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**Changing trends in management of gestational diabetes mellitus**

Poomalar GK. 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 right from 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 to favour 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. The 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

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**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 insulin Aspart, Lispro and Detemir provide better glycemic control than routinely used insulin. Continuous Glucose Monitoring Systems and insulin pump may be of use in women who require very high dose of insulin. Lifestyle intervention in GDM women helps 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 degree 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], in China it varies between 6.8% to 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 those criteria, the total incidence of GDM reaches almost 15%-20%[5].

The offspring of 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 cardiomyopathy 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 high body-mass index (BMI) (BMI cutoff of 30 kg/m2 in non-Hispanic whites, 26 kg/m2 in African Americans, 25 kg/m2 in Chinese and 24 kg/m2 in South Asians)[10], h/o diabetes in first degree relative, previous macrosomic infant, h/o GDM in previous pregnancies and women belonging to the ethnic origin of Asia, the Caribbean, and Arabia particularly of the Middle East. Numerous researches are 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 decrease appetite and thus lowers total energy intake. It also delays gastric emptying and slows glucose absorption, resulting in lesser absorption of glucose leading to glucose homeostasis and lesser 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 2.15-fold increased risk compared with the low-glycemic index and high-cereal fiber diet[11]. These findings suggest that 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, fruits 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 intake of red and processed meats were both significantly and positively associated with GDM risk[12]. It might be related to 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 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 show 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 to 0.82). The odds ratio of overweight, moderately obese and morbidly obese women to develop GDM were 1.97 (95%CI: 1.77 to 2.19), 3.01 (95%CI: 2.34 to 3.87) and 5.55 (95%CI: 4.27 to 7.21) respectively[20]. The risk of GDM is positively associated with pre-pregnancy BMI. This information is important when counselling 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 to 15 kg) and those who are underweight with BMI < 18.5 kg/m² should aim for 28-40 lb (12 to 18 kg) weight gain during pregnancy. Those who are overweight with 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 pre-pregnancy BMI of **≥** 30 kg/m² should aim for 11-20 lb (5 to 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 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 in whom they were randomized to receive probiotics or placebo. Probiotics given in that study were Lactobacillus rhamnosus GG (1010 colony forming units) and Bifidobacterium lactis Bb12 (1010 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 (1010 colony forming units) and Bifidobacterium lactis Bb12 (1010 colony forming units), reduced GDM frequency in diet/probiotic group (13%) compared to diet/placebo (36%) and control/placebo (34%) groups (*P* = 0.03)[27]. There was no adverse event in mothers or children who have taken probiotic 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 birth weight of infants, of women who were supplemented with probiotics[28]. All these evidences suggest that daily intake of probiotic capsules with Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12 with 1010 colony forming units may be effective in pregnant women who are at high risk for GDM.

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

Various studies support the beneficial relationship between fermented dairy products and 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 daily consumption of 200 mL of a shake containing Lactobacillus acidophilus (4 × 108 CFU/100 mL) and Bifidobacterium bifidum (4 × 108 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 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 labour[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 were able to raise serum 25-hydroxyvitamin D levels to > 30 ng/mL leading to decrease in insulin resistance[43].This dosage is associated with reduction in pregnancy complications without producing toxicity. But, as there are too low evidences supporting vitamin D role in GDM, Cochrane database has concluded that further more randomized trials are required to evaluate its role in pregnancy[44]. Vitamin D and lifestyle intervention, a European multicentre study results are awaited, which may throw light on our dilemma about the role of vitamin D in 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 incidence of GDM is < 3%, selective screening in 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 Gynecologists** **(ACOG)**: It recommends 1-h Glucose Challenge Test for screening GDM. If plasma glucose value is ≥ 140 mg/dL, 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: FPG ≥ 5.3 mmol/L (95 mg/dL); 1 h ≥ 10 mmol/L (180 mg/dL); 2 h ≥ 8.6 mmol/L (155 mg/dL); 3 h ≥ 7.8 mmol/L (140 mg/dL). GDM is diagnosed with ≥ 2 abnormal values.

