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CURRENT PRACTICES OF RISKS, PREVENTION & PHARMACOLOGICAL TREATMENT OF GESTATIONAL DIABETES MELLITUS

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Abstract

Based on the adverse pregnancy outcome study, new universal screening recommendations and cutoffs for gestational diabetes [GDM] have been proposed. In addition to the immediate perinatal risk,GDM carries an increased risk of metabolic disease in mother and child.

The negative impact of the gestational diabetes on the maternal and fetal health is well known and this impact is closely related to gestational age at which the diagnosis is made. Therefore, the use of therapeutic options able to prevent or delay the gestational diabetes occurrence has a positive impact on maternal and neonatal outcomes. Poorly controlled GDM results in maternal and fetal morbidity and mortality.Improved outcomes, therefore on early diagnosis and prevention of tight glycaemic control. While straightforward protocols exist for screening and management of diabetes mellitus in the general population, management of GDM remains controversial with conflicting guidelines and treatment protocols. This review highlights the prevention, detecting and management options for GDM in light of recent advances in care.

Introduction

Gestational Diabetes Mellitus [GDM] is defined as diabetes diagnosed in the second or third trimester pregnancy that was not clearly overt diabetes prior to gestation. Also known as carbohydrate intolerance of variable degree with onset recognition during pregnancy.[1]Gestational diabetes generally results in fewersymptoms;however it does increase the risk of pre- eclampsia, depression and requiring a caesarean section. Babies born to mothers with poorly treated gestational diabetes are at increased risk of being too large, having low blood sugar after birth, and jaundice. If un-treated it can also result of stillbirth. Long term, children are at higher risk of being overweight and developing type 2DM. Gestational Diabetes is caused by not enough insulin in the setting of insulin resistance.[2] Risk factors include being overweight, previously having gestational diabetes, a family history of type 2 diabetes, and having polycystic ovarian syndrome.[2]As per the International Diabetes Federation[IDF], Diabetes Atlas 2015, one in seven births are affected by GDMIndia,being the second dweller of diabetic, has become the ‘’diabetes capital of the world’’ hardening around four million women with GDM alone.IDF 2013 estimated a total of 21.4 million live births to be affected with hyper-glycaemia in pregnancy.[3]

Importance of screening for GDM

A pregnant woman diagnosed to have GDM is at an increased risk for developing type 2diabetes in the future. In addition, evidence is now emerging that women with past history of GDM also have prevalence of metabolic syndrome an cardiovascular diseases in comparison to those who had normal glucose tolerance during their

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antenatal period.[4]A recent study reported that GDM can be responsible for almost 19-30% of type2 diabetes mellitus among Saskatchewan first nation's residents in Canada[5] another study revealed that almost half of the proportion of diabetes [47.2%] in youth child bearing is increasing, thus creating a vicious cycle in which diabetes begets more diabetes.The vicious cycle influencing the prevalence of diabetes is well substantiated by the hypothesis "fetal origin of adult disease''. It status that glucose intolerance in continuum during pregnancy predisposes the offspring to a higher risk not only immediate complications such as macrosomia, hypoglycemia, jaundice, respiratory distress syndrome, polycythemia, and hypo-kalecemia but also for long-term complications such diabetes and hyperlipidemia in later life.[6]

If the child is a girl, there is an additional risk of her developing pre-gestational diabetes mellitus [pre-GDM] and GDM. Therefore, in view of the dramatic increase in obesity and diabetes targeting primary prevention strategies for diabetes in any community.Thus, well-timed screening of all pregnant women for glucose intolerance, early diagnosis, and prompt and adequate treatment during pregnancy worthwhile.[7]

Classification

The definition of GDM acknowledges the possibility that women may have previously undiagnosed diabetes mellitus, or may have developed-diabetes coincidentally with pregnancy. Whether symptoms subside after pregnancy is also irrelevant to the diagnosis. A woman is diagnosis with gestational diabetes when glucose intolerance continues beyond 24 -28 weeks of gestation.[8]The White classification, named after Priscilla White,who pioneered research on the effect of diabetes types on perinatal outcome, is widely used to assess maternal and fetal risk.It distinguishes between gestational diabetes [type A] and pre-gestational diabetes [diabetes that existed prior to pregnancy].[7]

The two subtypes of gestational diabetes are;

- Type A1: abnormal oral glucose tolerance test [OGTT], but normal blood glucose level during fasting and two hours after meals; diet modification is sufficient to control glucose levels.
- Type A2: abnormal OGTT compounded by abnormal glucose levels during fasting and/or after meals; additional therapy with insulin or other medications is required

