DOI: https://doi.org/10.36094/sc.v88.2022.Gestational_Diabetes_Mellitus.Bardhan.346

Research Communication

Sci. and Cult. 88 (9–10) : 346-353 (2022)

Gestational Diabetes Mellitus: Understanding the Mechanisms and Managing the Challenge

***Abstract*: Gestational diabetes mellitus (GDM) is an emerging public health challenge affecting 15.8% of live-birth globally and in India it ranges between 3.8 and 21% depending on geographical location and diagnostic criteria. GDM is associated with a number of health problems both in mother and the fetus; hence it is important to retard its prevalence and associated perinatal complications, in cost-effective manner. In this backdrop, the aim of the present work is to highlight the underlying pathophysiological mechanism and efficacy of dietary intervention to address the challenge of GDM.**

Key words: Insulin resistance, myo-inositol, perinatal complications, probiotics, T2DM

Gestational diabetes mellitus (GDM) is one of the most common pregnancy related complications characterised by spontaneous hyperglycaemia with prevalence varying between 1% and 14% around the world[1].GDM is defined as varying severity of glucose intolerance recognized during gestation[2]. Risk factors contributing to hyperglycemia in pregnancy(HIP) which may lead to GDM, include family history of diabetes mellitus, sedentary lifestyle, previous delivery of macrosomia or stillbirth, intrauterine fetal death, maternal obesity, and preterm delivery[3]. The high prevalence of diabetes in women at child bearing age imposes risks for both mother and the newborn[3-4]. The immediate maternal outcomes include caesarean section, preeclampsia, poly/oligohydramnios, abortion/miscarriage and like challenges. Complications in the new born include neonatal hypoglycemia, macrosomia, preterm birth, hyperinsulinemia, shoulder dystocia, respiratory distress syndrome and like. Although in most instances, GDM resolves immediately after delivery, upto 50% women with a history of GDM may develop Type 2 diabetes mellitus (T2DM) within ten year of pregnancy and are prone to face GDM in future pregnancies[5]. Maternal GDM increases the risks of glucose intolerance in about 20% of offsprings during their fifth to sixteenth year of age and are at higher risk of developing obesity and T2DM during adulthood[6]. An attempt, in this context, has been made to highlight the underlying pathophysiological mechanisms and efficacy of dietary interventions of GDM.

Findings

Definition and Classification: GDM is any degree of glucose intolerance, first diagnosed during the second or third trimester of gestation, that clearly does not refer to pre-existing or overt diabetes[7]. Previously GDM was defined as varying degree of glucose intolerance and hyperglycaemia recognized at any time during pregnancy irrespective of the degree and the onset of hyperglycaemia[8]. Borderline gestational diabetes mellitus (BGDM) is another concept in this regard where the values of glucose tolerance range intermediate between normal and gestational diabetes. The health risks associated with BGDM have been found to be similar to those for GDM[7]. Hyperglycaemia detected during pregnancy can be categorised into three types. They are mentioned below:

Table 1: Outlining Different Types of Diabetes in Pregnancy

Pre-existing diabetes (PED)	Women diagnosed with diabetes at first trimester of pregnancy or those who meet the diagnostic criteria for diabetes both type 1 and type 2 without pregnancy
Overt diabetes	Severe hyperglycaemia that mimick pre-existing diabetes (PED)[7]
Hyperglycaemia in pregnancy (HIP)	All type of diabetes observed in pregnancy comprising GDM and PED[8]

Prevalence: The prevalence of GDM has been increasing over the period of time in parallel with increasing rates of obesity and T2DM. Due to lack of universally accepted diagnostic criteria for screening of GDM, the estimation of exact prevalence of GDM remains unclear. World wide 15.8% of total live births were affected by HIP

The journal is in the category 'Group A' of UGC-CARE list and falls under the broad category of Multidisciplinary Sciences covering the areas Arts and Humanities, Science and Social Sciences.

in 2019 of which 83.6% were due to GDM[1]. The prevalence rate may vary with diversity of population, ethnicity and region. South-East Asia had the highest prevalence of GDM (27%), while the lowest prevalence was seen in Middle East and North Africa (7.5%). Almost 86.6% cases of HIP have been reported in low- and middle-income countries, where access to maternal healthcare is limited[2]. In India, the prevalence of GDM has increased from 2% in 1980 to 16.55% in 2000 with large variations within-countries[9], depending on race/ethnicity and socioeconomic status. Indian women are 11-fold more prone to develop diabetes mellitus during pregnancy compared to Caucasian women. In India it has been reported that 4 milion women are suffering from GDM and more specifically the rate of GDM among various states of India ranges from 3.8% in Kashmir, 6.6% in Rajasthan, 6.94% in Jammu, 7.1% in Haryana, 9.5% in Western India, 18.9% in Tamil Nadu, 35% in Punjab to 41% in Lucknow[10].

