REVIEW

Changing trends in management of gestational diabetes mellitus

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Abstract

Gestational diabetes mellitus (GDM) is on the rise globally. In view of the increasing prevalence of GDM and fetal and neonatal complications associated with it, there is a splurge of research in this field and management of GDM is undergoing a sea change. Trends are changing in prevention, screening, diagnosis, treatment and future follow up. There is emerging evidence regarding use of moderate exercise, probiotics and vitamin D in the prevention of GDM. Regarding treatment, newer insulin analogs like aspart, lispro and detemir are associated with better glycemic control than older insulins. Continuous glucose monitoring systems and continuous subcutaneous insulin systems may play a role in those who require higher doses of insulin for sugar control. Evidence exists that favors metformin as a safer alternative to insulin in view of good glycemic control and better perinatal outcomes. As the risk of developing GDM in subsequent pregnancies and also the risk of overt diabetes in later life is high, regular assessment of these women is required in future. Lifestyle interventions or metformin should be offered to women with a history of GDM who develop pre-diabetes. Further studies are required in the field of prevention of GDM for optimizing obstetric outcome.

Key words: Gestational diabetes mellitus; Prevention; Vitamin D; Probiotic; Insulin analogs; Oral hypoglycemic agents

Core tip: To summarize, the use of probiotics and vitamin D supplementation may help in preventing gestational diabetes mellitus (GDM) in high risk women. Glycemic targets need to be lower than current recommendations. Oral hypoglycemic agents are an effective and safe alternative to insulin in managing GDM. Newer insulins, aspart, lispro and detemir, provide better glycemic control than routinely used insulin. Continuous glucose monitoring systems and insulin pumps may be of use in women who require a very high dose of insulin. Lifestyle interventions in GDM women help to reduce the subsequent development of diabetes. Further studies are required in the field of prevention of GDM for optimizing obstetric outcome.

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INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance of variable degrees with onset or first recognition during pregnancy. The prevalence of gestational diabetes mellitus is increasing globally. In the United States, up to 14% of pregnancies are complicated by GDM, accounting for 200000 cases annually[1]. The prevalence of GDM in Canada is 8%-18%[2] and in China it varies between 6.8% and 10.4%[3]. In India, there is an exceptionally high estimated prevalence of GDM (27.5%) when compared to 9.9% in Sri Lanka and 9.8% in Bangladesh[4]. Recently, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommended new screening criteria for GDM based on the hyperglycemia and adverse pregnancy outcomes (HAPO) study. Based on these criteria, the total incidence of GDM reaches almost 15%-20%[5].

The offspring of a diabetic mother is at increased risk for fetal, neonatal and long term morbidities. They are at higher risks of developing macrosomia and stillbirths. Macrosomia is the most common morbidity, occurring in 15%-45% of infants, leading to shoulder dystocia and trauma during delivery[6-8]. Hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, hypocalcemia, polycythemia and hypertrophic cardio-myopathy are complications expected in the immediate postnatal period. They are also at increased risk of developing diabetes, obesity and metabolic syndrome in childhood and adult life[9]. The magnitude of fetal and neonatal risks is proportional to the severity of maternal hyperglycemia.

With this background of increasing prevalence of GDM worldwide and its established association with adverse fetal, neonatal and their long term complications, we need to look into available options for preventing and managing GDM.

PREVENTION OF GDM

High risk groups for development of GDM are those with a high body mass index (BMI) (BMI cutoff of 30 kg/m^2 in non-Hispanic whites, 26 kg/m^2 in African Americans, 25 kg/m^2 in Chinese and 24 kg/m^2 in South Asians)[10], history of diabetes in a first degree relative, previous macrosomic infant, history of GDM in previous pregnancies and women belonging to the ethnic origin of Asia, the Caribbean and Arabia, particularly of the Middle East. Much research is underway in the field of prevention of GDM. Various modalities like exercise and diet have been found to be useful for prevention of GDM in high risk groups. More recently, probiotics and vitamin D are being studied for the same. The effectiveness of the preventive modalities in pre-pregnant and pregnant women are detailed below.

Diet

Dietary fiber and glycemic index of food: Less dietary fiber intake has been associated positively with GDM. Intake of dietary fiber, in particular cereal and fruit fiber, were strongly and inversely associated with GDM risk. Each 10 g/d increment in total fiber intake was associated with a 26% reduction in risk; each 5 g/d increment in cereal fiber and fruit fiber was associated with 23% and 26% reduction in GDM risk, respectively. Increased dietary fiber intake leads to decreased appetite and thus lowers total energy intake. It also delays gastric emptying and slows glucose absorption, resulting in less absorption of glucose leading to glucose homeostasis and less increase in insulin levels[11].

Both dietary glycemic index and glycemic load have an influence on postprandial glycemia. The combination of high glycemic load and low cereal fiber diet was associated with a 2.15 fold increased risk compared with the low glycemic index and high cereal fiber diet[11]. These findings suggest that the pre-pregnancy diet pattern might be associated with women's GDM risk. In particular, diet with low fiber and high glycemic load was associated with an increased risk.

Western diet pattern: A study was conducted comparing the Western pattern and the prudent dietary pattern. The prudent dietary pattern includes high intake of poultry, fish, fruit and green leafy vegetables. The Western pattern includes high intake of red meat, processed meat, French fries, pizza, refined grain products and sweets. There were strong positive associations between the Western dietary pattern and GDM, whereas the prudent dietary pattern was significantly and inversely associated with GDM[12].

Pre-pregnancy intakes of red and processed meats were both significantly and positively associated with GDM risk[12]. It might be related to the presence of saturated fat and cholesterol content in red and processed meats affecting insulin sensitivity[13].

Exercise

Physical activity was not encouraged during pregnancy due to the fear of adverse effect on the fetus and mother, but various studies show no adverse maternal and fetal effects on women engaged in mild and moderate physical activities[14,15].

Daily stair climbing, when compared with no stair climbing, was associated with a 49%-78% reduction in GDM risk ($P < 0.011$). The amount of hours spent in recreational physical activity during the year before the index pregnancy was associated with statistically significant reductions in the incidence of GDM, but the greatest reduction in risk was observed in women who engaged in physical activity before and during pregnancy (OR = 0.40; 95%CI: 0.23-0.68)[16]. A

study conducted among Hispanic women by Chasan-Taber et al[17] also showed that exercise reduces the incidence of GDM. Vigorous physical activity before pregnancy and continuation of physical activity in early pregnancy may reduce a woman's risk for developing GDM[18]. In the absence of either medical or obstetric complications, moderate exercise for ≥ 30 min/d on most of the day of the week is recommended for a pregnant woman[19].

Pre-pregnancy BMI and GDM

Pre-pregnancy BMI has significant influence on GDM. Compared to women with a normal BMI, the odds ratio of an underweight woman developing GDM was 0.75 (95%CI: 0.69-0.82). The odds ratio of overweight, moderately obese and morbidly obese women to develop GDM were 1.97 (95%CI: 1.77-2.19), 3.01 (95%CI: 2.34-3.87) and 5.55 (95%CI: 4.27-7.21) respectively[20]. The risk of GDM is positively associated with pre-pregnancy BMI. This information is important when counseling women planning for a pregnancy.

Another parameter which is as important as pre-pregnancy weight is an acceptable weight gain during pregnancy. Guidelines for weight gain during pregnancy were released by the Institute of Medicine in 2009. These guidelines are based on pre-pregnancy BMI. Those who have a normal BMI between 18.5-24.9 kg/m² should aim for a weight gain of 25-35 lb (11-15 kg) and those who are underweight with BMI < 18.5 kg/m² should aim for 28-40 lb (12-18 kg) weight gain during pregnancy. Those who are overweight with a pre-pregnancy BMI between 26 and 29.9 kg/m² should aim for a weight gain of 15-25 lb (6.8-11.4 kg). Those who are obese with a pre-pregnancy BMI of ≥ 30 kg/m² should aim for 11-20 lb (5-9 kg) weight gain[21]. In women who have excessive weight gain in the first trimester, there is increased risk of development of GDM[22,23]. Counseling regarding acceptable weight gain in pregnancy is also required during the pre-pregnancy period.

