice
- Respiratory distress syndrome (RDS)
- Low calcium and magnesium levels in baby's blood

3) Screening and diagnostic investigation

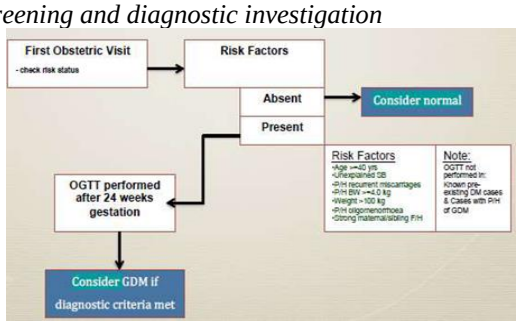

Fig. 2. Screening and diagnostic investigation

B. Diagnosis

Oral glucose tolerance test (OGTT) [3]

Procedure:

- Carbohydrate intake of at least 150 g/day 3 days prior to test, then fast for 10 to 16 hours.
- 100 grams or 75 grams of anhydrous dextrose powder.
- Drink within 5 minutes (first swallow is time zero).
- Terminate test should nausea and vomiting occur.
- Abstain from tobacco, coffee, tea, food and alcohol during test.

- Sit upright and quietly during the test, Slow walking is permitted but avoid vigorous exercise.
- Collect samples at 0, 1, 2 and 3 hours.

Table 1
Diagnostic criteria for the 75-g OGTT [3]

	Plasma or Serum Level Carpenter and Coustan	Plasma Level NDDG
Fasting blood glucose	≥5.3 mmol/L (95 mg/dL)	≥5.8mmol/L (105 mg/dL)
One hour	≥10.0mmol/L (180 mg/dL)	≥10.6 mmol/L (190 mg/dL)
Two hours	≥8.6 mmol/L (155 mg/dL)	≥9.2 mmol/L (165 mg/dL)
Three hours	≥7.8 mmol/L (140 mg/dL)	≥8.0 mmol/L (145 mg/dL)

C. Pathophysiology

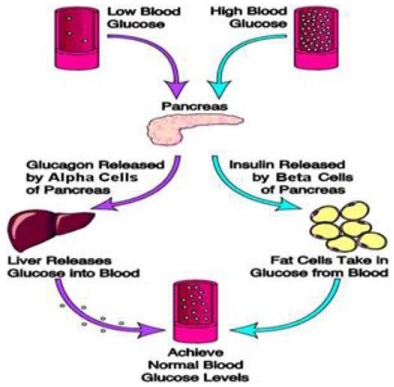

Fig. 3. Pathophysiology of insulin resistance

1) Management of GDM

Recent data provide strong evidence that proper treatment of GDM reduces adverse maternal and perinatal outcomes.

A. *Diet:* First-line therapy for women with gestational diabetes is dietary modification, often referred to as medical nutritional therapy (MNT). For normal-weight women (BMI: 20-24 kg/m^2) 30 kcal/kg. [4]

Gestational Diabetes Diet Plan-

- Eat small nourishing main meals three times a day, starting with breakfast
- If you suffer from morning sickness, have a slice of wholegrain toast or some wholegrain cereal before you get out of bed in the morning.
- Eat a nourishing snack, mid morning and mid afternoon, between meals.
- Choose foods high in fiber such as fresh fruits and vegetables and wholegrain breads, cereals, pasta and rice for meals and snacks
- Avoid fatty fried and greasy foods
- Avoid highly salted foods and snacks
- Avoid sugary- sweet foods and snacks
- Avoid high sugar drinks such as cola and soft drinks
- Avoid drinks high in caffeine (e.g. coffee and cola)
- Avoid alcohol while pregnant (especially in the first trimester)
- Limit fruit juice drinks (high in sugar) to one glass per day
- Drink at least 8 glasses of liquid a day (including 4 to 6 glasses of plain water)

B. *Exercise:* In the management of Type 2 DM in non-pregnant condition, physical exercise is advocated. Very few studies or reports on the effects of physical activity for the prevention or treatment of gestational diabetes are available at present. Dempsey et al.; in a prospective study and in a case-control study showed that lean as well as overweight women who were physically active before and/or during pregnancy experienced statistically significant reduced risks of GDM (48% risk reduction). [5]

C. *Insulin treatment:* Insulin is started at a dosage of 0.7 units per kg per day (based on pre-pregnancy weight), given in divided doses. A commonly used dosing regimen includes two thirds of the total insulin dose to be given in the morning, with the remainder before dinner [6].

