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GESTATIONAL DIABETES MELLITUS: AN OVERVIEW WITH EMPHASIS ON THERAPEUTIC APPROACHES

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ABSTRACT

Gestational diabetes is the most common complication of pregnancy. Morbidity and mortality of both the mother and infant are prone to increase in women with untreated gestational diabetes. However, over the years with proper screening, antenatal care, lifestyle and therapeutic interventions this has declined drastically. Risk of pre-eclampsia, cesarean section, premature delivery and excessive weight gain as well as neonatal complications like polyhydramnios, macrosomia, fetal hypoglycemia, shoulder dystocia and respiratory distress syndrome are increased in women having gestational diabetes mellitus. All women of reproductive age diagnosed to have diabetes should undergo preconception counseling to have improved materno-fetal outcomes. Medical nutritional therapy and physical activity are the main stay in the management of adequately controlled GDM; while insulin and oral hypoglycemic agents are required for the management of uncontrolled gestational diabetes. This article deals with definition, risk factors, pathophysiology, complications, and management approaches towards gestational diabetes. Other investigational approaches like probiotics, vitamin D and fish oil are also discussed under this article.

KEYWORDS: Gestational diabetes, metformin, insulin, management, medical nutritional therapy, probiotics, vitamin D.

INTRODUCTION

Gestational diabetes mellitus (GDM) defined as "any level of dysglycemia with onset or first recognition during pregnancy" affected around 12.8% pregnancies all over the globe in 2019 as stated by International Diabetes Federation.[1,2] Growing evidence from various studies indicate that women with GDM have an increased risk of developing diabetes, especially

type 2 diabetes mellitus later in life. However, whether intensive management of GDM is beneficial for the prevention of postpartum diabetes and development of diabetes later in life is uncertain.[1,2] Prevalence of GDM could be affected by several factors like maternal age, maternal weight, BMI, family history of diabetes, multiparity, and ethnicity.[3] Despite GDM being a transient problem, its consequences could last lifelong and due to its high prevalence, GDM poses as a major hazard in attaining improved materno-fetal outcomes.[4] Due to the innumerable guidelines available, several alternatives are at hand for the treatment of hyperglycemia during gestation depending on the resources and the health care provider.[3,5]

Pathophysiology of GDM

Physiologically, insulin requirement elevates during pregnancy particularly due to the increased maternal caloric intake, weight gain, placental hormones like lactogen and growth hormone, as well as elevated prolactin production. With advancing pregnancy, due to the need for increased insulin production, there is a simultaneous increase in pancreatic β-cell mass. Inadequate rise in insulin secretion due to the fault in expansion of β-cell mass leads to gestational diabetes mellitus.[5]

Concentration gradient between maternal and fetal glucose levels affects the transport of maternal glucose to the fetus across the placenta. As pregnancy advances, an increasing amount of glucose is drawn by the fetus, which leads to a reduction in the maternal glucose levels.[5] In order to maintain the concentration gradient of glucose across the placenta, the maternal hepatic glucose production and insulin resistance increases.[6]