Probiotics

Numerous studies show that probiotics can reduce the incidence of GDM. A systematic review by Lindsay et al[24] demonstrated that probiotic use in pregnancy could significantly reduce maternal fasting glucose levels. Also, there is a significant decrease in the incidence of GDM and pre-eclampsia rates. By supplementing the gut bacteria, they change the metabolism in individuals and help to prevent GDM. Among the list of various organisms, Lactobacillus rhamnosus and Bifidobacterium lactis are found to have an anti-diabetic effect[25]. A randomized controlled trial was conducted in 256 pregnant women randomized to receive probiotics or placebo. Probiotics given in that study were Lactobacillus rhamnosus GG (10^{10} colony forming units) and Bifidobacterium lactis Bb12 (10^{10} colony forming units). Significantly reduced plasma glucose ($P = 0.025$) and improved insulin sensitivity ($P = 0.028$) were

observed in the diet/probiotic group[26]. In yet another study, daily intake of Lactobacillus rhamnosus GG (10^{10} colony forming units) and Bifidobacterium lactis Bb12 (10^{10} colony forming units) reduced GDM frequency in the diet/probiotic group (13%) compared to the diet/placebo (36%) and control/placebo (34%) groups ($P = 0.03$)[27]. There were no adverse events in mothers or children who took probiotics during pregnancy. No significant difference in prenatal or postnatal growth rates among the study groups was detected. This shows that probiotics are a safe and cost-effective tool in preventing GDM.

The Cochrane review also states that the use of probiotics is associated with a reduction in the rate of GDM (relative risk 0.38). There was also a reduction in the birth weight of infants of women who were supplemented with probiotics[28]. All this evidence suggests that daily intake of probiotic capsules with Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12 with 10^{10} colony forming units may be effective in pregnant women who are at high risk for GDM.

SPRING, a multicenter randomized control trial of a high-risk group of overweight and obese pregnant women, is being conducted which will provide a clear idea about the usage of probiotics in preventing GDM in that group[29].

Various studies support the beneficial relationship between fermented dairy products and a reduced risk of diabetes[30-32]. An observational study conducted in > 6500 individuals found that yogurt consumers had reduced levels of glucose and insulin resistance compared with non-consumers[33]. A study shows a daily consumption of 200 mL of a shake containing Lactobacillus acidophilus (4×10^8 CFU/100 mL) and Bifidobacterium bifidum (4×10^8 CFU/100 mL) resulted in a blood glucose reduction in type 2 diabetes individuals[34]. It has also been shown that consumption of yogurt containing Lactobacillus acidophilus and Bifidobacterium lactis for a duration of 6 wk by type 2 diabetes individuals resulted in reduced fasting glucose, reduced glycosylated hemoglobin (HbA1c) levels and higher activity of superoxide dismutase and glutathione peroxidase when compared to a control group[35].

Probiotic food supplements are available from many sources but effectiveness is dependent on various factors like temperature, anaerobic storage conditions, the initial dose of the strain and its quality. It is not known to what extent these food sources alter the gut microbes and thereby have biological effects outside research settings.

Vitamin D

All over the world, there is a high prevalence of vitamin D deficiency irrespective of age. A study done in United States adults showed that the overall prevalence rate of vitamin D deficiency was 41.6%[36]. Vitamin D deficiency is known to cause musculoskeletal problems. Apart from that, it is associated with various cardiovascular

problems like myocardial dysfunction, heart failure and sudden cardiac deaths. Its deficiency also leads to respiratory problems, autoimmune diseases, certain cancers, hypertension and diabetes mellitus[37]. Various studies have shown that there is an increased prevalence of pre-eclampsia[38], gestational diabetes[39,40], preterm labor[41] and intrauterine growth restriction[42] in pregnant women with vitamin D deficiency. Supplementation of vitamin D during pregnancy may reduce these complications. Safe dosage of vitamin D in pregnancy has been studied. A dose of 4000 IU/d or 50000 IU every 2 wk was able to raise serum 25-hydroxyvitamin D levels to > 30 ng/mL, leading to a decrease in insulin resistance[43]. This dosage is associated with reduction in pregnancy complications without producing toxicity but, as there is insufficient evidence supporting a vitamin D role in GDM, the Cochrane database has concluded that more randomized trials are required to evaluate its role in pregnancy[44]. Results in a European multicenter study of vitamin D and lifestyle interventions are awaited, which may throw light on our dilemma about the role of vitamin D in the prevention of GDM[45].

DIAGNOSIS OF GDM

There is a dilemma whether to perform selective screening or universal screening for GDM in pregnant women. By screening only the high risk population, up to 30% of GDM women may be missed. In areas where the incidence of GDM is < 3%, selective screening in a high risk population is acceptable, but where the prevalence of GDM is > 3%, universal screening may be considered[46].

Diagnostic criteria

Various criteria are being utilized worldwide for diagnosing GDM.

American College of Obstetricians and Gyne-cologists (ACOG): It recommends a 1 h glucose challenge test for screening GDM. If plasma glucose value is $\geqslant$ 140 mg/dL, a 3 h 100 g oral glucose tolerance test (OGTT) should be performed for diagnosis. Carpenter Coustan criteria are used for diagnosing GDM. Abnormal values are as follows: Fasting plasma glucose (FPG) $\geqslant$ 5.3 mmol/L (95 mg/dL); 1 h $\geqslant$ 10 mmol/L (180 mg/dL); 2 h $\geqslant$ 8.6 mmol/L (155 mg/dL); 3 h $\geqslant$ 7.8 mmol/L (140 mg/dL). GDM is diagnosed with $\geqslant$ 2 abnormal values.

World Health Organization (WHO) 1999: (2 h 75 g OGTT). Fasting plasma glucose FPG $\geqslant$ 6.9 mmol/L (125 mg/dL); 2 h $\geqslant$ 7.8 mmol/L (140 mg/dL).

Australasian Diabetes in Pregnancy Society (ADIPS) 1991 Criteria: (2 h 75 g OGTT). FPG $\geqslant$ 5.5 mmol/L (100 mg/dL); 2-h $\geqslant$ 8.0 mmol/L (144 mg/dL).

Diabetes in Pregnancy Study Group India dia-

gnostic criterion: Seventy-five gram oral glucose load is performed irrespective of the last meal and blood sugar level is taken 2 h later. A value of $\geqslant$ 7.8 mmol/L (140 mg/dL) is diagnosed as GDM. This may be of use in limited resource settings and where patient compliance is doubtful.

International Association of Diabetes and Pregnancy Study Groups two-phase strategy for the detection of hyperglycemia in pregnancy

HAPO, a multicenter study, was done in a cohort of 25505 pregnant women. Participants were tested with 2 h, 75 g OGTT and their pregnancies were followed for adverse maternal and neonatal outcomes[47]. Based on the study results, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) consensus panel formulated the new diagnostic criteria for GDM[48]. The cut-off points were derived based on infant birth weight, cord blood C-peptide and neonatal body fat composition.

At the first antenatal visit: Screening is done with either FPG, HbA1c or random plasma glucose. Based on the prevalence of GDM in the locality, either all women or only high-risk women are screened. (1) GDM is diagnosed if FPG is between 5.1 and 7.0 mmol/L (92 to 126 mg/dL). A diagnosis of overt diabetes is made with one of the following values; (2) FPG $\geqslant$ 7.0 mmol/L (126 mg/dL); (3) HbA1c $\geqslant$ 6.5%; and (4) RPG $\geqslant$ 11.1 mmol/L (200 mg/dL), then confirm with FPG or HbA1c.

At 24-28 wk gestation: In all women previously not found to have GDM/overt DM, 2 h 75 g OGTT is done. If FPG $\geqslant$ 7.0 mmol/L (126 mg/dL), overt diabetes is diagnosed. GDM was diagnosed with $\geqslant$ one abnormal values: (1) FPG $\geqslant$ 5.1 mmol/L (92 mg/dL); (2) 1-h $\geqslant$ 10 mmol/L (180 mg/dL); and (3) 2-h $\geqslant$ 8.5 mmol/L (153 mg/dL).

Australasian Diabetes in Pregnancy Society (ADIPS) criteria 2013: It also recommends the same cut-off points suggested by IADPSG. A diagnosis of GDM is made if $\geqslant$ 1 of the following glucose levels is elevated: (1) FPG $\geqslant$ 5.1 mmol/L; (2) 1-h $\geqslant$ 10.0 mmol/L; and (3) 2-h $\geqslant$ 8.5 mmol/L.