Glucose Homeostasis in Pregnancy: During healthy pregnancy, multiple physiological adaptations take place in mother's body to support the foetus for normal growth and to maintain optimum maternal nutrition. A number of organs and systems contribute to the pathophysiology of GDM where tissue insulin resistance (IR) and α-cell impairment seem to be critically associated. Insulin sensitivity, one of the important regulators of glucose metabolism, gets altered during gestational period. Initially growth hormone level drops down leading to increase glucose sensitivity of the peripheral tissues; as a result of it, glucose uptake in adipose tissue is increased that is particularly important for fulfilling the increasing energy demands later in gestation[11]. As pregnancy progresses, circulating levels of local and placental hormones start to increase and together lead to a state of IR that reaches its peak during third trimester of pregnancy. In addition to it, inflammatory factors like cytokines, tumor necrosis factor-α also contribute in developing IR. As a result of IR, gluconeogenesis takes place, further enhancing the blood glucose level. To compensate the abnormal glucose environment, pancreatic α cell undergoes a number of structural changes causing hypertrophy and hyperplasia[12]. In healthy pregnancy, pancreatic α cells return to its normal state and IR decreases to pre-pregnancy level by placental hormones immediately after delivery. Oxidative stress (OS), an imbalance between production and utilization of reactive oxygen species leading to cellular damage, as in case of T2DM[13], has also been implicated in the pathogenesis of GDM due to overproduction of free radicals and impaired free-radical scavenging mechanisms.

Role of Lipoprotein Lipase (LPL) Activity: LPL also is a biomarker of IR in pregnant and non-pregnant women. LPL level has been found to be reduced in IR and T2DM though the actual mechanism responsible for this is not clearly understood. LPL activity is greatly regulated by plasma insulin level. In insulin deficient or insulin resistant state the activity of LPL can be reduced between 25% and 50% in adipose tissue[14]. Insulin is considered as a major regulator of adipose tissue LPL, through its effect on LPL transcription during adipocyte differentiation and through increasing LPL mRNA levels. A tissue-specific regulation of LPL action by insulin work in such a way that LPL activity in adipose tissue was stimulated by acute infusions of insulin while LPL activity in skeletal muscle was decreased by this hormone[15]. LPL influences the levels of intramyocellular lipid in order to improve the insulin sensitivity by controlling the delivery of free fatty acids to muscle[16].

LPL is a hydrolase, responsible for the hydrolysis of triglyceride rich lipoprotein like chylomicron and very low-density lipoprotein (VLDL) in endothelial cell. The activity of adipose tissue LPL is found to reduce in the late gestation and is associated with dyslipidemia, a major problem in GDM[17]. The main two changes in lipid metabolism that occur during the gestational period include the increased amount of fat depot in the adipose tissue in the early phase of gestation and development of dyslipidemia in late gestation. During the last third trimester of pregnancy, the activity of LPL gets reduced as a result of IR and some other factors like reduced level of transcription factor peroxisome proliferator-activated receptor gamma (PPAR-γ) that influence adipose tissue specific LPL synthesis[18]. As LPL activity is reduced, the production of VLDL-TAG by liver increases and their clearance from circulation decreases that together lead to the greatest increase in plasma TAGs corresponds to VLDLs[19]. Such results lead to TAG enrichment of high-density lipoprotein like LDL and HDL that carries TAGs in very small proportion. Cholesteryl ester transfer protein (CETP) facilitates the proportional accumulation of TAGs in buoyant TAG-rich HDL_{2b} subfractions at the expense of cholesterol rich and TAG-poor HDL_3[20]. Hyper-insulinemia, hyperglycemia and dyslipidemia together may contribute in the progression of atherosclerosis, hypertension and inflammation[21]. All these factors are linked in the progression of micro and macro vascular disturbances during pregnancy although many other factors like duration of diabetes mellitus, quality of glycaemic control, and degree of preexisting lesions also

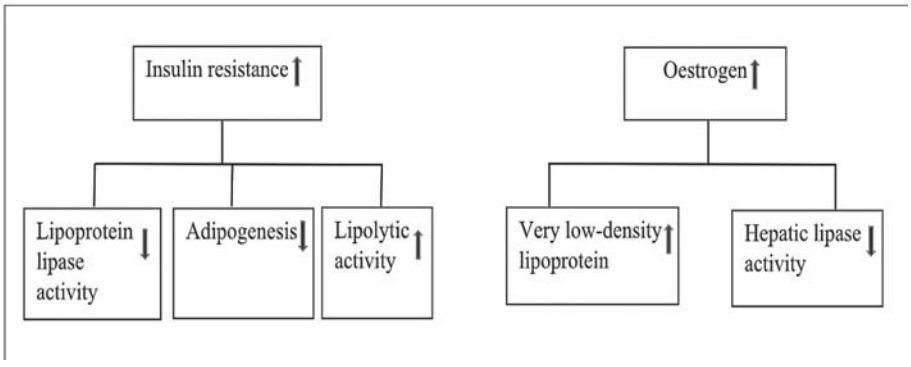

Figure 1: Contributing factors of hypertriglyceridemia mediated by Insulin resistant in late Pregnancy

play an important role in the development of maternal vascular complication.