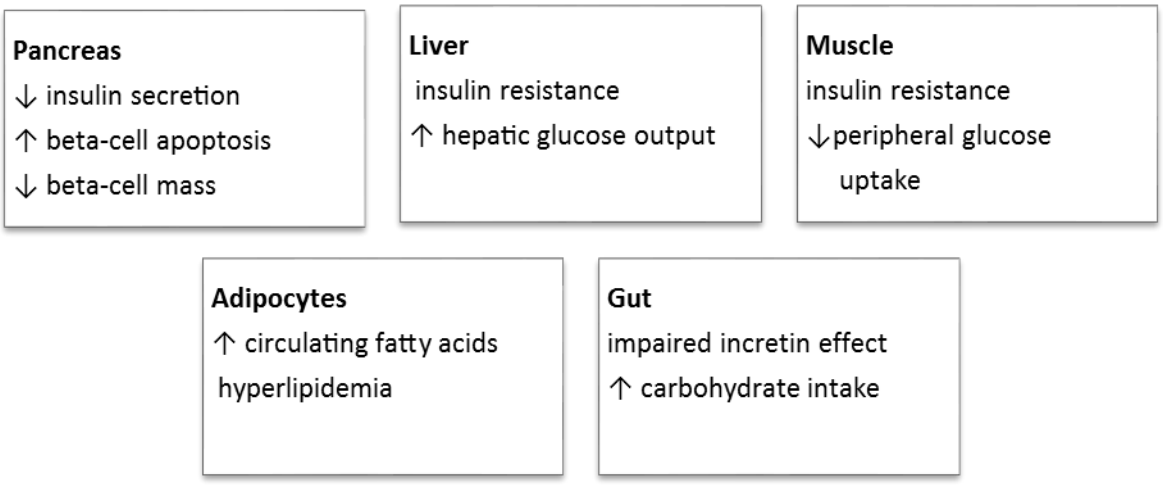

Figure 1: Pathophysiology of gestational diabetes.[7,8]

Risk Factors

1. Maternal factors

- Advanced maternal age
- Obesity
- Dietary pattern
- Cigarette smoking / passive smoking
- Excessive gestational weight gain
- Parity

2. Family history

- Family history of diabetes

3. History of disease

- History of GDM
- Polycystic ovary syndrome
- History of fetal macrosomia

4. Socioeconomic factor

- Low educational level[9]

Complications

Both mother and the fetus are susceptible to develop complications from GDM. Women with GDM could develop pre-eclampsia and are more prone to need delivery by cesarean section compared to women with normal pregnancy. Risk for obstetrical and neonatal complications are directly related to the degree of glycemic control during gestation, where poor glycemic control could lead to neonatal complications including polyhydraminos, macrosomia, premature delivery, shoulder dystocia, hyperbilirubinemia, hypoglycemia and respiratory distress syndrome. Women with GDM are also more susceptible to develop type 2 diabetes mellitus late in life.[11,15,16]

Management

Optimal management of gestational diabetes involves a multidisciplinary approach. Self monitoring of glucose levels, lifestyle interventions, medical nutritional therapy, and pharmacotherapy are involved in the management of GDM. No definite protocols on when pharmacotherapy should be initiated are currently available for determining the optimal time to initiate pharmacotherapy. Generally, if hyperglycemia persists even after 10-14 days of

medical nutritional therapy (MNT) and lifestyle interventions, pharmacotherapy should be initiated.[5]

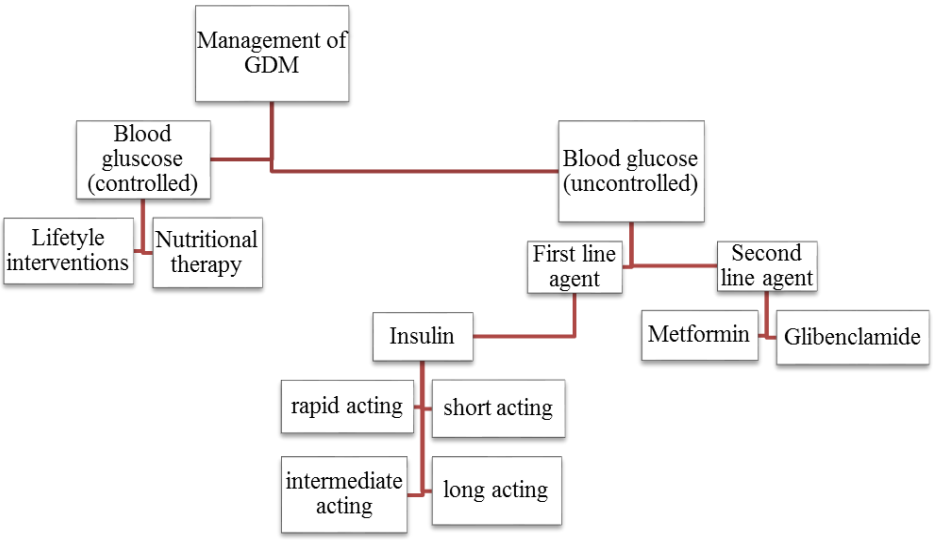

Figure 2: Management of gestational diabetes.[5]