Unlike IADPSG, ADIPS does not recommend the use of the term "overt diabetes" to describe marked hyperglycemia first detected during pregnancy. Glucose intolerance of any severity with onset or first recognition during pregnancy is labelled as GDM by this guideline.

WHO 2013 recommendations[49]

In the interest of moving towards a universal standard recommendation for the diagnosis of GDM, the WHO guideline development group has decided to accept the IADPSG criteria rather than introduce another set of arbitrary cut-off values.

The difference from IADPSG guidelines is that these new WHO guidelines provide a range of plasma

glucose levels to distinguish diabetes in pregnancy and GDM. Likewise, instead of using the terminology "overt diabetes", WHO uses "diabetes mellitus in pregnancy".

For diagnosing diabetes mellitus in pregnancy, WHO recommends its 2006 criteria.

Diabetes is diagnosed if one or more of the following criteria are met: (1) FPG $\geq$ 7.0 mmol/L (126 mg/dL); (2) 2 h plasma glucose $\geq$ 11.1 mmol/L (200 mg/dL) following a 75 g oral glucose load; and (3) Random plasma glucose $\geq$ 11.1 mmol/L (200 mg/dL).

Gestational diabetes mellitus should be diagnosed at any time during pregnancy based on any one of the following values: (1) Fasting plasma glucose = 5.1-6.9 mmol/L (92-125 mg/dL); (2) 1 h post 75 g oral glucose load $\geq$ 10.0 mmol/L (180 mg/dL) (there are no established criteria for the diagnosis of diabetes based on the 1 h post-load value); (3) 2 h post 75 g oral glucose load between 8.5-11.0 mmol/L (153-199 mg/dL).

As IADPSG guidelines use only one abnormal value to diagnose GDM, its prevalence is expected to significantly increase from 5%-6% to 15%-20%.

American Diabetes Association

The American Diabetes Association (ADA) also recommends these IADPSG cut-off points in its 2011 position statement. Although ADA recognizes that with these cut-off points there would be a significant increase in the incidence of GDM, it recommends these changes with the intention of optimizing gestational outcomes for women and their babies[5].

Falavigna et al[50] compared IADPSG criteria with WHO 1999 criteria. The IADPSG criteria gave better results than the WHO 1999 criteria. The adoption of the IADPSG criteria instead of the WHO criteria would reduce the incidence of LGA births by 0.32% ($P < 0.001$) and of pre-eclampsia by 0.12% ($P = 0.007$).

Other evidence also suggests that adopting IADPSG criteria may be more cost effective[51,52].

As IADPSG diagnostic criteria are based on prognostic accuracy (the risk of pregnant women developing an adverse outcome in a certain period of time), these guidelines appear to be more logical and can be adopted worldwide.

MicroRNA profiling in preventing GDM

Now there is emerging evidence that the use of microRNAs (miRNAs) is useful in predicting GDM. It has been generally assumed that most genetic information is transacted by proteins, but recent evidence suggests that the majority of the genomes of mammals and other complex organisms are in fact transcribed into non coding RNAs (ncRNAs), many of which are alternatively spliced and/or processed into smaller products. These ncRNAs include miRNAs, snoRNAs and many others. They contain internal signals that control various levels of gene expression in physiology and development[53]. The miRNAs have recently been demonstrated to

abundantly and stably exist in serum and to be potentially disease-specific. Specifically, miRNAs are required for pancreatic development and the regulation of glucose stimulated insulin secretion[54,55]. Serum miRNAs are differentially expressed between GDM women and controls and could be candidate biomarkers for predicting GDM. Particularly, the use of miR-29a, miR-222 and miR-132 as serum-based biomarkers in early second trimester (16-19 wk) has been shown to be effective, which warrants further evaluation and optimization[56].

TREATMENT FOR GDM

There is a greater dilemma whether it is worth treating mild cases of GDM if the outcome does not change much. The Cochrane review states that there are various benefits of diagnosing and treating mild GDM cases. There is a reduction in the proportion of infants weighing more than 4000 g (RR = 0.46, 95%CI: 0.34-0.63) and the proportion of infants weighing greater than the 90th birth centile (RR = 0.55, 95%CI: 0.30-0.99) in mothers receiving specific treatment for GDM compared to those not receiving specific treatment. Perinatal morbidity (shoulder dystocia, bone fracture, nerve palsy and death) was significantly reduced in women receiving intensive treatment for mild GDM compared to routine antenatal care (RR = 0.32, 95%CI: 0.14-0.73)[57].

Glycemic targets during pregnancy

Glycemic targets as recommended by the fifth international workshop conference on GDM[58] are capillary glucose concentrations of: (1) Pre-prandial: $\leq$ 5.3 mmol/L (96 mg/dL); (2) 1 h post meal: $\leq$ 7.8 mmol/L (140 mg/dL); and (3) 2 h post meal: $\leq$ 6.7 mmol/L (120 mg/dL).

In the metformin in gestational diabetes (MIG) trial, analysis of glycemia and its outcome showed that a fasting capillary glucose < 4.9 mmol/L (88 mg/dL) had significantly better outcomes than women with a fasting capillary glucose between 4.9 and $\geq$ 5.3 mmol/L (88 and $\geq$ 95 mg/dL). Two hours postprandial, capillary glucose values of $\leq$ 6.4 mmol/L ($\leq$ 115 mg/dL) were associated with improved outcomes. Further improvement was seen with mean postprandial capillary glucose < 5.9 mmol/L (< l06 mg/dL)[59].

A review by Hernandez et al[60] states that average glucose values in pregnant non-diabetic women are 4.5 mmol/L (81 mg/dL) for fasting, 6.8 mmol/L (122 mg/dL) for 1 h postprandial and 6.1 mmol/L (110 mg/dL) for 2 h postprandial.

All these studies implicate that targets for fasting and postprandial capillary glucose may need to be lower than what current guidelines recommend. Further studies are required in this field.

Adjustment of insulin therapy based on postprandial glucose values improves glycemic control better than pre-prandial glucose values and decreases the risk of neonatal hypoglycemia, macrosomia and cesarean

delivery[61].

Continuous glucose monitoring systems (CGMS) may be of use in pregnant women with overt diabetes who require a very high dose of insulin to achieve good glycemic control. CGMS during pregnancy is associated with improved glycemic control and a reduced risk of macrosomia[62]. A study in Finland showed that CGMS detects a markedly higher proportion of GDM mothers needing antihyperglycemic medication compared with self-monitoring of plasma glucose[63]. Further large scale studies are needed to evaluate whether CGMS guided initiation of antihyperglycemic therapy results in less macrosomia and perinatal complications related to GDM.

Diet
Calorie requirement for GDM women is 30-35 kcal/kg for normal weight, 25-30 kcal/kg for overweight and 35-40 kcal/kg for underweight subjects. Severe calorie restriction to < 1500 cal/d is not advisable. A study by Rizzo et al[64] has shown that severe calorie restriction to < 1500 cal/d is associated with increased incidence of ketonemia, resulting in lowered mental developmental index scores and average Stanford-Binet scores in the babies. The American Diabetes Association recommends a 30%-33% calorie restriction in obese women with GDM, with a minimum of 1800 cal/d[65].

Diets composed of 50%-60% carbohydrates will often result in hyperglycemia and excessive weight gain. So, calorie intake from carbohydrate has to be limited to 33%-40%, with the remaining calories divided between protein (20%) and fat (40%)[61]. Three meals and two to three snacks are recommended to distribute glucose intake and to reduce postprandial glucose fluctuations. Glycemic index of food may also be an important factor for sugar control. Low glycemic index (< 55) foods produce a better sugar control than foods with a high glycemic index (> 70). Studies have shown that the glycemic index of food has an influence on birth weight of the baby[66,67]. Studies on the effect of a high fiber diet on outcome of pregnancy in GDM have shown mixed results[68,69].

Insulin
When glycemic targets are not achieved by 1-2 wk of the diet, pharmacological treatment is recommended[70]. Short acting insulin is used to cover glucose excursions following the meal and intermediate acting insulin for hepatic glucose production in the fasting state. Regular human insulin (RHI) is a shorter acting insulin and neutral protamine hagedorn (NPH) is the intermediate acting insulin in common practice to date. Following each meal, glucose levels peak at approximately 1 h after the start of the meal and then return to pre-prandial levels within 2-3 h[71]. Short acting insulin starts its action 1/2 to 1 h after injection and its effect reaches a peak at 2-4 h. Therefore, at times, the pre-prandial administration of RHI is not able to control the peak

postprandial blood glucose. At the same time, delayed peak action and a longer duration of action may result in inappropriate hyperinsulinemia before the next meal, resulting in pre-prandial hypoglycemia[72].