D. *Oral Anti-diabetic agents:* Traditionally insulin is considered as the gold standard for management of GDM. But it can be problematic for some women as it is expensive and invasive. For this a safe and effective oral agent for the treatment of gestational diabetes is highly desired. The sulfonylurea glyburide is close to meeting these goals, with prospective and retrospective studies [7].

2) New approaches in the management of gestational diabetes

The main elements of the therapy include education, nutritional therapy, exercise, and medical treatment. The recommended daily calorie intake is 30 kcal/kg for women with a BMI of 22-25, 24 kcal/kg for women with a BMI of 26-29, and 12-15 kcal/kg for women with a BMI of >30. The recommended diet composition contains 33%-40% complex carbohydrates, 35%-40% fat, and 20% protein. This calorie intake may turn 75%-80% of women with GDM into normal glycemic state. [8]

The pregnant women in whom blood glucose control cannot be achieved with exercise and diet regulation must be switched to insulin or oral anti-diabetics. There is also no consensus on when to initiate insulin therapy, which has been reported to reduce the risk of macrosomia and other complications during infancy. The use of oral anti-diabetics (OAD) during pregnancy is a relatively new practice. In a review of the literature regarding this topic, 12 randomized studies were evaluated, and the effects of the use of oral anti-diabetic agents was investigated on pregnant women with a known diabetes and those with impaired glucose tolerance in the current or previous pregnancy.

3) Major oral anti-diabetic agents

Biguanides: Metformin falls into this group. These agents enhances peripheral glucose uptake, inhibit gluconeogenesis and reduce plasma triglyceride concentrations [9]. Metformin can pass across the placenta. In a study that compared the use of insulin versus metformin during pregnancy, use of metformin did not result in an increase in perinatal complications, and it was even less prone to cause severe neonatal hypoglycemia and it resulted in lesser maternal weight gain and provided better patient compliance

Safety: Maternal: The average weight gain and pregnancy-induced hypertension rates in women after enrollment was significant lower in the metformin group than in insulin group in meta-analysis.

Fetal: Metformin has been shown to pass freely across the

placenta. Two in vivo studies measured maternal and cord blood samples in women taking metformin throughout pregnancy. In meta-analysis, the average birth weight of neonates was slightly lower in the metformin group as compared with the insulin group

Sulfonylureas: Glyburide (glibenclamide) and Glimepiride fall into this group. These drugs increase insulin secretion and peripheral sensitivity to insulin and decrease hepatic clearance of insulin. [10] Glyburide is a second generation oral sulfonylurea hypoglycemic agent. It acts by enhancing the release of insulin from the pancreatic beta cells, therefore for its action, some degree of pancreatic insulin-releasing function is required. It is well-absorbed following oral administration and is metabolized by the liver. The initial dose of glyburide is 2.5-5.0 mg once or twice a day with a maximum dose of 20 mg/day. The rate of maternal hypoglycemia in the women who received insulin was higher (20%) as compared to glyburide (4%) in one study.

Safety: Maternal: The rate of maternal hypoglycemia in the women who received insulin was higher (20%) as compared to glyburide (4%) in one study.

Fetal: The maternal-to-fetal transport of second generation sulfonylureas (glyburide) is significantly lower than the first-generation drugs (chlorpropamide and tolbutamide).In the randomized study of glyburide versus insulin in gestational diabetes, glyburide was not detected in the cord blood of any infant. In a meta-analysis (10 studies on 471 exposed women to sulfonylureas and biguanides in first trimester), no significant difference was found in the rate of major malformations or neonatal death among women with first-trimester exposure to oral anti-diabetic agents compared with non-exposed women.

- Note: These drugs aren't approved for gestational diabetes by the Food and Drug Administration.

2. Pre-eclampsia

A. Introduction

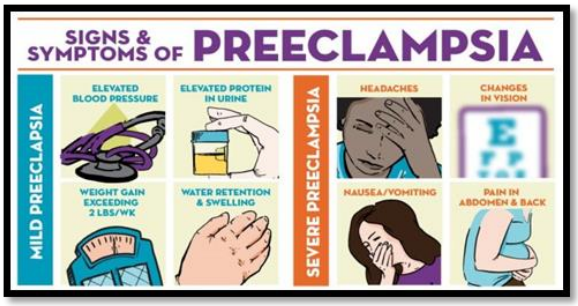

Fig. 4. Signs and symptoms of pre-eclampsia

Pre-eclampsia is a multisystem disorder of pregnancy that forms an integral part of the spectrum known as hypertensive diseases of pregnancy. The National High Blood Pressure Education Program (NHBPEP) Working Group [11] classifies hypertensive /diseases in pregnancy into 4 groups:

1) Gestational hypertension
2) Chronic hypertension
3) Pre-eclampsia/eclampsia
4) Superimposed pre-eclampsia (on chronic hypertension)

Definition: Pre-eclampsia can be defined as 'a blood pressure ≥140/90 mmHg after 20 weeks of gestation and involvement of one or more organ systems with previously normal blood pressure'.