Preconception Counseling

The importance of maintaining adequate glucose control before conception as well as throughout the gestational period should be informed to all women of reproductive age diagnosed with diabetes. Maintenance of HbA1C <6.5% is associated with lower risk of preeclampsia, congenital abnormalities, and premature delivery. Educating women of reproductive potential with diabetes about risks involved in unplanned pregnancies and the need for pregnancy planning for improved materno-fetal outcomes is essential. Discussion on family planning and prescription of effective contraception to be used until the women is ready to conceive helps reduce GDM risks.[13]

In order to minimize the complications associated with GDM, all women with diabetes of reproductive age should be educated about,

- Unplanned pregnancies being associated with an increased risk of neonatal abnormalities and maternal hyperglycemia
- Effective contraception should be used when needed to prevent pregnancy.[13]

Medication history should be reviewed thoroughly for the presence of potentially harmful drugs like statins, ACE inhibitors and angiotensin receptor blockers. Testing for diabetes must include HbA1C, urinary albumin: creatinine ratio and creatinine.[13]

The following points should be considered during preconception counseling,

- Routine diabetes care should incorporate preconception counseling in all women with diabetes starting from puberty and should be continued in all women of childbearing potential.
- Birth control and effective contraception should be suggested until a woman achieves adequate glycemic control.
- The importance of attaining glycemic levels near to normal as possible should be addressed, i.e, HbA1C <6.5%, to mitigate the risk associated with GDM like preeclampsia, neonatal abnormalities, macrosomia, premature delivery, and other complications.[13]

Counseling on matters specific to diabetes should include an explanation on

- Gestation related risks to mother and fetus.
- Reduction of risks by various strategies which include adequate glycemic control, nutritional therapy and lifestyle interventions.
- Attaining adequate glycemic control before conception.[13]

Nutritional Therapy

In women with adequate glucose control, medical nutritional therapy (MNT) is planned by a diabetes educator. Generally during gestation women are instructed on the consumption of three meals along with two snacks per day. The literature has pointed out several dietary approaches which include,

- low-carbohydrate diets
- low-glycemic index diets
- calorie-restricted diets
- the DASH diet (dietary approaches to stop hypertension),
- low-unsaturated fat diets, high-fiber diets, and soy-based diets.[5,12]

In order to attain optimal weight, achieve adequate glycemic control and boost maternal and fetal health, the dietary plan should incorporate adequate calorie intake according to the recommendations from Institute of Medicine.[13] Reducing carbohydrate intake is the basis of GDM treatment. Simple carbohydrates causes higher post meal excursions. Hence to reduce postprandial hyperglycemia and the need for insulin, complex carbohydrates having low glycemic indexes are preferred over simple carhohydrates. [14] Diet with high protein content

did not demonstrate any improvement in blood glucose levels. Studies also suggests that excessive protein intake could be linked to low birth weight of the fetus.[14] The Dietary Reference Intakes (DRI) recommends a minimum of 71 g of protein, 175 g of carbohydrate, and 28 g of fiber for all pregnant women.[13] Nutritional therapy involves limiting consumption of saturated fats and trans fats while emphasizing the intake of monounsaturated and polyunsaturated fats.[13]

Exercise

Exercise plays a vital role in the management of GDM along with dietary and pharmacological interventions.[17] Uncertainty of benefits and risks associated with exercise during gestation averts women from indulging in physical activity.[17] Other than those women who are contraindicated from engaging in exercise, under adequate guidance, it is beneficial as well as safe for the management of gestational diabetes mellitus.[17]

During pregnancy aerobic and resistance exercise is advised, especially those causing less pressure on the joints and involving large muscle groups like walking, jogging, stationary cycling, swimming, strength training, etc.[17,18] Currently, moderate intensity exercise for 30 minutes, 5 days a week is recommended.[5] Moderate intensity exercise refers to those activity requiring people to breath slightly harder than normal.[19] When difficult to carry out moderate intensity workout, light exercises like 10- 15 minutes of post meal walks is beneficial in reducing blood glucose levels. High-intensity workouts should be avoided as it could cause abdominal trauma.[5] However, before a pregnant women can begin any kind of physical activity, they should consult their gynecologist to rule out any contraindications or complications.[18]