Rapid acting insulin analogs
In order to overcome this problem, newer rapid acting insulin analogs can be used instead of short acting insulin. These rapid acting insulin analogs start their action within 15 min, reaches a peak by 31-70 min and acts for 2-4 h. Several studies have proven the safety of insulin aspart and lispro in pregnancy. United States Food and Drug Administration (FDA) has approved both insulins for use during pregnancy. Several clinical studies have shown fewer episodes of hypoglycemia, strict sugar control and higher reduction in HbA1c levels in pregnancy.

The latest rapid acting insulin analog, insulin glulisine, is available with the same action profile as that of aspart and lispro. As there are no clinical data available, to date, United States FDA has not approved it for use in pregnancy.

Long acting insulin
Commonly used NPH insulin starts its action in 1-2 h, with peak action at 4-8 h and effective up to 12-18 h. The night dose of NPH has its peak action in the early morning hours and produces hypoglycemia[72].

Compared to NPH, newer long acting insulin analog detemir starts its action in 1-2 h and has a flatter profile with a more even distribution of metabolic effect over 24 h[73]. Insulin detemir also shows lower rates of hypoglycemia. Various studies have proved the efficacy and safety of insulin detemir in pregnancy. Moreover, the United States FDA has approved insulin detemir as class B in pregnancy. Although the insulin glargine has same pharmacodynamic properties as detemir, the use of insulin glargine is not approved in pregnancy. Well controlled trials are needed to determine its safety in pregnancy.

Premixed insulin preparations
Premixed insulin preparations are commonly used everywhere. A combination of short acting and intermediate acting injections are available in different ratios of 30/70, 25/75, 50/50. Premixed insulin analogs provide better postprandial coverage and less hypoglycemic episodes between meals. Biphasic insulin aspart (BIAsp 30) comprises rapid acting aspart combined with protamine-crystallized insulin aspart in a 30:70 ratio. It requires twice daily dosing and provides better sugar control[74]. It has been found to be safe during pregnancy.

Insulin pump
Insulin pumps allow for flexible insulin administration with a profile that resembles the physiological insulin profile of the beta cells of the pancreas very closely.

Major advantages of administering insulin by continuous subcutaneous insulin infusion include decreased variability in insulin absorption (due to small insulin doses administered at one time), decreased risk of hypoglycemia (due to the lower total doses of insulin) and improved control of the dawn phenomenon[75].

CGMS and insulin pumps used together during pregnancy help improve glycemic control. Together, these devices could potentially constitute an artificial pancreas[76]. Real-time blood glucose readings are continuously relayed to the insulin pump. Based on glucose values, the insulin pump delivers an accurate dosage of insulin needed by the patient's body. A closed-loop system with physiologically responsive insulin adjustments capable of maintaining near normal glucose levels could be of great benefit for pregnant women with type 1 diabetes or GDM with high plasma glucose values.

The Helen Murphy group evaluated closed-loop insulin delivery with a model predictive control (MPC) algorithm[77]. The basal insulin infusion rate was calculated using women's weight, basal insulin requirements (measured by continuous glucose monitoring) and total daily insulin dose during the preceding 3 d. A nurse adjusts the basal insulin infusion rate from continuous glucose measurements and feeds into the MPC algorithm every 15 min. The total daily insulin dose was reduced by 30% for conversion to insulin pump. The advantage found with a closed-loop insulin delivery system over conventional multiple injections is its ability to respond rapidly to glucose excursions with more flexible insulin infusion rates despite comparable overall insulin doses.

Pump therapy can be especially beneficial for women who require high doses of insulin and experience repeated episodes of hypoglycemia with intermittent insulin injections[78]. Large scale trials are needed before widespread use.

Oral hypoglycemic agents for GDM

The traditional management of women with GDM is to treat with insulin if diet therapy fails. However, insulin therapy has its own drawbacks. Now there is emerging evidence for the role of oral medications in these women. ACOG and National Institute for Health and Care Excellence (NICE) guidelines suggest that insulin and oral medications are equivalent in efficacy and either can be an appropriate first-line therapy[61,79].

Metformin

Su et al[80] conducted a systematic review of six randomized clinical trials involving 1420 subjects. They found that by using metformin in women with gestational diabetes there was no increase in adverse maternal and neonatal outcomes compared to insulin. Moreover, metformin usage in pregnancy is associated with less weight gain and neonatal hypoglycemia.

A randomized control trial by Niromanesh et al[81] showed that the birth weight of the neonate was lower in the metformin group compared to the insulin group, although not statistically significant. Maternal weight gain was significantly reduced in the metformin group.

A retrospective study done by Marques et al[82] showed that there was no statistical differences between insulin and metformin groups with regard to the rates of abortion, preeclampsia, macrosomia, prematurity, small for gestational age or large for gestational age newborns, perinatal deaths, cesarean deliveries, neonatal intensive care unit admissions and birth malformations or neonatal injuries.

There is no significant difference in postprandial glucose control between women on insulin and those taking oral hypoglycemic agents. This finding is reflected in similar rates of fetal macrosomia and mean birth weight in women receiving insulin or oral hypoglycemic agents as first-line treatment[83].

However, there are studies which show that metformin can induce neural tube defects when it is taken during first trimester of pregnancy. Expression of Pax3 gene is essential for neural tube closure. Adenosine monophosphate-activated protein kinase (AMPK) is stimulated in embryos during diabetic pregnancy by maternal hyperglycemia[84]. This stimulated AMPK inhibits expression of Pax3 gene and induces neural tube defects. Studies have shown that apart from maternal hyperglycemia, metformin has also been shown to stimulate AMPK activity in skeletal muscle and liver[85,86]. This stimulation of AMPK activity by metformin causes neural tube defects. However, a study by Lee et al[87] showed that metformin increases activated AMPK in the maternal liver but it did not have an effect on AMPK in embryos or maternal skeletal muscle. Because of the absence of AMPK activity, metformin did not inhibit Pax3 expression in embryos and thus did not cause neural tube defects. The absence of metformin responsiveness on embryos may be explained by insufficient expression of metformin transporters during neurulation. Thus, in their study, they showed that metformin does not stimulate embryo AMPK activity and consequent embryopathy.

The MIG trial by Rowan et al[88] showed that women receiving metformin had less weight gain between the time of enrollment and 36 wk of gestation than those receiving insulin. Similarly, there was a greater weight loss between the time of enrollment and the postpartum visit in women receiving metformin compared to insulin. There were significantly less episodes of neonatal hypoglycemia events in infants of women taking metformin. The MIG trial concluded that metformin had similar perinatal complications compared to insulin. Due to the convenience, women preferred metformin to insulin treatment.

The follow up of exposed children up to 2 years in the MiG-TOFU trial revealed that metformin-exposed infants had more subcutaneous fat and less visceral fat. This may result in an increased insulin sensitivity pattern of growth in future[89].

Glyburide

In the treatment of GDM, metformin and glyburide were equally efficacious to insulin in blood sugar control[90-92]. The only significant difference in outcome between the 2 drugs was that maternal weight gain during pregnancy was lower with metformin. A few studies showed that the incidence of macrosomia[91,93] and neonatal hypoglycemia[91] is higher in babies of GDM mothers treated with glyburide. In contrast to this, a meta-analysis showed that there is no consistent evidence for increase in any adverse maternal or neonatal outcomes with the use of glyburide or metformin compared with the use of insulin[94].

Oral agents are better in pregnancy because they are patient friendly and convenient, resulting in increased compliance with treatment regimens. Oral agents do not require instruction at the time of initiation of therapy. Glycemic control and perinatal outcomes produced by oral hypoglycemic agents (OHAs) were comparable to insulin. Insulin is costlier, inconvenient to use and needs ideal storage conditions, which makes it difficult in developing countries. So, OHAs should be considered safe alternatives to insulin which should be reserved as a second-line agent for patients in whom oral treatment does not achieve glycemic control[83].