B. Pathophysiologic concepts in Pre-eclampsia

The exact mechanism of pre-eclampsia is unclear. However, most current theories attribute pre-eclampsia to poor placental perfusion, secondary to abnormal placentation. In normal placentation, the trophoblast invades the myometrium and the spiral arteries of the uterus, destroying the tunica muscularis media. This renders the spiral arteries dilated and unable to constrict, providing the pregnancy with a high flow, low resistance circulation. In pre-eclampsia, the remodeling of spiral arteries is incomplete. A high resistance, low-flow uteroplacental circulation develops, as the constrictive muscular walls of the spiral arterioles are maintained. The resultant increase in blood pressure, combined with hypoxia and oxidative stress from inadequate uteroplacental perfusion, leads to a systemic inflammatory response and endothelial cell dysfunction (resulting in leaky blood vessels).

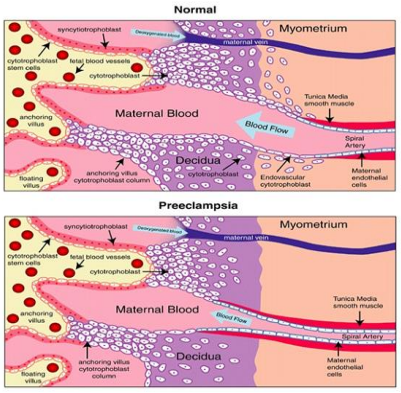

Fig. 5. Abnormal placentation in pre-eclampsia

New developments in prediction

An important focus for improving the antenatal management of pre-eclampsia is to develop accurate prediction models that identify women at high risk of disease. This would enable more appropriate targeting of prophylaxis from the first trimester as well as increased surveillance of those at high risk of disease. Lack of recognition of risk contributes to substandard care associated with maternal deaths. [12] Early administration of prophylactic aspirin in high-risk women prior to 16 weeks' gestation appears to reduce the risk of pre-eclampsia by 17%. Furthermore, there is an 8% relative risk reduction of preterm birth and a 14% reduction in fetal and neonatal death.

C. Risk Factors

The National Institute for Health and Care Excellence

(NICE) recommends a list of maternal risk factors that can be used to identify women at high risk for pre-eclampsia in whom aspirin should be started from 12 weeks' gestation. Strong risk factors include previous pre-eclampsia or hypertension in pregnancy, chronic kidney disease, chronic hypertension, diabetes (type 1 or 2), and autoimmune disorders such as systemic lupus erythematous or antiphosphospholipid syndrome. Women should also be advised to take aspirin if they have more than one of the following moderate risk factors: first pregnancy, age of 40 years or more, a pregnancy interval of greater than 10 years, body mass index of 35 kg/m^2 or more, family history of pre-eclampsia, and multiple pregnancies. [13]

Maternal Considerations

- Age < 20 or 35–40 years
- Nulliparity
- Prior or family history of PE or cardiovascular disease
- Woman born small for gestational age Medical conditions
- Obesity
- Chronic hypertension
- Chronic renal disease
- Diabetes mellitus (insulin resistance, type 1, and gestational)

D. Diagnostic criteria

Hypertension
- Measure 6 h apart on ≥2 occasions
- SBP >140 mmHg
- DBP ≥90 mmHg

Proteinuria
- ≥300 mg in a 24-h urine specimen

DBP: diastolic blood pressure; SBP: systolic blood pressure.
Source: References 1, 2.

E. Conservative management of pre-eclampsia

Risk of mortality decreases by reduction of severe hypertension. With the help of antihypertensive drugs peripheral resistance decreases and perfusion of uterus increases, which in turn help in decreasing fetal complications.