Predisposing factors of GDM: ***Obesity:*** Increased sedentarism, both in habitual and occupational, is leading to high prevalence of obesity, which is an established risk factor for various metabolic derangements including GDM. Maternal obesity is an important risk factor for gestational diabetes mellitus; women who are obese or severely obese before pregnancy are four to eight times more likely to develop gestational diabetes mellitus, respectively, compared with normal weight women[22]. Adipose tissue is considered as an endocrine gland that produces adipocytokines including both pro and anti-inflammatory mediators. In obese mother the inflammatory markers are found to be produced in excess that alter the post receptor insulin signaling ultimately resulting in increased insulin resistance[23]. Adiponectin, an adipocytokine is produced in white adipose tissue, possesses an antidiabetic effect by activating AMP-kinase and PPAR-γ which regulates insulin resistance and fasting glucose level. Adiponectin level is inversely associated with body fat percentage. The other adipocytokines like tumor necrosis factor-α (TNF-α), leptin potentially reduced the insulin sensitivity[24].

Other Co-morbidities: In chronic pancreatitis, a disease characterized by pancreatic inflammatory and fibrotic injury resulting in irreversible parenchymal damage, progressive nutrient maldigestion and disturbance of the timing and the interactions between nutrient digestion and absorption is observed which may lead to severe metabolic derangements including GDM[25].

Diagnostic Criteria of GDM: GDM can be screened by two main approaches. In two-step approach, 50g one hour glucose test is carried out at first, followed by 100g or 75g three hour oral glucose tolerance test (OGTT) for individuals who are screened positive. On the other hand, in one step process, screening is done by using 75g 2 hour OGTT[26]. Various criteria to diagnose GDM are presented in Table 2.

Screening Criteria in Indian Context: In low and middle-income countries like India, bringing all women in fasting state and getting venous plasma glucose are quite challenging. To address it, Diabetes in Pregnancy Study Group India (DIPSI) adopted the WHO 1999 screening criteria but in non-fasting state and recommended to perform the test using 75g OGTT either in fasting or post-prandial state where 140mg.dl^{-1} 2-h venous plasma value is used to diagnose and screen GDM[28]. All pregnant women may be tested using DIPSI non-fasting criteria initially, then those who tested positive should be screened by a definitive fasting OGTT[29]. As Indian women have shown to have higher risk of developing GDM, they should go for screening after 24 week of gestation or at first antenatal visit.

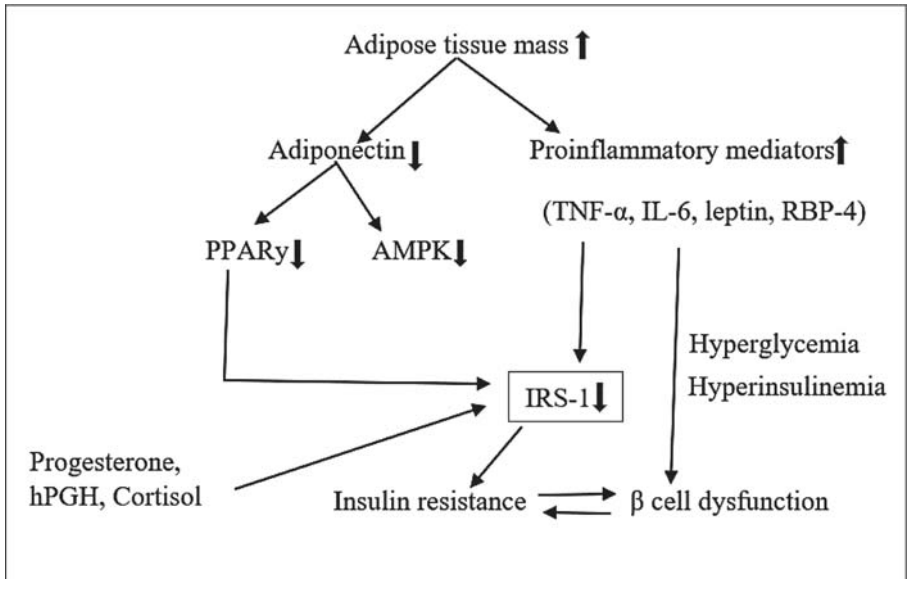

Figure 2: Contributing factor in the altered glucose metabolism in GDM

Prevention and Management of Gestational Diabetes: Due to the overall increasing prevalence of

Table 2: Criteria from various organizations to Diagnose GDM[27]

