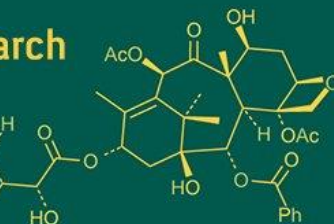


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Effects of gestational diabetes on mothers and infants in Pakistan review article

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Abstract

Gestational diabetes mellitus is the type of diabetes that occur during pregnancy and ended after pregnancy in many cases. The term gestation was used in the late twenty century. The release of glucose increases during normal pregnancy and insulin releases from the pancreas and control the glucose level. During the gestational period, the insulin release fell down and glucose molecules are not properly break down into their substrates. The prevalence of GDM has been observed in the age group of 27 years. GDM affects both children and mother as it causes retinopathy, neuropathy and CVDs. In children, it causes the broad shoulder of fetus and can affect many organs of baby. The high level of glucose can cause complications during delivery. Insulin therapy and metformin are safe treatment for the gestational diabetes. The mechanism underlying the effect cause in the fetus due to gestational diabetes are still known. The studies can be done to find out these mechanisms.

Keywords: GDM, CVDs, metformin, mechanisms

Introduction

Diabetes mellitus is long lasting chronic disorder that describes the utilization and metabolism of food into glucose molecules into the bloodstreams. In Greek, diabetes means “to pass through” and mellitus is Latin word which means “honey and sweetness”. Diabetes mellitus is long term illness and it is also called as premature mortality. There are three types of diabetes mellitus which are diabetes mellitus type 1 and type 2 and gestational diabetes (Kaul *et al.*, 2013) ^[34].

Gestational diabetes is a type of hyperglycemia that is not properly overt diabetes and occur during the pregnancy time duration and it ended after the gestation. The term gestational diabetes (GD) was named by scientist Carrington in the year of 1957 and this term get fame after the publication of articles in 1964. This type of diabetes usually start with the increase in glucose intolerance to increasing glucose fasting and can cause type 1 diabetes in women (McIntyre *et al.*, 2019) ^[8]. GD usually indicated after the three months (13 weeks) during pregnancy and their prevalence has increased due to increase in obesity and premature pregnancy. About 5% women are diagnosed with the GD during the childbearing age because of obesity, age and demographic region. The occurrence of this diseases varies in every country due to their food and life style (Kampmann *et al.*, 2015) ^[6].

When GD is related with the dysfunction of β cells, it cause slight hyperglycemia that's lead to gestational diabetic (Catalano, 2014) ^[3]. The conditions are often considering as the adverse effect of pregnancy which are neonatal metabolic disorders, stillbirth and their related other disorders. During the GD, the mother pancreas is producing less quantity of insulin. As the blood glucose level of mother increases, the insulin start releasing from the fetal pancreas. The release of this pancreas can cause severe effects on the fetus such as broad shoulder, respiratory disorders, liver diseases and complications in delivery of baby (Coustan, 2013) ^[4].

The given picture shows that the lactation process reduces the blood glucose level in the plasma and also decreases the release of insulin. Thus, this process effects the sensitivity of insulin. The utilization of glucose for the production of milk is increased. While prolactin is a hormone that produces during milk production.

This hormone production causes the increase of release of β cells from the pancreas and increases the proliferation of β cells which leads to the increase in the release of insulin in

the body. If the load of production of β cells is controlled then it can reduce the long-term effects of type 2 diabetic mellitus.