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

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

**Diabetes in Pregnancy Study Group India diagnostic criterion**: 75 g oral glucose load is performed irrespective of the last meal and blood sugar level is taken 2-h later. A value of ≥ 7.8 mmol/L (140 mg/dL) is diagnosed as GDM. This may be of use in the limited resource settings and where compliance of the patient is doubtful.

***IADPSG Two- phase Strategy for the detection of hyperglycemia in pregnancy***

The HAPO, a multicentre study was done in a cohort of 25505 pregnant women. Participants were tested with 2-h, 75 g OGTT and their pregnancy were followed for adverse maternal and neonatal outcomes[47]. Based on the study results, the IADPSG consensus panel has formulated the new diagnostic criteria for GDM[48]. The cutoff 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 of 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.

* GDM is diagnosed if FPG is between 5.1 to 7.0 mmol/L (92 to 126 mg/dL).

A diagnosis of Overt Diabetes is made with one of the following values:

* FPG ≥ 7.0 mmol/L (126 mg/dL);
* HbA1C ≥ 6.5%;
* RPG ≥ 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 ≥ 7.0 mmol/L (126 mg/dL), Overt Diabetes was diagnosed.

GDM was diagnosed with ≥ one abnormal values:

* FPG ≥ 5.1mmol/L (92 mg/dL);
* 1-h ≥ 10mmo/L (180 mg/dL);
* 2-h ≥ 8.5mmol/L (153 mg/dL).

**ADIPS criteria 2013:** It also recommends same cut off points as suggested by IADPSG. A diagnosis of GDM is made if ≥ 1 of the following glucose levels is elevated:

* FPG ≥ 5.1 mmol/L;
* 1-h ≥ 10.0 mmol/L;
* 2‐ h ≥ 8.5 mmol/L.

But 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 cutoff 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 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:

* FPG ≥ 7.0 mmol/L (126 mg/dL);
* 2-h plasma glucose ≥ 11.1 mmol/L (200 mg/dL) following a 75 g oral glucose load;
* Random plasma glucose ≥ 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:

* Fasting plasma glucose = 5.1-6.9 mmol/L (92 -125 mg/dL);
* 1-h post 75 g oral glucose load ≥ 10.0 mmol/L (180 mg/dL) \*;
* 2-h post 75 g oral glucose load between 8.5–11.0 mmol/L (153-199 mg/dL).

\*there are no established criteria for the diagnosis of diabetes based on the 1-h post-load value.

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***

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 incidence of GDM, it recommends these changes with the intention of optimizing gestational outcomes for women and their babies[5].

Falavigna *et al*[50] has 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 evidences also suggest 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 an 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 the 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 to 0.63) and the proportion of infants weighing greater than the 90th birth centile (RR 0.55, 95%CI: 0.30 to 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 to 0.73)[57].

***Glycemic targets during pregnancy***

 Glycemic targets as recommended by Fifth International Workshop-Conference on GDM[58] are capillary glucose concentrations of:

Pre-prandial: ≤ 5.3 mmol/L (96 mg/dL);

1-h post meal: ≤ 7.8 mmol/L (140 mg/dL);

2-h post meal: ≤ 6.7 mmol/L (120 mg/dL).

In Metformin In Gestational diabetes (MIG) trial, analysis of glycemia and its outcome showed that fasting capillary glucose < 4.9 mmol/L (88 mg/dL) had significantly better outcomes than women with fasting capillary glucose between 4.9 and ≥ 5.3 mmol/L (88 and ≥ 95 mg/dL). At 2 h postprandial, capillary glucose values of ≤ 6.4 mmol/L (≤ 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 lowered than what current guidelines recommend. Further studies are required in this field.

Adjustment of insulin therapy based on postprandial glucose values improve glycemic control better than pre-prandial glucose values and decreases the risk of neonatal hypoglycemia, macrosomia, and caesarean delivery[61].