Criteria	Type of approaches	OGTT load (g)	Glucose Threshold ($mg.dl^{-1}$)				Cut-off values required
			Fasting	1-hour	2-hour	3-hour	
O'Sullivan (1964)	Two step	100	90	165	145	125	Two
National Diabetes Data Group (1979)	Two step	100	105	190	165	145	Two
WHO (1999)	One step	75	126	Not required	140	Not required	One
ADA (2004)	One step	100	95	180	155	140	-
ACOG	Two step	100	105	190	165	145	-
IADPSG(2010)	One step	75	92	180	153	Not required	One
WHO (2013)	One step	75	92	180	153	Not required	One

diabetes mellitus in child bearing age and its adverse effects on both mother and child, preventive measures must be taken and implemented as early as possible. As there is no universally accepted data to define hyperglycaemia in pregnancy, misconception and disagreement remain about the treatment and prevention strategy of GDM. Emerging studies reveal that Nutritional intervention and the key to prevent GDM, as drug therapy alone can not alter the adverse conditions as well as confusion remains regarding the efficacy of insulin and oral pharmacological therapy on mother and foetus health. In addition to these, diet supplements have also shown promising results. In combination with regular physical exercise, and dietary modifications have been found to be effective in reducing the incidence of GDM[30]. Regular practicing of structured form of exercise without any dietary modifications has also been found to impact favourably on various risk factors of diabetes [31-41] which may be beneficial for GDM also.

*Medical Nutrition Therapy***:** Nutritional intervention is one of the key factors in the management of various metabolic diseases [42-43] and GDM is not an exception. All pregnant women diagnosed positive for GDM or glucose intolerance should start proper nutritional intervention to ensure optimum nutritional achievement of both mother and fetus that will result in optional fetal growth and maintenance of normoglycemia[44]. The goals of dietary modifications in GDM are to attain the desired level of glycemic control, adequate weight gain which contribute to maternal and fetal well-being and prevent the development of ketosis. Nutrition therapy of GDM is the beginning to adopt a healthy eating habit that may be continued even after delivery. However, there is no such consensus that can identify a specific diet responsible to achieve optimum goal. Roles of nutrients of special importance in addressing GDM are briefly mentioned below.

Calorie: In pregnancy, energy requirement represents total energy required for the mother's physiological activity and for fetal growth. Strict calorie restricted diet is not recommended in pregnancy as it may interfere with the optimal growth and health of the fetus and mother. Calorie requirement of women with GDM are same as for women without GDM and require minimum 175g of carbohydrate, 71g of protein and 28g of fibre[45]. Calorie restricted diet cannot show any differences in pregnancy outcome compared with those without restriction hence should not encouraged although moderate calorie restriction in obese women (30% of estimated energy needs) with GDM may improve glycemic control without ketonemia and reduce maternal weight gain. The recommended daily energy intake from macronutrients is 33-40% complex carbohydrates, 35-40% fat and 20% proteins[46].

Carbohydrate: Carbohydrate is an ambiguous term containing simple sugars to longer-chain oligo- and poly-saccharides which response differently in glucose homeostasis. Restricted carbohydrate intake is one of the keys to combat GDM in women as it is the major nutrient affecting postprandial blood glucose levels. Although carbohydrate would not be restricted more than 30–40% of the total caloric to avoid ketosis. Manipulation of dietary intake by restricting carbohydrate to less than 42% of total calorie requirement can help to avoid the need for insulin therapy. However, the approach facilitates high fat intake that promotes IR[47]. Recent studies reported that instead of strict carbohydrate restriction that support consumption of 40% carbohydrate and 45% fat, liberal consumption of "complex" carbohydrates containing 60% carbohydrate and 20% fat effectively control maternal glycemia[48]. Patients with GDM should be encourage to select carbohydrate sources with a low GI, such as whole grains, fruits, and vegetable. Substitution of high GI sucrose with slowly digested carbohydrate including iso-

maltulose and resistant maltodextrins, can improve maternal blood glucose[49]. Along with quality, patients with GDM should be trained in carbohydrate counting. When insulin therapy is needed, consistency of carbohydrate intake with meals and snacks is an important focus to prevent sudden hypoglycemia.

Protein: Protein and amino acids are important modulators of glucose metabolism that increases gluconeogenesis and IR. A study in US reported that higher intake of animal protein was significantly associated with the risk of developing GDM. In contrast, a study in Mediterranean countries and United States reported that protein dense food such as red meat and dairy foods were not associated with the risk of GDM[50]. In mid pregnancy, intake of higher than required amount of protein increases the risk of developing GDM by 92%[51].

Fat: Substantial evidence indicates that intake of high fat and low carbohydrate diet may have an association in the development of GDM. Pregnant women who consume higher percentage of energy from fat and lower percentage from carbohydrate have the greater risk of developing GDM and Impaired glucose tolerance (IGT)[52]. Diets high in fat may promote IR in part through elevation of tumor necrosis factor α and Free Fatly Acids (FFAs), resulting in impaired insulin signaling. Elevated FFAs may also promote α-cell defect and evidence suggests that higher intake of animal fats and cholesterol in pre and early pregnancy is associated with increased risk for GDM, implicating an effect of dietary fat and cholesterol on exacerbation of IR.