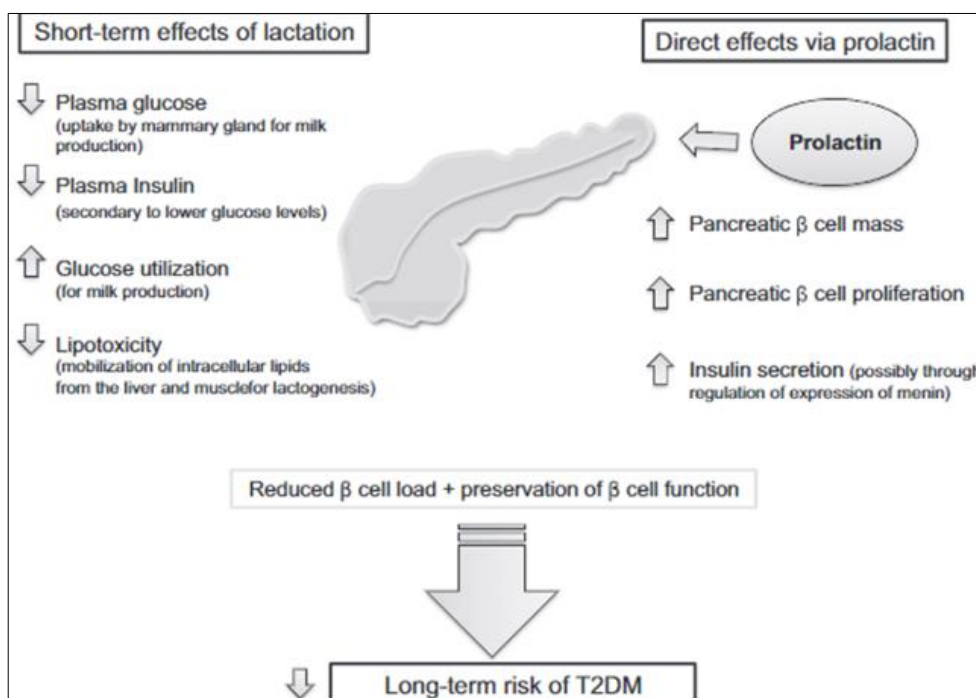


Fig 1: Effects of lactation and prolactin on GDM (Much *et al.*, 2014) ^[14].

Another effect that can cause from the GDM is Macrosomia. It means the excessive weight of fetus after the delivery of baby. The production of insulin is increases that cause the broad shoulders of baby thus it can cause complications during the delivery. There are no proper evidences are present till yet that confirm the effects of use of insulin on fetus. However, many literatures showed that the use of insulin secretagogues is safest type of insulin that can be sue to control the increase of blood glucose level of mother (Padayachee & Coombes, 2015) ^[12].

There are several risk factors that are involved in causing diseases such as age, modern lifestyle, different ethnicity and emerging new health problems. The women with more than 40 years of age are at the risk of two times fold then women with less than 30 years of age. It has also been observed in the diagnosis that those women who carries

male fetus are at the higher risk of getting disease as compared to female fetus (Retnakaran *et al.*, 2015) ^[15].

Literature review: The prevalence of disease varied in every ethnicity and country. The outbreak of GD has observed in almost every country of the world such as US, Canada, Australia, Japan, India and Pakistan etc. GD is less than 5% in Asian countries such as Pakistan and Bangladesh while highest prevalence is observed in the Nepal (Zhu & Zhang, 2016) ^[16]. According to research of GD prevalence on PubMed, it showed almost 1.7–11.6% trend of this disease. The data was collected by the different clinical tests, family history and medical diagnosis. The given picture shows the prevalence of GD in different countries by WHO. The variations were mostly observed in the Europe and highest peak in the south east Asia (Schneider *et al.*, 2012) ^[16].