Continuous Glucose Monitoring Systems (CGMS) may be of use in pregnant women with overt diabetes who require very high dose insulin to achieve good glycemic control. CGMS during pregnancy is associated with improved glycemic control and reduced risk of macrosomia[62]. A study in Finland showed that CGMS detect 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 per day is not advisable. A study by Rizzo et al has shown that severe calorie restriction to < 1500 cal per day is associated with increased incidence of ketonemia resulting in lowered mental developmental index scores and average Stanford-Binet scores in the babies[64]. 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 baby[66,67]. Studies on the effect of 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 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 fasting state. Regular human insulin (RHI) is shorter acting Insulin and Neutral Protamines Hagedorn (NPH) is the intermediate acting insulin in common practice till now. Following each meal glucose levels peak at ∼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 ½ to 1 h after injection and its effect reaches 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 its action within 15 min, reaches 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 (US) 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.

Latest rapid acting insulin analog, insulin Glulisine is available with same action profile to that of Aspart and Lispro. As there are no clinical data available, till now US FDA has not approved 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, 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 US FDA has approved Insulin Detemir as class B in pregnancy. Though insulin glargine has same pharmacodynamic properties to 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 is found to be safe during pregnancy.

***Insulin pump***

Insulin pumps allow for flexible insulin administration with a profile that resembles very closely the physiological insulin profile of the beta-cell of pancreas. 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 us to 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, 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.

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 close-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 they can be used widespread.

***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 are emerging evidences for role of oral medications in these women. ACOG and 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 is 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. Top of Form

A randomized control trial by Niromanesh *et al*[81] showed that the birth weight of the neonate was less in the metformin group compared to the insulin group, though not statistically significant. Maternal weight gain is 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, caesarean deliveries, neonatal intensive care unit admissions and birth malformations or neonatal injuries.

There is no significant difference in postprandial glucose control between women

taking 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].

 But there are studies which show that metformin can induce neural tube defect 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 cause neural tube defects. But, 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 absence of AMPK activity, metformin did not inhibit Pax3expression in embryos and thus does 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.Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Women Hospital, Tehran University of Medical Sciences, Tehran, Iran

Metformin in gestational diabetes trial (MIG trial) by Rowen *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. MIG trial concluded that metformin had similar perinatal complications compared to insulin. Because of easiness, women preferred metformin to insulin treatment.

The follow up of those exposed children up to 2 years in the MiG–TOFU trial revealed that metformin-exposed infants had a more subcutaneous fat and less visceral fat. This may probably result in 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 less in the metformin. A few studies show 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 shows 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 as with insulin. Glycemic control and perinatal outcomes produced by OHAs were comparable to insulin. Insulin is costlier, inconvenient to use and it needs ideal storage conditions, which makes it difficult to practice 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 increased risk of fetal demise in patients with poor glycemic control. To improve the 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 IUGR, macrosomia or in those with co-morbid conditions, such as preeclampsia. There is no consensus regarding antepartum testing in women with GDM well controlled with diet.

**INDUCTION OF LABOUR**

The timing and the mode of delivery is still debatable. For the timing of delivery, 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 labour after 38 completed weeks[79]. ACOG did not recommend routine delivery before 40 wk in GDM women well controlled with diet or medication[61]. Induction of labour at term helps to reduce the incidence of shoulder dystocia in women with gestational diabetes[95]. The option of induction of labour in GDM still remains a controversy. Further studies are needed in this field.

 For the mode of delivery, caesarean would only be suggested for an estimated fetal weight of ≥ 4500 g in mothers with GDM[79,96].

**GLYCEMIC CONTROL DURING LABOUR**

During labour 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 labour 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 prediabetes 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. Those who are diagnosed with impaired fasting glucose or impaired glucose tolerance, annual testing should be done.

Women who had GDM in first pregnancy, there is 13.2 fold increased risk (95%CI: 12.0-14.6) of developing GDM during 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].

The Lifestyle interventions or metformin should be offered to women with a history of GDM who develop prediabetes. 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, very obese women)[5].

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