A typical daily meal plan for women with GDM should include three small to moderate-sized meals and two to four snacks, one of which should be at bedtime to prevent the development of ketosis overnight. A suggested recommendation for calorie distribution across meals and snacks consists of 10% of total calories at breakfast, 30% at lunch, 30% at dinner, and 30% divided between the snacks. To reduce postprandial hyperglycemia, protein should be included with all meals and snacks.

*Dietary Supplement***:** Recently diet supplements have gained considerable attention in correcting several metabolic disorders including hyperglycaemic parameters in pregnancy. Currently, the recommended first step management includes lifestyle and dietary modifications and, if non-pharmacological intervention proves insufficient, administering oral antihyperglycemic agents or insulin may be recommended. Insulin, the most well-known therapy for GDM, is known to cause various side effects. Its cumbersome administration method and the high chance of side effects such as hypoglycemia and weight gain have made insulin a debatable option[53]. Treatment using nutritional supplements by incorporating bioactive agents possessing anti-diabetic effects, such as myo-inositol and probiotics, have shown effective results. Besides, some micronutrients have been proved to be potentially beneficial in attenuating carbohydrate intolerance in pregnancy[54]. The results from observational studies have shown associations between low levels of specific micronutrients (e.g., vitamin D, iron, selenium) and glucose intolerance. Dietary supplements are beneficial particularly when oral food intake is not sufficient to acquire optimum health and it needs to be considered that supplements are not substitute for whole food items.

- **Inositol:** Inositol, a cyclic polyol, belongs to vitamin B complex and is naturally present in plants beans, nuts and cereals and animals has attained a significant consideration in management of GDM due to its insulin like effect. Inositol is the key precursor of nine stereoisomer including myo-inositol (MI) and D-chiro-inositol (DCI) that exerts a beneficial effect in the management of diabetes by modulating glucose metabolism[53]. Inositol metabolites, inositolphos phoglycans (IPGs) act as second messengers of insulin receptors and play an important role in activation and inhibition of specific enzymes that regulate glucose metabolism[55]. Activation of insulin receptors releases IPGs outside the cells and reimports that in turn activate mitochondrial pyruvate dehydrogenase and cytosolic phosphoprotein phosphatase 2C-α (PP2Cα). These two reduce the blood glucose level by elevating oxidative glucose metabolism and glucose uptake by cell. Furthermore, inositol can reduce the duodenal absorption of glucose by competitive inhibition. Biochemical studies have indicated that cellular inositol uptake is counteracted by glucose as they both shares a common transporter system. Myo-inositol is the most abundant form of inositol and its epimerization form is known as D-Chiro-inositol. These two isomers found to also have a beneficial role in the treatment of polycystic ovary syndrome, one of the contributing factors of GDM[56]. Studies have used inositol supplement at the dose of 4g along with 400µg folic acid per day. Supplementation of myo-inositol early in the pregnancy was proved to have the ability to reduce the incidence of GDM in women with elevated fasting glucose. Administration of 2g myo-inositol along with 200µg folic acid twice a

day from early gestation has shown to reduce the incidence of GDM to 6% in non-obese diabetic women compared to control who reported to have GDM incidence rate of 71%, who received only 200µg folic acid. Myo-inositol supplement along with folic acid can also reduce the incidence of GDM in pregnant woman who had a family history of type 2 diabetes in first degree relatives compared with the control who received only folic acid at the same dose. Supplimentation of Inositol at a daily dose of 4g is well to lerated and can be considered in the prevention of GDM in at risk group women without any adverse effects. All the above-mentioned studies were not identified any difference in the rate of preterm delivery and neonatal hypoglycemia between control and experimental group[57].Another study demonstrated that myo-inositol in addition with D-Chiro-inositol along with Zinc, methylsulfonylmethane and folic acid can prevent the occurrence of GDM in women diagnosed with hyperglycaemia during early gestational period[57].

- **Vitamin D:** Now it is well established that vitamin D is linked with many other physiological functions beyond its traditional role in bone health. In recent decade much concern has been received by vitamin D after discovery of its involvement in the prevention of several metabolic disorders including type 1 and 2 diabetes by improving insulin sensitivity and secretion through several mechanisms. The potential involvement of vitamin D in glucose homeostasis is indicative of its association with GDM. An observational study revealed that 45% participants had the chance to develop GDM due to reduced level of serum vitamin D[58]. Interventions with Vitamin D supplement at the first and second trimester of gestation lowered the risk of GDM in third trimester[59]. Women with GDM when treated with Vitamin D supplementation at high dose of 50000IU at 24-28th week of gestation for every two weeks until delivery showed promising results in improving IR, however its effect on FPG and other inflammatory indices was not reported[49].