FETAL SURVEILLANCE

There is an increased risk of fetal demise in patients with poor glycemic control. To improve fetal outcome, all women with GDM should be instructed to monitor fetal movements during the last 8-10 wk of pregnancy. They should report immediately if there is any reduction in the perception of fetal movements. Antepartum fetal surveillance should be started from 32 wk in insulin treated GDM women. Non-stress testing should be done after 32 wk gestation in women on insulin. Biophysical profile testing and Doppler velocimetry to assess umbilical blood flow may be considered in those with associated intra uterine growth restriction, macrosomia or in those with co-morbid conditions, such as pre-eclampsia. There is no consensus regarding antepartum testing in women with GDM well controlled with diet.

INDUCTION OF LABOR

The timing and the mode of delivery is still debatable. For the timing of delivery, the ADA in 2004 recommended delivery at 38 wk unless obstetric considerations dictated alternative management[65]. Similarly, NICE in 2008 recommended that pregnant women with diabetes should be offered elective birth through induction of labor after 38 completed weeks[79]. The ACOG did not recommend routine delivery before 40 wk in GDM women well controlled with diet or medication[61]. Induction of labor at term helps to reduce the incidence of shoulder dystocia in women with gestational diabetes[95]. The option of induction of labor in GDM is still controversial. Further studies are needed in this field.

For the mode of delivery, a cesarean delivery would only be suggested for an estimated fetal weight of $\geqslant$ 4500 g in mothers with GDM[79,96].

GLYCEMIC CONTROL DURING LABOR

During labor and birth, capillary blood glucose should be monitored on an hourly basis in women with diabetes and maintained at 4-7 mmol/L. Intravenous dextrose and insulin infusion is recommended during labor and birth in women with diabetes whose blood glucose is not maintained between 4-7 mmol/L.

FUTURE PREVENTION

Women with a history of GDM have a greatly increased subsequent diabetes risk and should be followed up with subsequent screening for the development of pre-diabetes or diabetes. Women who had GDM in pregnancy should have a 75 g 2 h OGTT (WHO criteria), preferably at 6-12 wk post-partum. Women with a normal result should be reassessed once in 3 years. For those who are diagnosed with impaired fasting glucose or impaired glucose tolerance, annual testing should be done.

For women who had GDM in the first pregnancy, there is 13.2 fold increased risk (95%CI: 12.0-14.6) of developing GDM during the second pregnancy. The recurrence risk of GDM in the third pregnancy was stronger when women had GDM in both prior pregnancies (25.9 fold increased risk; 95%CI: 17.4-38.4)[97]. The cumulative proportion of women developing diabetes at 1 year postpartum was 1.7%. At the end of 10 years, 17% of women developed diabetes and at the end of 15 years, 25% developed diabetes[98].

Lifestyle interventions or metformin should be offered to women with a history of GDM who develop pre-diabetes. Subsequent diabetes risk after a history of GDM was significantly lower in women who followed healthy eating patterns[99]. In the diabetes prevention program, administering metformin and intensive lifestyle modification in women with a history of GDM led to 50% reduction in diabetes risk[100]. Metformin therefore might reasonably be recommended for very high-risk individuals (those with a history of GDM or very obese women)[5].

REFERENCES

1   **American Diabetes Association**. Standards of medical care in diabetes--2009. *Diabetes Care* 2009; **32** Suppl 1: S13-S61 [PMID: 19118286 DOI: 10.2337/dc09-S013]
2   **Canadian Diabetes Association**. 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2008; **32** (suppl 1): S1-S201
3   **Hirst JE**, Raynes-Greenow CH, Jeffery HE. A systematic review of trends of gestational diabetes mellitus in Asia. *Journal of Diabetology* 2012; **3**: 4
4   **Guariguata L**, Linnenkamp U, Beagley J, Whiting DR, Cho NH. Global estimates of the prevalence of hyperglycaemia in pregnancy. *Diabetes Res Clin Pract* 2014; **103**: 176-185 [PMID:

24300020 DOI: 10.1016/j.diabres.2013.11.003]

5   **American Diabetes Association**. Standards of medical care in diabetes--2014. *Diabetes Care* 2014; **37** Suppl 1: S14-S80 [PMID: 24357209 DOI: 10.2337/dc14-S014]

6   **Yessoufou A**, Moutairou K. Maternal diabetes in pregnancy: early and long-term outcomes on the offspring and the concept of "metabolic memory". *Exp Diabetes Res* 2011; **2011**: 218598 [PMID: 22144985 DOI: 10.1155/2011/218598]

7   **Mitanchez D**. Foetal and neonatal complications in gestational diabetes: perinatal mortality, congenital malformations, macrosomia, shoulder dystocia, birth injuries, neonatal complications. *Diabetes Metab* 2010; **36**: 617-627 [PMID: 21163425 DOI: 10.1016/j.diabet.2010.11.013]

8   **Suhonen L**, Hiilesmaa V, Kaaja R, Teramo K. Detection of pregnancies with high risk of fetal macrosomia among women with gestational diabetes mellitus. *Acta Obstet Gynecol Scand* 2008; **87**: 940-945 [PMID: 18728914 DOI: 10.1080/00016340802334377]

9   **Boney CM**, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics* 2005; **115**: e290-e296 [PMID: 15741354 DOI: 10.1542/peds.2004-1808]

10   **Chiu M**, Austin PC, Manuel DG, Shah BR, Tu JV. Deriving ethnic-specific BMI cutoff points for assessing diabetes risk. *Diabetes Care* 2011; **34**: 1741-1748 [PMID: 21680722 DOI: 10.2337/dc10-2300]

11   **Zhang C**, Liu S, Solomon CG, Hu FB. Dietary fiber intake, dietary glycemic load, and the risk for gestational diabetes mellitus. *Diabetes Care* 2006; **29**: 2223-2230 [PMID: 17003297 DOI: 10.2337/dc06-0266]

12   **Zhang C**, Schulze MB, Solomon CG, Hu FB. A prospective study of dietary patterns, meat intake and the risk of gestational diabetes mellitus. *Diabetologia* 2006; **49**: 2604-2613 [PMID: 16957814 DOI: 10.1007/s00125-006-0422-1]

13   **Zhang C**. Risk factors for gestation diabetes-from an epidemiological standpoint. In: Kim C, Ferrara A, editors. Gestational diabetes during and after pregancy. London, United Kingdom: Springer-Verlag London Limited, 2010: 71-81

14   **Dempsey JC**, Butler CL, Williams MA. No need for a pregnant pause: physical activity may reduce the occurrence of gestational diabetes mellitus and preeclampsia. *Exerc Sport Sci Rev* 2005; **33**: 141-149 [PMID: 16006822 DOI: 10.1097/00003677-200507000-00007]

15   **Kasawara KT**, Burgos CS, do Nascimento SL, Ferreira NO, Surita FG, Pinto E Silva JL. Maternal and Perinatal Outcomes of Exercise in Pregnant Women with Chronic Hypertension and/or Previous Preeclampsia: A Randomized Controlled Trial. *ISRN Obstet Gynecol* 2013; **2013**: 857047 [PMID: 23997960 DOI: 10.1155/2013/857047]

16   **Dempsey JC**, Butler CL, Sorensen TK, Lee IM, Thompson ML, Miller RS, Frederick IO, Williams MA. A case-control study of maternal recreational physical activity and risk of gestational diabetes mellitus. *Diabetes Res Clin Pract* 2004; **66**: 203-215 [PMID: 15533588 DOI: 10.1016/j.diabres.2004.03.010]

17   **Chasan-Taber L**, Schmidt MD, Pekow P, Sternfeld B, Manson JE, Solomon CG, Braun B, Markenson G. Physical activity and gestational diabetes mellitus among Hispanic women. *J Womens Health* (Larchmt) 2008; **17**: 999-1008 [PMID: 18582171 DOI: 10.1089/jwh.2007.0560]

18   **Oken E**, Ning Y, Rifas-Shiman SL, Radesky JS, Rich-Edwards JW, Gillman MW. Associations of physical activity and inactivity before and during pregnancy with glucose tolerance. *Obstet Gynecol* 2006; **108**: 1200-1207 [PMID: 17077243 DOI: 10.1097/01.AOG.0000241088.60745.70]