Diabetes which existed prior to pregnancy is also split into several subtypes,

- Type B: onset at age 20 or older and duration of less than 10 years.
- Type C: onset at age 10-19 or duration of 10-19 years.
- Type D: onset before age 10 or duration greater than 20 years.
- Type E: overt diabetes mellitus with calcified pelvic vessels.
- Type F: diabetic nephropathy.
- Type R: proliferative retinopathy.
- Type RF: retinopathy and nephropathy.
- Type H: ischemic heart disease.
- Type T: prior kidney transplant.[9]

Risk factors

- Marked obesity.
- Polycystic ovary syndrome.
- A previous diagnosis of gestational diabetes or pre-diabetes, impaired glucose tolerance, or impaired fasting glycaemia
- A family history, revealing a first-degree relative with type 2 diabetes.
- Maternal age – a women's risk factor increases as she gets older [especially for women over 35 years of age].
- A previous pregnancy which resulted in a child with a macrosomia.
- Ethnicity [higher risks include African-Americans, Afro-Caribbean, Native Americans, Hispanics, Pacific Islanders, and also people originating from South Asia.
- High risk in smokers.

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- Other genetic risk factors: There are at least 10 genes where certain polymorphism is associated with an increased risk of gestational diabetes, most notably TCF7L2.[8]

Complication

- GDM poses a risk to mother and child. This risk is largely related to uncontrolled high blood glucose levels and its consequences.
- Two main risks on baby are growth abnormalities and chemical imbalances after birth.[2]
- Infants born to mothers with GDM are at risk of being both large for gestational age [macrocosmic] in unmanaged GDM and small for gestational age and intrauterine growth retardation in managed GDM.
- Shoulder dystocia risk increases during instrumental deliveries or during vaginal delivery
- Hypoglycemia,
- Jaundice,
- Polycythemia,
- Hypocalcaemia,
- Hypomagnesaemia
- Dysmature babies prone to respiratory distress syndrome,
- GDM has a higher risk of preeclampsia and also have risk factors for birth defects.[9]

Diagnosis

The test includes,

- Fasting glucose test
- Postprandial glucose test
- Random glucose test
- Screening glucose challenge test
- Oral glucose tolerance test [OGTT]
- Urinary glucose testing.[10]

Prevention

China is a country with a high burden of diabetes, and the age at onset of T2DM among women is decreasing. Furthermore, women of reproductive age usually do not receive regular physical examination or know their blood glucose levels. Studies have shown that hyperglycemia during organogenesis can markedly increase the risk of spontaneous abortions and congenital anomalies, while satisfactory glycemic control could reduce these risks.[11] Thus, all women, especially women with diabetes, impaired glucose tolerance, impaired fasting glucose, and a history of GDM need to plan for pregnancy and seek pre-pregnancy counseling early.[1]

Women with diabetes who are planning pregnancy and those using insulin should control their hemoglobin A1C (HbA1c) levels at <6.5% and <7.0%, respectively, to prevent hyperglycemia.[13]

- You can't prevent gestational diabetes. Lifestyle changes may help reduce your risk.
- Gestational diabetes resolves after pregnancy, but it may increase your risk for developing type 2 diabetes later in life.
- It's important to treat gestational diabetes. It can cause complications for you and your baby.[1]

Pharmacological treatment

Non pharmacological treatment

Caloric intake

The cornerstone of management of the GDM pregnancy is medical nutrition therapy. There is broad consensus that the goals of such therapy are to allow appropriate weight gain based on the mother's pre-pregnancy and prenatal weight, along with normal glycemic and absence of urine ketones. However, the degree of caloric restriction is not agreed upon. Short-term examination of energy restriction demonstrated that severe, i.e., 50%, energy restriction was associated with ketonemia and ketouria even as glucose and insulin levels declinedwhereas more moderate energy restriction, i.e., 1600–1800 kcal/day was not associated with ketonemia.[14]

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Longer-term studies of energy restriction were not powered to evaluate effects on birthweight, although the rate of fetal growth, need for insulin, and amount of insulin eventually needed for some women were reduced When obese women consume at least 25 kcal/kg/day, ketosis and intrauterine growth retardation do not occur.[15]

The composition of the calories to be consumed is controversial. In one study, low carbohydrate diets were associated with fewer macrocosmic infants, cesarean deliveries, and pharmacotherapy.[16]

Physical activity

Physical activity may improve glucose tolerance by improving insulin sensitivity involving muscle glucose uptake and glycogen synthesis and therefore physical activity is a logical adjunct to dietary therapy. Historically, this potential benefit has been outweighed by the concern that exercise could theoretically lead to an increase in secretion of insulin, free fatty acids, and ketones, with a concomitant decrease in glucose levels.[18]