- **Omega 3 fatty acids:** The intake of omega-3 fatty acid has been potentially linked with improving insulin action and glucose tolerance. Supplementation with docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) at a daily dose of 3.4 g for 2–3 weeks has shown to possess anti-diabetic effect by regulating gene expression of PPAR-γ. As very few randomize control trials has been carried out to investigate the effects of omega-3 supplementation in eliminating risk of GDM, the association between them is inconclusive[50].

- **Probiotics:** Probiotics are the microorganisms that have potential role to provide defined health benefit to the host. The intestinal microbiota is responsible for playing a number of metabolic functions when present in optimum level[60]. The beneficial gut microbiota that are proved to exert positive effects on health, tend to decrease throughout the pregnancy that is associated with several adverse outcome including elevated circulatory pro-inflammatory cytokines, blood glucose and IR in mother. Moreover, these changes are more predominant in obese and overweight pregnant women. Probiotics, as an intervention of GDM, gained interest after establishment of the fact that administration of probiotics in adequate amount can modulate the composition of the gut microbiota that have been linked to improve glucose homeostasis[61]. They can be given as biological supplements or in food such as yogurt making them readily available for consumption. The most promising probiotic species that confer health benefits include members of the Lactobacillus family, Bifidobacterium and Enterococcus[60]. Supplementation of probiotic in healthy pregnant women may improve blood glucose during the third trimester and potentially reduce the risk of developing GDM. Consumption of probiotic yogurt containing two species of microorganisms, Streptococcus thermophilus and Lactobacillus bulgaricus, proved to be more beneficial to correct the glucose metabolism issues than conventional yogurt[62]. But when examined the effect of probiotics in glucose metabolism and weight management of newly diagnosed GDM cases, it did not show any significant difference in IR between probiotic consumed group and placebo group. However, the weight gain of the intervention group was lower only in the last two weeks of the study in comparison with the control group[50]. The minimum effective dose of probiotics for a single physiological effect is observed in the daily doses of 108–1010-unit colony producing. Unfortunately, there is currently no universally accepted treatment or prevention strategy for GDM, except lifestyle intervention (diet

and exercise)[63-65] and occasionally insulin therapy—which is also of limited effectiveness. While emerging oral antidiabetics, such as glyburide and metformin, are promising, concern still remains about their long-term safety for both mother and child[66].

Conclusion: It may be mentioned that the onset and progression of GDM involve various modifiable risk factors and complex pathophysiological pathways, which if addressed early, may be prevented. Judicious combination of dietary and physical activity strategy may help to combat the situation, if not preventable. Nutritional supplementations especially myo-inositol and probiotics show promising result but require further evaluation in large randomized trials. ❐

SWEETY BARDHAN[1]
SAYANTIKA SAHA[1]
AYANA DAS[1]
NEEPA BANERJEE[1,2]
SHANKARASHIS MUKHERJEE[1]*

[1]PHAU, Department of Food and Nutrition,
West Bengal State University,
Kolkata 700126, India