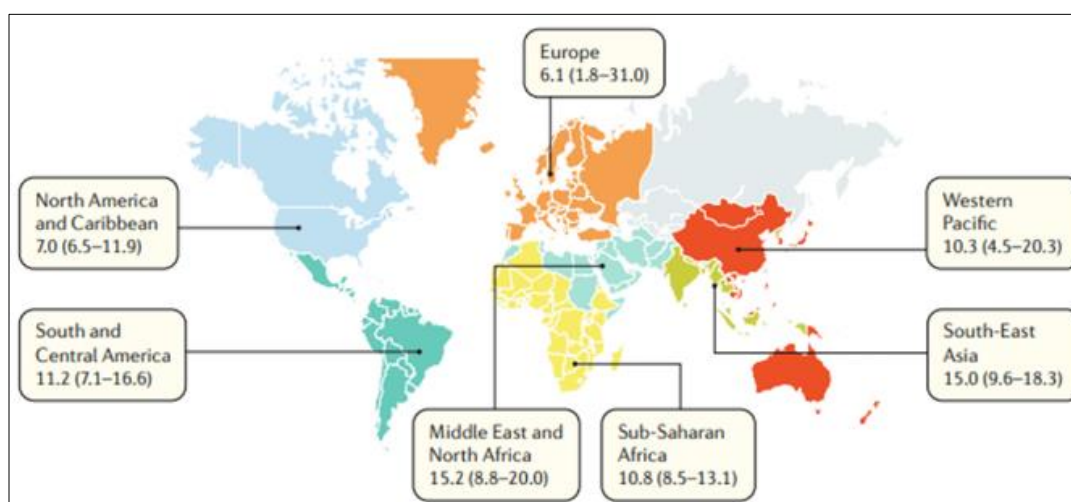


Fig 2: Prevalence of gestational diabetes in different countries (Schneider *et al.*, 2012) ^[16]

Women with gestational diabetes has showed low insulin sensitivity as compared to the women with normal glucose during the pregnancy. Almost 60% insulin sensitivity has decreased during the gestation period due to the different reasons such as obesity, hyperglycemia and inflammation.

The diversity of ethnicity has been observed in the European countries such as US, Australia and Canada. In these countries there are diversity in the population of people. In Australia, Asian Australian women are at the high risk of getting GD as compared to women of Australia. In US, Hispanic American are at the lowest risk (4.6%) of getting gestational diabetes while GD prevalence is (10.9%) in the women of Philippines living in the northern California. Different attitudes of living style cause high risk of GD (Morikawa *et al.*, 2015) ^[9].

During the GDM, women are advised to properly monitor their blood glucose level in fasting and after one or two hours of taking meal. During the fasting the sugar level should be almost 95mg/dL and after the two hours, their concentration is 120mg/dL (Szmilowicz, 2019) ^[49].

Other factors includes the breathing difficulty of baby after the birth, liver or lungs issues and women after the delivery of baby can face hypoglycemia due to the sudden change in the internal environment of body (Moss JR *et al.*, 2005) ^[10]. The baby can be kept in the intense care unit for the long time due to the severe health problems. Mother with GD can also face sever issues such as urgent caesarean section due to increase blood glucose level in the blood or increase or decrease blood pressure. As the treatment is not properly done on time then it can effects the mother of baby life (Reece, 2010) ^[14].

The gestational diabetic can be cured and by the usage of proper precautions and preventions. It includes proper intake of healthy diet according to doctor prescription, daily exercise of mother, taking proper medications either it is metformin or insulin therapy according to the condition of glucose level in the blood. Another important precaution is proper checkup of fetus and evaluated their health (Plows *et al.*, 2019) ^[13].

According to American Diabetes Association, they recommend that pregnant women of earlier three months (6-12 weeks) should be properly checked to prevent the life-long gestational disease. If the women diagnosed with the gestational disease then metformin can be use to treat diabetics. There are minor effects of metformin has observed till yet. Thus, the use of metformin can reduce the blood glucose level in the body of women and protect the fetus from severe effects (Ziegler *et al.*, 2012) ^[19]. The women with intensive lifestyle intervention (ILS) has reduced the chances of causing diabetics in women up to 58% and remaining is treated by the metformin. However, metformin proves a good source to treat GD in the women with GD history and without gestational diabetes history (Aroda *et al.*, 2015) ^[1].

Smoking of pregnant women or their parents (Bao *et al.*, 2016) ^[2], physical activity before and after the pregnancy

(Tobias *et al.*, 2011) ^[17], increased body mass index (BMI) before pregnancy and dietary intake are the major concerns of causing GD (Tobias *et al.*, 2011) ^[17]. Usually it is observed that level of vitamin C and vitamin D are reduced in the earlier months of pregnancy and the intake of fat is increases then the normal concentration that leads to causing diabetes in the women. For example, proteins intake, sugar and sweet drinks, high fat intake, potatoes, fast foods and chocolates (Bao *et al.*, 2016) ^[2]. The direct exposure of women with the hazardous pollutants and smog such as octane, endocrine disruptor and increasing the use of octane in our daily life (Zhu & Zhang, 2016) ^[16]. In this review article, the main concerns are study of gestational diabetes, prevalence of GDM in Pakistan and their effects on mother and children.