19   **American College of Obstetricians and Gynecologists**. Exercise during pregnancy and the postpartum period. *Clin Obstet Gynecol* 2003; **46**: 496-499 [PMID: 12808399 DOI: 10.1097/00003081-200306000-00028]

20   **Torloni MR**, Betrán AP, Horta BL, Nakamura MU, Atallah AN, Moron AF, Valente O. Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. *Obes Rev* 2009; **10**: 194-203 [PMID: 19055539 DOI: 10.1111/j.1467-789X.2008.00541.x]

21   **Rasmussen KM**, Catalano PM, Yaktine AL. New guidelines for weight gain during pregnancy: what obstetrician/gynecologists should know. *Curr Opin Obstet Gynecol* 2009; **21**: 521-526 [PMID: 19809317 DOI: 10.1097/GCO.0b013e328332d24e]

22   **Hedderson MM**, Gunderson EP, Ferrara A. Gestational weight gain and risk of gestational diabetes mellitus. *Obstet Gynecol* 2010; **115**: 597-604 [PMID: 20177292 DOI: 10.1097/AOG.0b013e3181cfce4f]

23   **Chu SY**, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, Dietz PM. Maternal obesity and risk of gestational diabetes mellitus. *Diabetes Care* 2007; **30**: 2070-2076 [PMID: 17416786 DOI: 10.2337/dc06-2559a]

24   **Lindsay KL**, Walsh CA, Brennan L, McAuliffe FM. Probiotics in pregnancy and maternal outcomes: a systematic review. *J Matern Fetal Neonatal Med* 2013; **26**: 772-778 [PMID: 23205866 DOI: 10.3109/14767058.2012.755166]

25   **Lye HS**, Kuan CY, Ewe JA, Fung WY, Liong MT. The improvement of hypertension by probiotics: effects on cholesterol, diabetes, renin, and phytoestrogens. *Int J Mol Sci* 2009; **10**: 3755-3775 [PMID: 19865517 DOI: 10.3390/ijms10093755]

26   **Laitinen K**, Poussa T, Isolauri E. Probiotics and dietary counselling contribute to glucose regulation during and after pregnancy: a randomised controlled trial. *Br J Nutr* 2009; **101**: 1679-1687 [PMID: 19017418 DOI: 10.1017/S0007114508111461]

27   **Luoto R**, Laitinen K, Nermes M, Isolauri E. Impact of maternal probiotic-supplemented dietary counselling on pregnancy outcome and prenatal and postnatal growth: a double-blind, placebo-controlled study. *Br J Nutr* 2010; **103**: 1792-1799 [PMID: 20128938 DOI: 10.1017/S0007114509993898]

28   **Barrett HL**, Dekker Nitert M, Conwell LS, Callaway LK. Probiotics for preventing gestational diabetes. *Cochrane Database Syst Rev* 2014; **2**: CD009951 [PMID: 24574258 DOI: 10.1002/14651858.CD009951.pub2]

29   **Nitert MD**, Barrett HL, Foxcroft K, Tremellen A, Wilkinson S, Lingwood B, Tobin JM, McSweeney C, O'Rourke P, McIntyre HD, Callaway LK. SPRING: an RCT study of probiotics in the prevention of gestational diabetes mellitus in overweight and obese women. *BMC Pregnancy Childbirth* 2013; **13**: 50 [PMID: 23442391 DOI: 10.1186/1471-2393-13-50]

30   **Tong X**, Dong JY, Wu ZW, Li W, Qin LQ. Dairy consumption and risk of type 2 diabetes mellitus: a meta-analysis of cohort studies. *Eur J Clin Nutr* 2011; **65**: 1027-1031 [PMID: 21559046 DOI: 10.1038/ejcn.2011.62]

31   **Struijk EA**, Heraclides A, Witte DR, Soedamah-Muthu SS, Geleijnse JM, Toft U, Lau CJ. Dairy product intake in relation to glucose regulation indices and risk of type 2 diabetes. *Nutr Metab Cardiovasc Dis* 2013; **23**: 822-828 [PMID: 22831954 DOI: 10.1016/j.numecd.2012.05.011]

32   **Sluijs I**, Forouhi NG, Beulens JW, van der Schouw YT, Agnoli C, Arriola L, Balkau B, Barricarte A, Boeing H, Bueno-de-Mesquita HB, Clavel-Chapelon F, Crowe FL, de Lauzon-Guillain B, Drogan D, Franks PW, Gavrila D, Gonzalez C, Halkjaer J, Kaaks R, Moskal A, Nilsson P, Overvad K, Palli D, Panico S, Quirós JR, Ricceri F, Rinaldi S, Rolandsson O, Sacerdote C, Sánchez MJ, Slimani N, Spijkerman AM, Teucher B, Tjonneland A, Tormo MJ, Tumino R, van der A DL, Sharp SJ, Langenberg C, Feskens EJ, Riboli E, Wareham NJ. The amount and type of dairy product intake and incident type 2 diabetes: results from the EPIC-InterAct Study. *Am J Clin Nutr* 2012; **96**: 382-390 [PMID: 22760573 DOI: 10.3945/ajcn.111.021907]

33   **Wang H**, Livingston KA, Fox CS, Meigs JB, Jacques PF. Yogurt consumption is associated with better diet quality and metabolic profile in American men and women. *Nutr Res* 2013; **33**: 18-26 [PMID: 23351406 DOI: 10.1016/j.nutres.2012.11.009]

34   **Moroti C**, Souza Magri LF, de Rezende Costa M, Cavallini DC, Sivieri K. Effect of the consumption of a new symbiotic shake on glycemia and cholesterol levels in elderly people with

type 2 diabetes mellitus. *Lipids Health Dis* 2012; **11**: 29 [PMID: 22356933 DOI: 10.1186/1476-511X-11-29]

35   **Ejtahed HS**, Mohtadi-Nia J, Homayouni-Rad A, Niafar M, Asghari-Jafarabadi M, Mofid V. Probiotic yogurt improves antioxidant status in type 2 diabetic patients. *Nutrition* 2012; **28**: 539-543 [PMID: 22129852 DOI: 10.1016/j.nut.2011.08.003]

36   **Forrest KY**, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. *Nutr Res* 2011; **31**: 48-54 [PMID: 21310306 DOI: 10.1016/j.nutres.2010.12.001]

37   **Holick MF**, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr* 2008; **87**: 1080S-1086S [PMID: 18400738]

38   **Reeves IV**, Bamji ZD, Rosario GB, Lewis KM, Young MA, Washington KN. Vitamin D deficiency in pregnant women of ethnic minority: a potential contributor to preeclampsia. *J Perinatol* 2014; **34**: 767-773 [PMID: 24854625]

39   **Maghbooli Z**, Hossein-Nezhad A, Karimi F, Shafaei AR, Larijani B. Correlation between vitamin D3 deficiency and insulin resistance in pregnancy. *Diabetes Metab Res Rev* 2008; **24**: 27-32 [PMID: 17607661 DOI: 10.1002/dmrr.737]

40   **Zhang C**, Qiu C, Hu FB, David RM, van Dam RM, Bralley A, Williams MA. Maternal plasma 25-hydroxyvitamin D concentrations and the risk for gestational diabetes mellitus. *PLoS One* 2008; **3**: e3753 [PMID: 19015731 DOI: 10.1371/journal.pone.0003753]

41   **Thota C**, Menon R, Fortunato SJ, Brou L, Lee JE, Al-Hendy A. 1,25-Dihydroxyvitamin D deficiency is associated with preterm birth in African American and Caucasian women. *Reprod Sci* 2014; **21**: 244-250 [PMID: 23793474 DOI: 10.1177/1933719113493513]

42   **Gernand AD**, Simhan HN, Caritis S, Bodnar LM. Maternal vitamin D status and small-for-gestational-age offspring in women at high risk for preeclampsia. *Obstet Gynecol* 2014; **123**: 40-48 [PMID: 24463662 DOI: 10.1097/AOG.0000000000000049]

43   **Soheilykhah S**, Mojibian M, Moghadam MJ, Shojaoddiny-Ardekani A. The effect of different doses of vitamin D supplementation on insulin resistance during pregnancy. *Gynecol Endocrinol* 2013; **29**: 396-399 [PMID: 23350644 DOI: 10.3109/09513590.2012.752456]