However, several small studies that demonstrate the safety of exercise during pregnancy and the association with either better cardiorespiratory fitness or mean glucose values.[19]

General guidelines encourage at least 30 minutes of physical activity on several days a week, or the equivalent.More tailored activity based on women's fitness and pre-pregnancy physical activity levels might be more effective at addressing glucose and weight targets in individual women, although the study addressing this question is yet to be conducted.[17]

Fetal monitoring

Although specific antepartum assessment techniques are not specifically endorsed by ACOG and other organizations, their use in clinical practice is routine. The most commonly used test is the twice-weekly non-stress test, which consists of continuous external fetal heart rate monitoring and evaluation of amniotic fluid volume.[18]In GDM pregnancies that are managed without pharmacotherapy and are norm glycemic, such testing commonly begins at approximately 37 weeks, and in more complicated GDM pregnancies, testing commonly begins at approximately 32 weeks. Intervention in the form of induction can then occur if indicated.[19]

Fetal ultrasonography is generally performed for assessment of fetal growth, as well as for detection of anomalies. The first ultrasound usually occurs at diagnosis of GDM.Thereafter, it may occur as often as every three weeks, particularly in the presence of comorbidities that can also affect fetal growth such as hypertension, but the timing and frequency are controversial.[17]

Labor management

Timing of induction of labor in women with GDM, with its mixture of risk and benefits. Risks include cesarean section with its attendant complications, and benefits include decreased fetal growth, dystocia, and stillbirth. Currently, women with GDM are monitored closely for excess fetal growth, and induction is usually recommended when women exceed those parameters, with fairly low thresholds to induce or after 40 weeks.[21]

During induced and spontaneous labor, insulin requirements generally increase due to the work of the uterus. However, women may still require continuous insulin, particularly if they required pharmacotherapy during the pregnancy.[22]In these women, glucose is monitored continuously or at least every two hours, and insulin infusions are started when the woman is mildly hyperglycemic at 120 mg/dl.[20]

As with insulin use during pregnancy, insulin and glucose management during labor are based primarily on trials of women with preconception diabetes.[22]

Dietary therapy

The aim is to achieve normoglycemia whilst providing the required nutrients for normal fetal growth and maternal health. A secondary aim is to prevent excessive maternal weight gain, particularly in women who are overweight or have gained excess weight in pregnancy.[23]

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There are few trials examining the efficacy of dietary therapy for GDM, However, a cluster randomized controlled study has provided support for Medical Nutrition Therapy (MNT) for GDM, as recommended by the American Diabetes Association (ADA) (2004). In this study, 215 women with GDM were seen at sites randomized to deliver either MNT or standard care.[23]

For obese women, a 30%–33% calorie restriction to approximately 25 kcal/kg actual weight per day is recommended. Carbohydrate should be restricted to 35%–40% of calories.[24]

Pharmacological treatment

If women cannot achieve glycemic goals with the strategies outlined above, pharmacotherapy with insulin is recommended. The mainstay of pharmacotherapy during pregnancy has been neutral protamine Haledon insulin for basal injections 2–4 times daily. Continuous insulin infusion of a rapid-acting insulin analog, such as bistro and aspart, are sometimes used instead if patients are able to check their blood glucose levels and glucose monitoring devices frequently.[18]

Insulin may be administered according to the woman's pattern of glucose administration. If the fasting glucose is elevated in the morning, evening neutral protamine Haledon insulin can be used, at a typical starting dose of 0.2 units/kg body weight. If post-prandial glucoses are elevated, short-acting insulin at doses of 1.5 units per 10 g per carbohydrate per breakfast and 1.0 unit per 10 g per carbohydrate per lunch and dinner can be used.[19]

If both pre- and postprandial glucoses are elevated, four injections per day can be used at 0.9–1.0 units/kg. Insulin can be divided into 50% neutral protamine Haledon insulin and 50% as three pre-prandial rapid-acting injections.[23]These regimens are largely adapted from those used in women with preconception diabetes during pregnancy.[20]

Insulin

Insulin therapy is the most commonly used pharmacotherapy once MNT fails to achieve desired outcomes. Insulin regimens often include intermediate-acting insulin such as ecophene and short-acting agents such as regular recombinant insulin (Hamelin R). Pharmacotherapy can also involve the insulin analogues as part and bistro.[25]

Insulin therapy decreases the frequency of fetal macrosomia and the risk of perinatal morbidity. Positive history of diabetes mellitus in a first-degree relative and multiple abnormal values in the OGTT were strongly found to predict the need for insulin management in women with GDM.[25]

Insulin analogues bistro and as part have been widely studied and found to be clinically effective with minimal transfer across the placenta; these agents have similar safety profiles to human insulin, Because the insulin analogues have shorter durations of action and more rapid onsets of action than regular insulin, they are associated with improved postprandial glycemic control and less postprandial hypo-glycemic glucose values.[27]