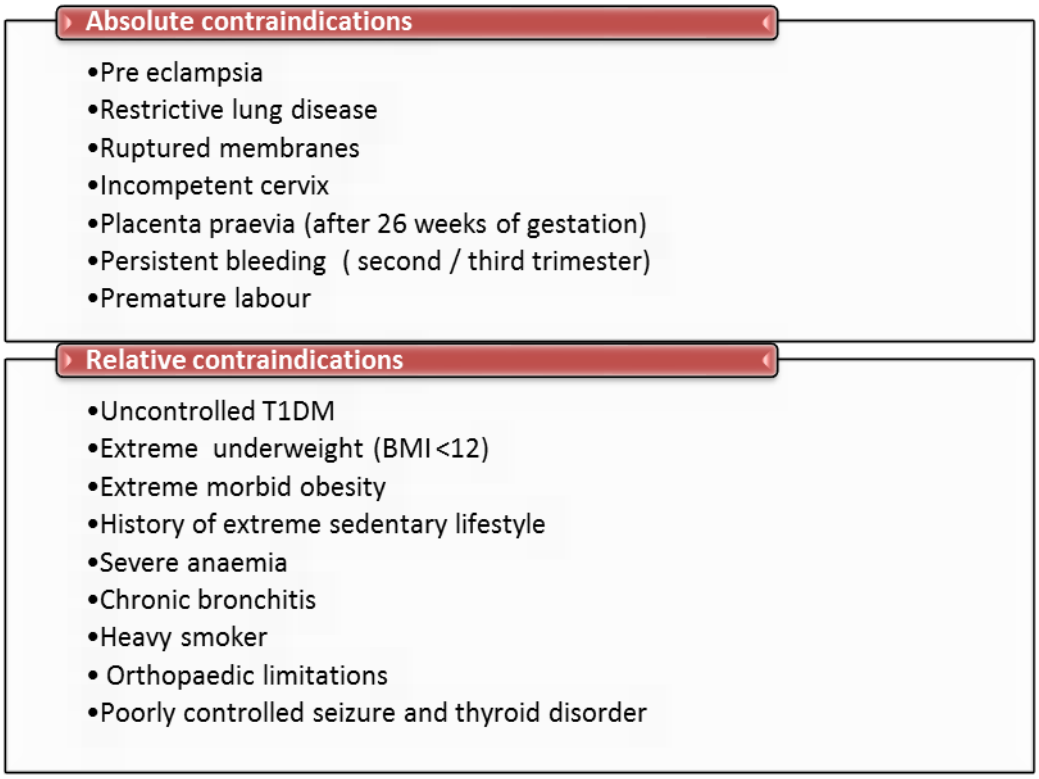

Figure 3: Contraindications for exercise during gestation.[17,18,19]

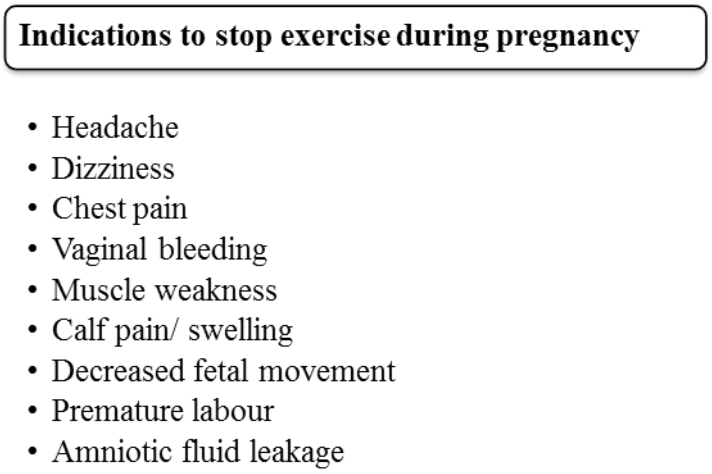

Figure 4: Indication to stop exercise during preganacy.[17,19]

Lacks of proper guidelines on the type, duration and intensity of physical activity during gestation have contributed to the low prevalence of physical activity during gestation around the world.[18] Additionally, people's traditional belief of requiring rest during gestation also contribute to the reduced prevalence rate.[18]

Pharmacotherapy

Gestational diabetes mellitus can be managed by several approaches.[5] GDM, that remains uncontrolled despite nutritional and lifestyle interventions require pharmacotherapeutic management.[5] Insulin and oral hypoglycemic agents are widely being used for therapeutic management of uncontrolled GDM.