44   **De-Regil LM**, Palacios C, Ansary A, Kulier R, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. *Cochrane Database Syst Rev* 2012; **2**: CD008873 [PMID: 22336854 DOI: 10.1002/14651858.CD008873.pub2]

45   **Jelsma JG**, van Poppel MN, Galjaard S, Desoye G, Corcoy R, Devlieger R, van Assche A, Timmerman D, Jans G, Harreiter J, Kautzky-Willer A, Damm P, Mathiesen ER, Jensen DM, Andersen L, Dunne F, Lapolla A, Di Cianni G, Bertolotto A, Wender-Oegowska E, Zawiejska A, Blumska K, Hill D, Rebollo P, Snoek FJ, Simmons D. DALI: Vitamin D and lifestyle intervention for gestational diabetes mellitus (GDM) prevention: an European multicentre, randomised trial - study protocol. *BMC Pregnancy Childbirth* 2013; **13**: 142 [PMID: 23829946 DOI: 10.1186/1471-2393-13-142]

46   **James D**, Steer PJ, Weiner CP, Gonik B, Crowther CA, Robson SC. High Risk Pregnancy: management options. 4th ed. Elsevier Saunders, 2011: 800

47   **Metzger BE**, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks DA. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008; **358**: 1991-2002 [PMID: 18463375 DOI: 10.1056/NEJMoa0707943]

48   **Metzger BE**, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva Ad, Hod M, Kitzmiler JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y, Schmidt MI. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010; **33**: 676-682 [PMID: 20190296 DOI: 10.2337/dc09-1848]

49   Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. Geneva: World Health Organization, 2013: 63

50   **Falavigna M**, Prestes I, Schmidt MI, Duncan BB, Colagiuri S, Roglic G. Impact of gestational diabetes mellitus screening strategies on perinatal outcomes: a simulation study. *Diabetes Res Clin Pract* 2013; **99**: 358-365 [PMID: 23332050 DOI: 10.1016/j.diabres.2012.12.009]

51   **Mission JF**, Ohno MS, Cheng YW, Caughey AB. Gestational diabetes screening with the new IADPSG guidelines: a cost-effectiveness analysis. *Am J Obstet Gynecol* 2012; **207**: 326.e1-326.e9 [PMID: 22840972 DOI: 10.1016/j.ajog.2012.06.048]

52   **Werner EF**, Pettker CM, Zuckerwise L, Reel M, Funai EF, Henderson J, Thung SF. Screening for gestational diabetes mellitus: are the criteria proposed by the international association of the Diabetes and Pregnancy Study Groups cost-effective? *Diabetes Care* 2012; **35**: 529-535 [PMID: 22266735 DOI: 10.2337/dc11-1643]

53   **Mattick JS**, Makunin IV. Non-coding RNA. *Hum Mol Genet* 2006; **15** Spec No 1: R17-R29 [PMID: 16651366 DOI: 10.1093/hmg/ddl046]

54   **Lynn FC**, Skewes-Cox P, Kosaka Y, McManus MT, Harfe BD, German MS. MicroRNA expression is required for pancreatic islet cell genesis in the mouse. *Diabetes* 2007; **56**: 2938-2945 [PMID: 17804764 DOI: 10.2337/db07-0175]

55   **Plaisance V**, Abderrahmani A, Perret-Menoud V, Jacquemin P, Lemaigre F, Regazzi R. MicroRNA-9 controls the expression of Granuphilin/Slp4 and the secretory response of insulin-producing cells. *J Biol Chem* 2006; **281**: 26932-26942 [PMID: 16831872 DOI: 10.1074/jbc.M601225200]

56   **Zhao C**, Dong J, Jiang T, Shi Z, Yu B, Zhu Y, Chen D, Xu J, Huo R, Dai J, Xia Y, Pan S, Hu Z, Sha J. Early second-trimester serum miRNA profiling predicts gestational diabetes mellitus. *PLoS One* 2011; **6**: e23925 [PMID: 21887347 DOI: 10.1371/journal.pone.0023925]

57   **Alwan N**, Tuffnell DJ, West J. Treatments for gestational diabetes. *Cochrane Database Syst Rev* 2009; (**3**): CD003395 [PMID: 19588341 DOI: 10.1002/14651858.CD003395.pub2]

58   **Metzger BE**, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR, Hod M, Kitzmiller JL, Kjos SL, Oats JN, Pettitt DJ, Sacks DA, Zoupas C. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care* 2007; **30** Suppl 2: S251-S260 [PMID: 17596481 DOI: 10.2337/dc07-s225]

59   **Rowan JA**, Gao W, Hague WM, McIntyre HD. Glycemia and its relationship to outcomes in the metformin in gestational diabetes trial. *Diabetes Care* 2010; **33**: 9-16 [PMID: 19846793 DOI: 10.2337/dc09-1407]

60   **Hernandez TL**, Friedman JE, Van Pelt RE, Barbour LA. Patterns of glycemia in normal pregnancy: should the current therapeutic targets be challenged? *Diabetes Care* 2011; **34**: 1660-1668 [PMID: 21709299 DOI: 10.2337/dc11-0241]

61   **Committee on Practice Bulletins-Obstetrics**. Practice Bulletin No. 137: Gestational diabetes mellitus. *Obstet Gynecol* 2013; **122**: 406-416 [PMID: 23969827 DOI: 10.1097/01.AOG.0000433006.09219.f1]

62   **Murphy HR**, Rayman G, Lewis K, Kelly S, Johal B, Duffield K, Fowler D, Campbell PJ, Temple RC. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. *BMJ* 2008; **337**: a1680 [PMID: 18818254 DOI: 10.1136/bmj.a1680]

63   **Kestilä KK**, Ekblad UU, Rönnemaa T. Continuous glucose monitoring versus self-monitoring of blood glucose in the treatment of gestational diabetes mellitus. *Diabetes Res Clin Pract* 2007; **77**: 174-179 [PMID: 17234297 DOI: 10.1016/j.diabres.2006.12.012]

64   **Rizzo T**, Metzger BE, Burns WJ, Burns K. Correlations between antepartum maternal metabolism and child intelligence. *N Engl J Med* 1991; **325**: 911-916 [PMID: 1881416 DOI: 10.1056/NEJM199109263251303]

65   **American Diabetes Association**. Gestational diabetes mellitus. *Diabetes Care* 2004; **27** Suppl 1: S88-S90 [PMID: 14693936 DOI: 10.2337/diacare.27.2007.S88]

66   **Moses RG**, Luebcke M, Davis WS, Coleman KJ, Tapsell LC, Petocz P, Brand-Miller JC. Effect of a low-glycemic-index diet during pregnancy on obstetric outcomes. *Am J Clin Nutr* 2006; **84**:

807-812 [PMID: 17023707]

67   **Scholl TO**, Chen X, Khoo CS, Lenders C. The dietary glycemic index during pregnancy: influence on infant birth weight, fetal growth, and biomarkers of carbohydrate metabolism. *Am J Epidemiol* 2004; **159**: 467-474 [PMID: 14977642 DOI: 10.1093/aje/kwh068]

68   **Han S**, Crowther CA, Middleton P, Heatley E. Different types of dietary advice for women with gestational diabetes mellitus. *Cochrane Database Syst Rev* 2013; **3**: CD009275 [PMID: 23543574 DOI: 10.1002/14651858.CD009275.pub2]

69   **Louie JC**, Markovic TP, Perera N, Foote D, Petocz P, Ross GP, Brand-Miller JC. A randomized controlled trial investigating the effects of a low-glycemic index diet on pregnancy outcomes in gestational diabetes mellitus. *Diabetes Care* 2011; **34**: 2341-2346 [PMID: 21900148 DOI: 10.2337/dc11-0985]

70   **Balaji V**, Seshiah V. Management of diabetes in pregnancy. *J Assoc Physicians India* 2011; **59** Suppl: 33-36 [PMID: 21823253]

71   **American Diabetes Association**. Postprandial blood glucose. American Diabetes Association. *Diabetes Care* 2001; **24**: 775-778 [PMID: 11315848 DOI: 10.2337/diacare.24.4.775]

72   **Magon N**, Seshiah V. Gestational diabetes mellitus: insulinic management. *J Obstet Gynaecol India* 2014; **64**: 82-90 [PMID: 24757334 DOI: 10.1007/s13224-014-0525-4]