Table 1.Glucose level cut-off points requiring insulin initiation in gestational diabetes mellitus.[27]

Guideline	Fastingmg/dl [mmol/l])	1-h postprandial (mg/dl [mmol/l])	2-h postprandial (mg/dl [mmol/l])
ACOG(22)	>95 (5.3)	>130-140 (7.2-7.8)	>120 (6.7)
ADA(15)	>90-99 (5.0-5.5)	>140 (7.8)	>120-127 (6.7-7.1)

ACOG = American College of Obstetrics and Gynecology, ADA = American Diabetes Association

Oral hypo-glycemic

Oral hypoglycemic agents used in the management of GDM should be both effective and safe for the woman and developing fetus. With the exception of glyburide and metformin, oral hypoglycemic drugs are generally not

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recommended due to concerns about potential teratogenicity or prolonged neonatal hypo-glycaemia from drug transport across the placenta.[28]

Glyburide

Glyburide, one of the two oral hypo-glycemic drugs used for the management of GDM, acts primarily to enhance insulin secretion by the pancreas. It can be used as an alternative for women who are unable or unwilling to take insulin or, in some cases, as a first-line pharmacological therapy. Studies have shown that glyburide, unlike other sulphonylureas, does not cross the placenta in vivo or in vitro.[27]

Studies examining the use of glyburide and insulin for the management of GDM have found comparative maternal and neonatal outcomes. Regarding glyburide therapy, certain factors are associated with higher rates of success, including initiation after 30 weeks gestation or fasting blood glucose levels <110 mg/dl and 1-h postprandial glucose levels <140 mg/dl. Despite several studies supporting the efficacy and safety of glyburide for women with GDM, ACOG and ADA guidelines do not recommend its use until larger randomized controlled trials are completed on the subject. However, a survey conducted by ACOG found that up to 13 % of American fellows prescribe glyburide as a first-line pharmacological agent in women with GDM.[27]

Glucose monitoring

In patients requiring insulin, the ideal frequency for glucose monitoring has not been established. In common practice, the patient generally checks glucose levels four times a day once upon waking in the morning, before meals, before bed and one or two hours post-prandial to ensure adequate glycemic control. Postprandial glucose levels are preferable to fasting glucose levels, because they are more strongly associated with macrosomiaInsulin dose adjustments based on postprandial glucose levels rather than pre-prandial levels were shown to be associated with improvement in glycemic control and reduction of both maternal and fetal adverse outcomes.[15]

Intra-partum management

During labor, women on pharmacological therapy require hourly evaluations of their glucose values, while those with diet-controlled GDM do not require active glucose management. Patients on insulin usually have normal levels of glucose at the time of labor and also do not need active management.[29]

Delivery

There is no definitive data on the timing and mode of delivery for pregnant women with GDM. If the patient has normal or near normal glucose values, it is recommended that she should deliver at term. The general recommendation is that pregnancies complicated by GDM should not extend beyond the term. Elective cesarean section has not been associated with significant reduction of birth trauma and has not been found to be cost effective. Earlier delivery was associated with a reduction of macrosomia but not with reduction of other neonatal complications.[27]

Postpartum management

After delivery, insulin resistance usually resolves quickly, as does the need for pharmacological management.[26] However, approximately 40–60 % of affected women will develop type 2 DM later in life. They are also at an increased risk of recurrent GDM that presents earlier in future pregnancies. In these women, regular screening for type 2 DM is strongly encouraged, beginning at 6 weeks post-delivery and annually thereafter. An OGTT should be performed postpartum, 1 year post-delivery, and every 3 years thereafter.[27]

Inositol

Inositol is a xylitol naturally present in animal and plant cells, either in its free form or as a bound-component of phospholipids or inositol derivatives. It plays an important role in various cellular processes as the structural basis for secondary messengers in eukaryotic cells.[29]

It exists under nine stereo isomeric forms depending on the spatial orientation of its six hydroxyl groups. Myo-inositol (MI) is the predominant isomeric form and is considered to belong to the vitamin B family. The conversion

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of MI in d-chiroinositol (DCI) can occur in tissues expressing the specific epimerize. Pak et al. Measured a conversion rate of MI to DCI of about 7.6% in rat blood and 8.8% in rat muscle and liver.[30]

Conclusion

Evidence shows that packages of care are effective in reducing the risk of most adverse perinatal outcomes. However, trials often include few women, are poorly reported with unclear or high risk of bias and report few outcomes. The contribution of each treatment within the packages of care remains unclear. Large well-designed and well-conducted trials are urgently needed.[30]

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