- **Insulin Therapy**

Insulin is currently recommended as the first line pharmacological agent in the management of GDM as it is effective and none of the available preparations have demonstrated their ability to cross the placenta.[13,20] Insulin acts upon specific receptors present on the cell-membrane of nearly all cells. Insulin receptor is a tyrosine kinase receptor comprising of 2 α and 2 β subunits linked by disulfide bonds. The insulin binding sites are present on the α subunits and β subunits have the tyrosine kinase activity. Insulin binds to α subunits and induces aggregation as well as internalization of the bound insulin molecules along with the receptor. This in turn activates the tyrosine kinase activity of β subunits and phosphorylates tyrosine residues onto each other, which in turn results in a series of reactions (phosphorylation and dephosphorylation), causing stimulation/ inhibition of the enzymes that are involved in rapid metabolic actions produced by insulin.[21]

Insulin also stimulates transport of glucose across the cell membrane to plasma membrane by a glucose transporter (GLUT4). The insulin-receptor complex that is internalized either undergo degradation intracellularly or return back to surface and insulin is then released extracellularly.[21]

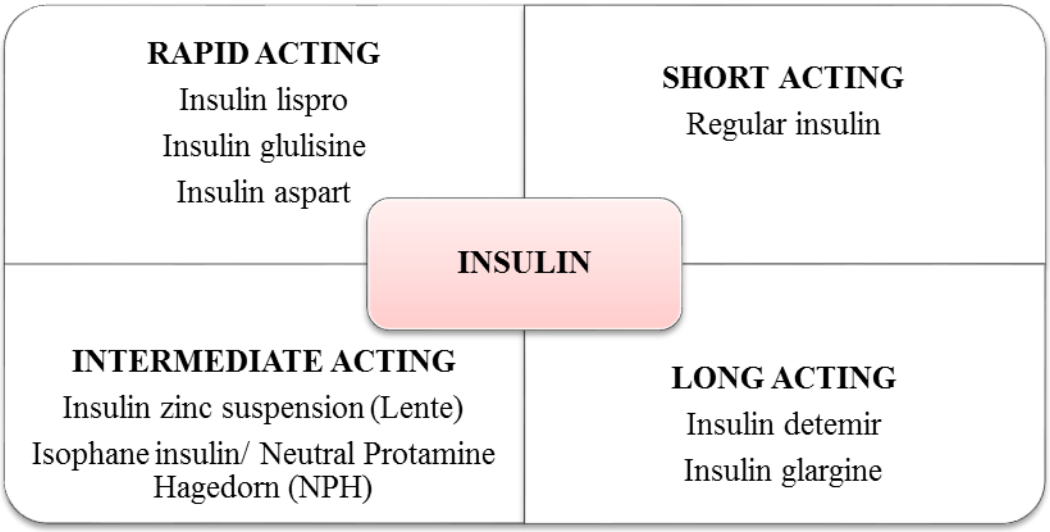

Figure 5: Insulin classification.[21]

For women diagnosed with type 1/ type 2 diabetes, ADA recommended targets are,

- Fasting blood glucose (70–95 mg/dL)
- Postprandial glucose after 1 hour (110–140 mg/dL)
- Postprandial glucose after 2 hour (100–120 mg/dL).[13]