73   **Korsatko S**, Glettler K, Olsen KJ, Wutte A, Bock G, Koehler G, Mader JK, Semlitsch B, Pieber TR. A direct comparison of the pharmacodynamic properties of insulin detemir and neutral protamine lispro insulin in patients with type 1 diabetes. *Diabetes Obes Metab* 2013; **15**: 241-245 [PMID: 23013357 DOI: 10.1111/dom.12016]

74   **Balaji V**, Balaji MS, Alexander C, Ashalata S, Sheela Suganthi R, Suresh S, Seshiah V. Premixed insulin aspart 30 (Biasp 30) vs. premixed human insulin 30 (BHI 30) in gestational diabetes mellitus--a pilot study. *J Assoc Physicians India* 2010; **58**: 99-101 [PMID: 20653150]

75   **Pickup JC**, Renard E. Long-acting insulin analogs versus insulin pump therapy for the treatment of type 1 and type 2 diabetes. *Diabetes Care* 2008; **31** Suppl 2: S140-S145 [PMID: 18227475 DOI: 10.2337/dc08-s235]

76   **Combs CA**. Continuous glucose monitoring and insulin pump therapy for diabetes in pregnancy. *J Matern Fetal Neonatal Med* 2012; **25**: 2025-2027 [PMID: 22384837 DOI: 10.3109/14767058.2012.670409]

77   **Murphy HR**, Elleri D, Allen JM, Harris J, Simmons D, Rayman G, Temple R, Dunger DB, Haidar A, Nodale M, Wilinska ME, Hovorka R. Closed-loop insulin delivery during pregnancy complicated by type 1 diabetes. *Diabetes Care* 2011; **34**: 406-411 [PMID: 21216859 DOI: 10.2337/dc10-1796]

78   **Bernasko J**. Insulin pump therapy for pregnancy: a primer. *J Matern Fetal Neonatal Med* 2012; **25**: 552-557 [PMID: 22092002 DOI: 10.3109/14767058.2011.598586]

79   **Walker JD**. NICE guidance on diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. NICE clinical guideline 63. London, March 2008. *Diabet Med* 2008; **25**: 1025-1027 [PMID: 19183306 DOI: 10.1111/j.1464-5491.2008.02532.x]

80   **Su DF**, Wang XY. Metformin vs insulin in the management of gestational diabetes: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2014; **104**: 353-357 [PMID: 24768511 DOI: 10.1016/j.diabres.2013.12.056]

81   **Niromanesh S**, Alavi A, Sharbaf FR, Amjadi N, Moosavi S, Akbari S. Metformin compared with insulin in the management of gestational diabetes mellitus: a randomized clinical trial. *Diabetes Res Clin Pract* 2012; **98**: 422-429 [PMID: 23068960 DOI: 10.1016/j.diabres.2012.09.031]

82   **Marques P**, Carvalho MR, Pinto L, Guerra S. Metformin safety in the management of gestational diabetes. *Endocr Pract* 2014; **20**: 1022-1031 [PMID: 24793923 DOI: 10.4158/EP14018.OR]

83   **Dhulkotia JS**, Ola B, Fraser R, Farrell T. Oral hypoglycemic agents vs insulin in management of gestational diabetes: a systematic review and metaanalysis. *Am J Obstet Gynecol*

2010; **203**: 457.e1-457.e9 [PMID: 20739011 DOI: 10.1016/j.ajog.2010.06.044]

84   **Wu Y**, Viana M, Thirumangalathu S, Loeken MR. AMP-activated protein kinase mediates effects of oxidative stress on embryo gene expression in a mouse model of diabetic embryopathy. *Diabetologia* 2012; **55**: 245-254 [PMID: 21993711 DOI: 10.1007/s00125-011-2326-y]

85   **Zhou G**, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, Wu M, Ventre J, Doebber T, Fujii N, Musi N, Hirshman MF, Goodyear LJ, Moller DE. Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest* 2001; **108**: 1167-1174 [PMID: 11602624 DOI: 10.1172/JCI13505]

86   **Hawley SA**, Gadalla AE, Olsen GS, Hardie DG. The antidiabetic drug metformin activates the AMP-activated protein kinase cascade via an adenine nucleotide-independent mechanism. *Diabetes* 2002; **51**: 2420-2425 [PMID: 12145153 DOI: 10.2337/diabetes.51.8.2420]

87   **Lee HY**, Wei D, Loeken MR. Lack of metformin effect on mouse embryo AMPK activity: implications for metformin treatment during pregnancy. *Diabetes Metab Res Rev* 2014; **30**: 23-30 [PMID: 23983188 DOI: 10.1002/dmrr.2451]

88   **Rowan JA**, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med* 2008; **358**: 2003-2015 [PMID: 18463376 DOI: 10.1056/NEJMoa0707193]

89   **Rowan JA**, Rush EC, Obolonkin V, Battin M, Wouldes T, Hague WM. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition at 2 years of age. *Diabetes Care* 2011; **34**: 2279-2284 [PMID: 21949222 DOI: 10.2337/dc11-0660]

90   **Silva JC**, Pacheco C, Bizato J, de Souza BV, Ribeiro TE, Bertini AM. Metformin compared with glyburide for the management of gestational diabetes. *Int J Gynaecol Obstet* 2010; **111**: 37-40 [PMID: 20542272 DOI: 10.1016/j.ijgo.2010.04.028]

91   **Zeng YC**, Li MJ, Chen Y, Jiang L, Wang SM, Mo XL, Li BY. The use of glyburide in the management of gestational diabetes mellitus: a meta-analysis. *Adv Med Sci* 2014; **59**: 95-101 [PMID: 24797983 DOI: 10.1016/j.advms.2014.03.001]

92   **Kavitha N**, De S, Kanagasabai S. Oral Hypoglycemic Agents in pregnancy: An Update. *J Obstet Gynaecol India* 2013; **63**: 82-87 [PMID: 24431611 DOI: 10.1007/s13224-012-0312-z]

93   **Cheng YW**, Chung JH, Block-Kurbisch I, Inturrisi M, Caughey AB. Treatment of gestational diabetes mellitus: glyburide compared to subcutaneous insulin therapy and associated perinatal outcomes. *J Matern Fetal Neonatal Med* 2012; **25**: 379-384 [PMID: 21631239 DOI: 10.3109/14767058.2011.580402]

94   **Nicholson W**, Bolen S, Witkop CT, Neale D, Wilson L, Bass E. Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes: a systematic review. *Obstet Gynecol* 2009; **113**: 193-205 [PMID: 19104375 DOI: 10.1097/AOG.0b013e318190a459]

95   **Royal College of Obstetricians and Gynaecologist**. Shoulder dystocia: Green top guideline No. 42, 2nd ed. 2012. Available from: URL: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg42_25112013.pdf

96   **Rouse DJ**, Owen J, Goldenberg RL, Cliver SP. The effectiveness and costs of elective cesarean delivery for fetal macrosomia diagnosed by ultrasound. *JAMA* 1996; **276**: 1480-1486 [PMID: 8903259 DOI: 10.1001/jama.1996.03540180036030]

97   **Getahun D**, Fassett MJ, Jacobsen SJ. Gestational diabetes: risk of recurrence in subsequent pregnancies. *Am J Obstet Gynecol* 2010; **203**: 467.e1-467.e6 [PMID: 20630491 DOI: 10.1016/j.ajog.2010.05.032]

98   **Lee AJ**, Hiscock RJ, Wein P, Walker SP, Permezel M. Gestational diabetes mellitus: clinical predictors and long-term risk of developing type 2 diabetes: a retrospective cohort study using survival analysis. *Diabetes Care* 2007; **30**: 878-883 [PMID: 17392549 DOI: 10.2337/dc06-1816]

99   **Tobias DK**, Hu FB, Chavarro J, Rosner B, Mozaffarian D, Zhang C. Healthful dietary patterns and type 2 diabetes mellitus risk among

women with a history of gestational diabetes mellitus. *Arch Intern Med* 2012; **172**: 1566-1572 [PMID: 22987062 DOI: 10.1001/archinternmed.2012.3747]

100 **Ratner RE**, Christophi CA, Metzger BE, Dabelea D, Bennett PH, Pi-Sunyer X, Fowler S, Kahn SE. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *J Clin Endocrinol Metab* 2008; **93**: 4774-4779 [PMID: 18826999 DOI: 10.1210/jc.2008-0772]

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