For systolic BP between 140-159 mmHg and diastolic BP 90-109 mmHg, oral labetalol is the drug of choice. Methyl dopa and nifedipine are safe alternatives. For systolic BP ≥ 160 mmHg and diastolic BP ≥ 110 mmHg, the choice of drug should depend upon experience with that particular agent.15 The preferred drugs include oral or intravenous labetalol, oral nifedipine (sublingual not recommended) and intravenous hydralazine (5-10 mg boluses every 20 min up to a cumulative dose of 30 mg). Cautious preloading with 500 ml Nifedipine

Calcium channel blocker. Peripheral oedema, dizziness, flushing, headache, constipation. crystalloid is recommended to avoid maternal hypotension. Labetalol is not suitable for asthmatics. Nifedipine may cause profound muscle weakness and maternal hypotension with fetal distress in patients receiving magnesium sulphate. Labetalol and nifedipine are better choices than hydralazine as recent evidences suggests. In all cases blood pressure should be monitored carefully along with fetal heart rate monitoring. In patients with pre-eclampsia and acute pulmonary edema, the preferred drug is glyceryltrinitrate as an intravenous infusion at the rate of 5µg/min which can be increased every 3-5 min to a maximum dose of 100µg/min.

F. Management

Table 2
Anti-hypertensive medication used in pregnancy

Medication:	Drug Class:	Common Side-Effects:
Labetalol (1st line)	Beta-blocker.	Postural hypotension, fatigue, headache, nausea and vomiting, epigastric pain.
Nifedipine	Calcium channel blocker.	Peripheral oedema, dizziness, flushing, headache, constipation.

Blood pressure

The NICE recommends keeping systolic blood pressure below 150 mmHg and diastolic blood pressure below 80–100 mmHg 7 and using labetalol as first-line treatment for hypertension over this threshold. The results of the Control of Hypertension in Pregnancy Study (CHIPS) were reported in 2016. This trial compared "tight" (target diastolic blood pressure of 85 mmHg) versus "less tight" (target diastolic blood

Table 3
Management strategies for chronic hypertension and gestational hypertension

	Preconception	**Antenatal**	**Delivery**	**Postpartum**	**Further follow-up**
Chronic Hypertension	Optimiseanti hypertensives, change ACE inhibitors, diet and lifestyle modification	Continue treatment to maintain BP <150/100. Offer uterine artery dopplers to detect risk of developing pre-eclampsia/IUGR	At 37 weeks, if BP is controlled.	Aim to maintain BP <140/90 with antihypertensives	Medical review at 6-8 weeks
Gestational Hypertension	Assessment of risk factors	Hospital admission if severe hypertension. Antihypertensive if BP >150/100. Test for proteinuria at each visit, blood tests as indicated	At 37 weeks, if BP <160/110,with/without antihypertensivs	Titrate antihypertensives to keep BP <140/90	Medical review at 6-8 weeks, or earlier if need to continue antihypertensives
Pre- eclampsia	Assessment of risk factors.	Hospital admission at diagnosis. Anti hypertensivesto be started if BP>150/100. Regular blood investigations (2-3/week)	Delivery between 34-37 weeks, depending on maternal/ foetal condition	Initial monitoring as inpatient, to be discharged to the community when BP <149/99 with/without treatment and blood results are stable	Medical review at 2 weeks, if continuing anti hypertensives. Otherwise at 6-8 weeks

pressure of 100 mmHg) control of hypertension in women with non-severe, non-proteinuric maternal hypertension at 14–33 weeks [14]. The results demonstrated that those with "tight" control achieved a lower blood pressure (by 5 mmHg) and there was no increase in adverse perinatal outcome (adjusted OR 0.98, 95% CI 0.74–1.3) and birth weight less than the tenth percentile (1.3, 0.93–1.8). However, there were reduced rates of severe maternal hypertension ($p<0.001$) with tighter control.

Oral antihypertensive

Traditionally, severe hypertension has been treated with short-acting parenteral antihypertensive agents, most frequently intravenous hydralazine or labetalol. This is because of the speed of onset of action but means that they require more intensive monitoring and can affect the fetus if large shifts in blood pressure occur. A systematic review showed that, in most women, nifedipine achieved treatment success similar to that of hydralazine or labetalol [15]. Less than 2% of women who received nifedipine experienced hypotension. There were no differences in adverse maternal or fetal outcomes. Thus, the authors suggest that oral nifedipine is a suitable treatment for severe hypertension in pregnancy and post-partum.

3. Conclusion

Gestational diabetes is a condition that complicates significant portion of the pregnancies and having significant consequences on the health status of the mother and the baby. It still remains unclear which treatment option would be more appropriate when the women with a known GDM or diabetes become pregnant. The use of oral anti-diabetic agents during pregnancy is a relatively recent matter of debate. The current reports suggest that metformin and glyburide could be used during pregnancy. Important evidence regarding the optimum methods of diagnosis and management of pre-eclampsia is still emerging. Until effective treatments are established, their biggest impact will remain in women presenting with suspected disease. Magnesium sulphate protects the preterm baby from neurological insults, and a low threshold for use in preterm pre-eclampsia is justified.

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