Prescribing insulin based on the time of recurrent hyperglycemia is one of the main approaches. Insulin is either administered as single daily dose or can be given in divided doses depending on the time of hyperglycemia. Intermediate insulin (NPH)/ long acting insulin (determir/ glargine) is administered during bedtime as single dose in those women having morning fasting state hyperglycemia. Rapid acting insulin is administered before meals in women experiencing postprandial hyperglycemia and combination of short acting and intermediate/ long acting insulin is prescribed when hyperglycemia is experienced throughout the day; where intermediate/ long acting insulin is administered at morning or bedtime and short acting insulin is administered prior to meals.[5,22] Insulin is also administered by dividing the total daily dose into two; one half given at bedtime as basal insulin, and the other half given as regular/ rapid acting insulin prior to meals in divided doses between three meals.[23,24] Based on the patient's weight basal insulin dose may be calculated, i.e, 0.2 units/kg/day. Insulin dose is initiated with 2-4 units if hyperglycemia occurs following a meal. In the first trimester, the total daily insulin requirement is 0.7 units/kg/day, second trimester (0.8 units/kg/day) and in the third trimester, it increases to 0.9 to 1.0 units/kg/day.[23,24] When insulin is prescribed, close monitoring of blood glucose levels is essential to avoid episodes of hypoglycemia or hyperglycemia.[5]

- **Oral Hypoglycemic Agents**
  - **Metformin**

Metformin belongs to the class of biguanides (AMPK activator). Studies have shown the activation of AMPK (AMP dependent protein kinase) which play a crucial role in the actions of metformin, by suppressing hepatic gluconeogenesis , enhancing glucose uptake mediated by insulin, intervene in mitochondrial respiratory chain and aiding peripheral glucose utilization through anaerobic glycosis.[21] However, in GDM use of metformin is still being debated. At present, the use of metformin as a first line agent in GDM is not recommended by ADA; due to the lack of safety studies (long term) on in utero metformin exposure and most patients require insulin additionally for the management of hyperglycemia.[25,13] The NICE guidelines recommend the use of metformin if diet and physical activity for 1-2 weeks

fail to control blood glucose levels.[25,26] This is especially recommended when FPG (fasting plasma glucose) is <126mg/dl. If FPG >126 mg/dl, the guideline recommends use of insulin with/ without metformin. However, this guideline mentions off label use of metformin.[25]

Based on the patient's blood glucose levels, metformin is given orally at an initial dose of 500mg once or twice daily and can be titrated to a maximum dose of 2500–3000 mg/day during pregnancy, which is higher compared to the dose administered during the non-pregnant state.[5,24]

- **Glibenclamide**

Glibenclamide belongs to the class of second generation sulfonylureas (K_{ATP} Channel Blockers). They block SUR1 (sulfonylurea receptor), a subunit of the K_{ATP} (ATP sensitive K+ channel) present on the membrane of β cells. As a result, inward flow of K+ ions is restricted, thereby concentration of intracellular K+ falls and the membrane undergoes partial depolarization stimulating Ca^{2+} channel opening. Thus, from the intracellular stores release of Ca^{2+} ions takes place. Ca^{2+} promote fusion of intracellular granules containing insulin with plasma membrane and thus promoting release of insulin by exocytosis.[21]

Based on the blood glucose levels, glibenclamide is started at an initial dose of 2.5 mg/ day or every 12 hour and titrated to a maximum dose of 20mg.[5,24] During gestation, 30-60 minutes after intake, concentration of serum glibenclamide rises and in 2–3 hours peak concentration is attained, the peak concentration coincides with peak blood glucose after a meal. As peak concentration of glibenclamide is attained 2–3 hours following administration, higher glucose levels may be seen when tested 1-2 hours following a meal, with a decrease later.[5]

Probiotics

Probiotics is defined by Food and Agriculture Organizaion/WHO as "live microorganisms which when administered in adequate amounts conferred health benefit on the host". They may be taken as biological supplements and are also present in food such as yogurt.[27] In a study carried out in Finland, consumption of probiotics was found to reduce the risk of GDM in women having normal weight.[28] As a result, a greater interest was provoked in using probiotics as low risk agent for the prevention of GDM.[28] However, in case of high risk pregnancy with pre-pregnancy obesity results have been unfavorable.[28] Similarly, in a double-blind randomized controlled trial, women with GDM (diet controlled), were supplemented with four weeks of probiotics during the second and third trimester. This

resulted in a reduction in fasting blood glucose and high insulin sensitivity.[29] Additionally, probiotic supplementation is thought to improve glycemic control, lipid profile, oxidative stress and inflammation in women with GDM and reduce the incidence of newborn hyperbilirubinemia.[27] High-certainty evidence from conducted trials suggests that there is an increased risk of developing pre-eclampsia with probiotic administration (according to the results obtained from 4 studies, involving 955 women).[30] However, due to variability among available studies, the clinical significance of the findings remain vague. Limitations of the currently available evidence should be addressed by further studies in the future.[27]