[2]Bhairab Ganguly College affiliated to
West Bengal State University

*e-mail: msasish@yahoo.co.in, mail.drsmlab@gmail.com

Received: 24 December, 2020

Revised: 08 October, 2021

1. International Diabetes Federation, IDF Diabetes atlas , Ninth edition, 15-17 (2019) (2)
2. A. Kayal, V. Mohan, B. Malanda, R.M. Anjana, B. Bhavadharini, M.M. Mahalakshmi, K. Maheswari, R. Uma, R. Unnikrishnan, G. Kalaiyarasi, L. Ninov, A. Belton, *Indian J EndocrMetab.* **20**, 707-15 (2016). DOI: 10.4103/2230-8210.189230.
3. E.M. Wendland, M.R. Torloni, M. Falavigna, J. Trujillo, M.A. Dode, M .A. Campos. *BMC Pregnancy Childbirth*, **12**(1), 23 (2012).
4. B.C.T. Mpondo, Ax. Ernest, H. E. Dee, *J Diabetes MetabDisord.* **14**(42), (2015). doi: 10.1186/s40200-015-0169-7.
5. B. Baz, J. P. Riveline, J. F. Gautier, *Eur J Endocrinol.***174**(2), (2016)
6. C. Kim, K M. Newton, R H. Knopp, *Diabetes Care.* **25**, 1862–1868 (2002). doi: 10.1530/EJE-15-0378.
7. A. Goyal, Y. Gupta, R. Singla, S. Kalra and N. Tandon, *Diabetes Ther.* **11**(8), 1639–1644 (2020). doi:10.1007/s13300-020-00865-3
8. Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy, World Health Organization. (2013)
9. R. K. Chudasama, A. M. Kadri, A. Ratnu , and C. P. Kamariya, *Indian J Community Med* .**44**, 142-6 (2019).
10. A. Kayal, R.M. Anjana, V. Mohan, *Diabetes Voice*. **58**,(2013).
11. D. Newbern and M. Freemark, *CurrOpinEndocrinol Diabetes Obes.* **18**(6), 409–416 (2011).
12. J. F. Plows , J.L .Stanley , P. N.Baker , C. M. Reynolds and M. H .Vickers , *Int. J. Mol. Sci.* **19**(11), 3342 (2018). doi:10.3390/ijms19113342
13. P. Biswas, N. Banerjee, P. Bhattachary., A. Adhikari, S Mukherjee, M. De, *Int J Current Advanced Research* (ISSN: O: 2319-6475, ISSN: P: 2319 – 6505). **6**(3), 2366- 2371 (2017). doi: 10.24327/ijcar.2017. 2371.0011
14. M. C. Andrade Jr, *Insights Enzyme Res*. **2**(1:3), 2018. doi: 10.21767/2573-4466.100013.
15. R.V. JrFarese, T. J. Yost, R.H. Eckel, *Metabolism*.**40**(2), 214–216 (1991). doi: 10.1016/0026-0495(91)90178-y
16. L. K. Pulawa, R. H. Eckel, *CurrOpinClinNutrMetab Care*. **5** 569–574 (2002).
17. E. Herrera, H. Ortega-Senovilla, *Current Pharmaceutical Biotechnology*. **15**, 24-31(2014).
18. N. Zeghari, H. Vidal, M. Younsi, O. Ziegler, P. Drouin, M. Donner, *Am J PhysiolEndocrinolMetab*. (2000).
19. J. J. Alvarez, A. Montelongo, A. Iglesias, M. A. Lasuncion, E. Herrera, *J. Lipid Res*. **37** (2), 299-308 (1996).
20. E. Herrera, *Endocrine.***19**(1), 43-55 (2002). doi: 10.1385/ENDO:19:1:43.
21. Q. Yu, F. Gao, M. XL, *Cardiovasc Res*. **89**, 516-24 (2011).
22. S. Y. Chu, W. M. Callaghan, S. Y. Kim, *Diabetes Care.* **30**, 2070–2076 (2007).
23. S.E. Shoelson, L. Herrero, A, Naaz. *Gastroenterology*. **132,** 2169-2180 (2007). doi: 10.1053/j.gastro.2007.03.059
24. P. M. Catalano, *Reproduction*. **140** (3), 365-371 (2010). doi: 10.1530/REP-10-0088
25. N. Ewald, P. D. Hardt, World J Gastroenterol. **19**(42), 7276-7281(2013).
26. K. P. Fuller and A. F. Borgida, ***Clin Diabetes.* 32(4), 148-150 (2014).**
27. B. Bhavadharini, R. Uma, P. Saravanan, V. Mohan, *Clin Diabetes Endocrinol.* **2**(13), (2016). doi: 10.1186/s40842-016-0031-y.
28. V. Mohan, S. Usha and R. Uma, *J Postgrad Med.* **61**, 151-4 (2015).
29. B. Bhavadharini, M. M. Mahalakshmi, R. M. Anjana, M. Deepa, *ActaDiabetol*. **53**(1), 91-7 (2016).
30. J. Brown, N. A. Alwan, J. West, S. Brown, C. J. McKinlay, D.Farrar, *Cochrane Database Syst Rev*. **5**(5), (2017). doi:10.1002/14651858.
31. S. Mukherjee, N. Banerjee, S. Chatterjee, *Ind J Biol Sci*. **18**, 9-15 (2012).
32. S. Mukherjee, N. Banerjee, S. Chatterjee, B. Chakrabarti, *Sci Cult.* **79**(11 – 12), 503 – 506 (2013).
33. N. Banerjee, S. Chatterjee, S. Kundu, S. Bhattacharjee, S. Mukherjee, *Ind J ClinAnat Physiol.* **1**(1), 29 – 33 (2014).
34. S. Mukherjee, N. Banerjee, S. Chatterjee, S. Chatterjee, *Ind J Biol Sci*. **20**, 40 – 48 (2014).
35. S. Mukherjee, N. Banerjee, S. Chatterjee, S. Chatterjee, *Sci Cult.* **80**(9–10), 279 – 282 (2014).