Fish Oil

Omega 3-polyunsaturated fatty acids (ω-3 PUFAs) are popularly being used during gestation and GDM.[31] Omega 3 fatty acids play a vital role in the control of fetal and maternal metabolic function, immunity, oxidative stress, preeclampsia, premature delivery, intrauterine growth, macrosomia, and fetal neurodevelopment.[31] Transporters, intracellular proteins, and enzymes are involved in the transport of omega 3 fatty acids through the maternal circulation; which in turn activate receptors to carry out essential metabolic processes in the placenta.[31] In women with gestational diabetes, the placental functioning becomes abnormal and the above process is compromised, affecting the normal materno-fetal transport.[31] This in turn causes a decline in omega-3-fatty-acid levels in the fetus and negatively affects the fetal growth, development and metabolic function.[31]

Supplementation of fish oil has been proposed to reduce the development of chronic diseases like type 2 diabetes mellitus, cancers and cardiovascular diseases. However, the evidence regarding the effect of fish oil supplementation in GDM is minimal.[32] Use of dietary fatty acids as a therapy in lowering the development of gestational diabetes and in reducing the percentage of premature birth has been recommended.[28] A multicentre double-blind, randomized control trial ie; the DOMInO trial (DHA to Optimize Mother Infant Outcome) included pregnant women with <21 week gestation who randomly received fish oil enriched with DHA (800 mg/day) / capsules containing vegetable oil without DHA from entry into the trial till the birth of the fetus. No significant difference in results between the two groups was observed. According to the trial, 800 mg of DHA supplementation per day in the second half of gestation did not decrease the risk of preeclampsia and gestational diabetes. Further studies are required to assess whether fish oil supplementation could reduce the risk of neonatal convulsions and prenatal death.[28,33]

Vitamin D

Vitamin D levels have been proposed to play a possible role in lowering GDM risk.[34] Risk of developing gestational diabetes is associated with low levels of serum 25 hydroxy vitamin D.[28] However, results obtained from the conducted trials were mixed.[28] Supplementation of vitamin D in women with GDM greatly reduced maternal events including maternal hospitalization, cesarean section, postpartum bleeding and neonatal adverse events including polyhydramnios, hyperbilirubinemia, fetal distress and preterm birth.[35]

Recent Cochrane review, that included studies mainly from the Middle East, found out that risk of gestational diabetes and pre-eclampsia could be reduced with vitamin D supplementation alone.[28] Combinations of vitamin D with calcium or vitamin D, calcium and other minerals showed no benefit in lowering risk of pre-eclampsia and GDM.[28] Also, evidence obtained from conducted trials is considered to be of low quality.[28] Another study conducted in China provides evidence that there was no significant linear association of 25 hydroxy vitamin D concentrations with glucose metabolism and GDM risk.[36] The risk of developing GDM was significantly decreased only in those women taking vitamin D concentrations >50nmol and in women taking vitamin D(400-600 IU) with mean concentration of 50nmol/l.[36] However, the relationship between supplementation of vitamin D and gestational diabetes mellitus has not been established yet.[36]

CONCLUSION

Gestational diabetes poses a major obstacle for both the mother and the infant, leading to short term as well as long term complications. Lifestyle changes and medical nutritional therapy is an essential component in management of gestational diabetes mellitus and may suffice for the management of GDM for most women. However, in case of inadequate glucose control insulin or oral hypoglycemic agents may be added. Various other treatment possibilities are also under investigation with limited evidence and mixed results regarding their effect on the management of GDM. Good antenatal, intrapartum and postpartum care could reduce the risk from GDM and optimize the health of both the mother and child.

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DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest with respect to the authorship, research or publication of the article.

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