36. N. Banerjee, S. Chatterjee, S. Chaterjee, A. Chatterjee, S. Bhattacharjee, T. Santra, B. Saha, S. Mukherjee, I. Manna, *Am J Sports Sci* (ISSN: 2330-8559 (Print); ISSN: 2330-8540(Online). **2**(6-1), 19-23 (2014), doi: 10.11648/j.ajss.s.2014020601.14.
37. S. Bhattacharjee, S. Chatterjee, N. Banerjee, T. Santra, P. Mondal, S. Mukherjee, *In: User Centered Design and Occupational Wellbeing,* McGraw Hill Education. 311 – 315 (2014).
38. S. Chatterjee, N. Banerjee, T. Santra, A. Chatterjee, S. Chatterjee, I. Manna, U. Banerjee, S. Mukherjee, *Am J Sport Sci Med.* **2**(5A), 40-44 (2014). doi: 10.12691/ajssm-2-5A-9.
39. S. Kundu, N. Banerjee, T. Santra, S. Chatterjee, S. Mukherjee, *In: User Centered Design and Occupational Wellbeing,* McGraw Hill Education, 328 – 331 (2014).
40. N. Banerjee, S. Chatterjee, A. Chatterjee, S. Kundu, S. De, S. Mukherjee, *Int. Physiol.***2**(2), 41 – 49 (2014).
41. N. Banerjee, S. Chatterjee, S. Chaterjee, S. Bhattacharjee, B. Bhattacharya, S. Mukherjee, *Sci Cult*. **84**(9-10), 339-343 (2018).
42. S. Bhattacharjee, N. Banerjee, S. Chatterjee, T. Santra, S. Chatterjee, A. Chatterjee, P. Biswas, S. De, S. Mukherjee, *World J Pharm Pharm Sci.* **6**(7), 1767-1778 (2017). doi: 10.20959/wjpps20177-9600.
43. N. Banerjee, S. Chatterjee, S. Bhattacharjee, B. Bhattacharya, S. De, S. Mukherjee, *J Pharm Res.***12**(3), 402-407 (2018).
44. Diagnosis & Management of Gestational Diabetes Mellitus, Technical and Operational Guidelines, Maternal Health Division Ministry of Health and Family Welfare Government of India (2018)
45. D. A. J. M. Schoenaker, G. D. Mishra, L. K. Callaway, S. S. Soedamah-Muthu, *Diabetes Care.* **39,** 16-23(2016).
46. C. M. Castilla, D. Mauricio, M. Hernandez, *CurrDiab Rep.* **16**(22), (2016).
47. T.L. Hernandez, R. E. Van Pelt, M. A. Anderson, L. J. Daniels, N. A. West, W.T. Donahoo, J. E. Friedman and L. A. Barbour, *Diabetes Care*. **37**, 1254–1262 (2014).
48. T. L. Hernandez, J. C. Brand-Mille, *Diabetes Care*. **41**, 1343–1345 (2018)
49. Q. Zhang, Y. Cheng, M. He, T. Li, Z. Ma and H. Cheng, *ExpTher Med*. **12**, 1889-95 (2016).
50. J. S. Radesky, E. Oken, S. L. Rifas-Shiman, *PaedPerinatEpidemiol*. **22**, 47–59 (2008).
51. Y. Liang, Y. Gong, X. Zhang, D. Yang, D. Zhao, L. Quan, R. Zhou, W. Bao, G. Cheng, *Front Endocrino*. **9**, (2018). doi: 10.3389/fendo.2018.00596
52. F. Tahir Z. Majid, *Cureus.* **11**(9), (2019). doi: 10.7759/cureus.5671.
53. I. S. Zolezzi, T. M. Samuel, J. Spieldenner, *Nutr Rev*. **75**(S1), 32–50 (2016).
54. A. Bevilacqua, M.Bizzarr, *Int. J. Endocrinol*. (2018). doi: 10.1155/2018/1968450
55. A. S. Grzeszyk, M. KuŸmickiand J. Szamatowicz, *J. Diabetes Res*. (2019).
56. D.Dell'edera, F. Sarlo, A. Allegretti, F. Simone, M.G.Lupo, A. A. Epifania, *Biomed. Rep*. **7**,169-172 (2017).
57. M. Lu, Y. Xu, L. Lv, *Arch Gynecol Obstet*. **293**, 959–966 (2016).
58. S. Shahgheibi, F. Farhadifar, B. Pouya, *J Res Med Sci.* **21**(2), (2016).
59. S. J Zhou, L. Yelland and A. J. McPhee, *Am J ClinNutr*. **95**, 1378–1384 (2012).
60. A. L. Taylor, G. E. Woodfall, K. E. Sheedy, M. L. O'Riley, K. A. Rainbow, E. L. Bramwell and N. J. Kellow, *Nutrients*. **9**(461), (2017). doi:10.3390/nu9050461
61. F. Facchinetti, G. Dante, E. Petrella and I. Neri, *ObstetGynecolSurv*. **69**(11), 669-680 (2014).
62. N. Dolatkhah, M. Hajifaraji, F. Abbasalizadehand M. M.Abbasi, *J Health PopulNutr*. **33**(25), (2015).
63. N. Banerjee, S. Chatterjee, S. Chatterjee, K. Ghosh, S. De and S. Mukherjee, *Int Physiol.* **3,** 11-15 (2015).
64. N. Banerjee, S. Chatterjee, A. Chatterjee, S. Mukherjee, *Ergonomics for Rural Development* (ISBN 978-93-5174-905-9). 448 – 455 (2015).
65. S. Chatterjee, N. Banerjee, S. Chatterjee, S. Mukherjee, *Ergonomics for Rural Development* (ISBN 978-93-5174-905-9). 461 – 467 (2015).
66. A. Castillo, W. Boggess, K. Stürmer, D. K. Jonsson, M. Funk, *JAMA Pediatr*. **169**, 452–458 (2015).