Increasing weight in the second trimester is studies carefully and the outcomes showed that the gain of weight in the second trimester period is not complicated and has no serious effects on women body. Hence, the weight gain in the first trimester is health hazardous and can cause severe health issues such as gestational diabetes (MacDonald *et al.*, 2017) ^[7]. The women with gestational diabetes are at the high risk of getting type 2 diabetes mellitus. Breastfeeding is considered as blessing for the children as it protects the children from life threatening diseases such as cancer, osteoporosis, bone diseases and diabetic mellitus. According to a research, the ratio of breastfeeding in women with gestational diabetics is lowered as compared to healthy women. In the case of those women who are treated with insulin therapy are usually recommended not to breastfeed their children (Much *et al.*, 2014) ^[14]. Another treatment is use of glyburide to control the increase level of glucose as it can cross the placental barrier due to its small size. Glyburide is a type of medication that help the β cells of pancreas to release insulin to control glucose level (Finneran & Landon, 2018) ^[5].

Objectives

The main objectives of this article are as follow

- To study the mechanism of β cells, involve in normal pregnancy and gestational diabetes pregnancy
- To determine the effects of diabetes on women and children

Mechanism of GDM

Pancreas releases β cells that are involve in the formation of insulin normally. Insulin molecules combine with the insulin receptor signals (IRS-1) and act on the glucose molecule and convert into the glycogen, pyruvate and fatty acids and store as energy molecules. During the normal pregnancy, hyperplasia take place in the β cells and the concentration of β cells are increased thus glucose stimulation is increases due to fall of insulin sensitivity. After the pregnancy, concentration of β cells com to their normal value and thus insulin sensitivity come normal (Plows *et al.*, 2018) ^[38].

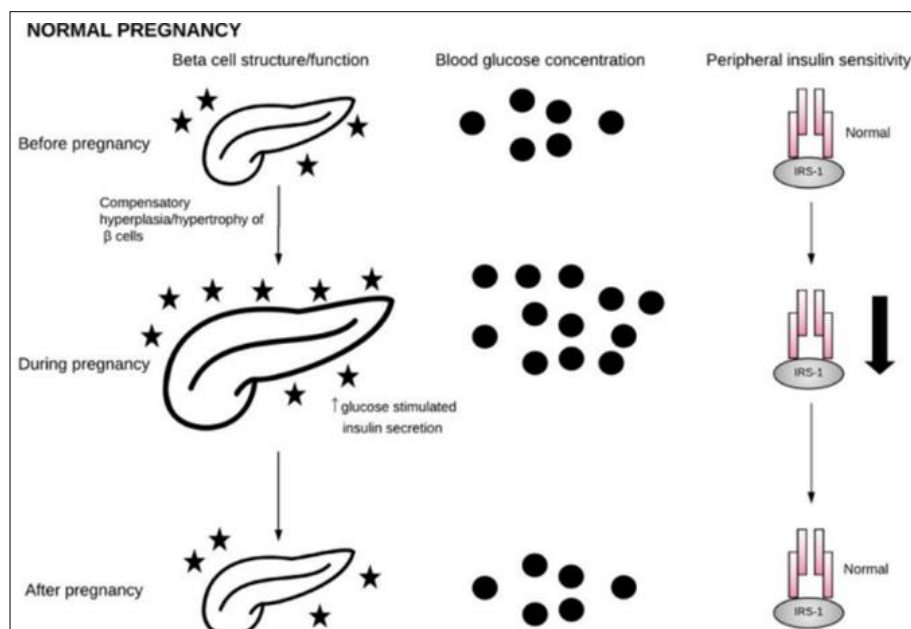


Fig 3: Function of B cells during normal pregnancy (Plows *et al.*, 2018)

During the gestational diabetic, β cells are unable to compete for the increased concentration of glucose, thus the glucose molecules are increasing in the number and the sensitivity of insulin decreased two times on IRS-1. After

the pregnancy, the release of β cells remains unpaired. In some conditions, glucose level goes normal and sometimes it remains unpaired and insulin sensitivity impaired.

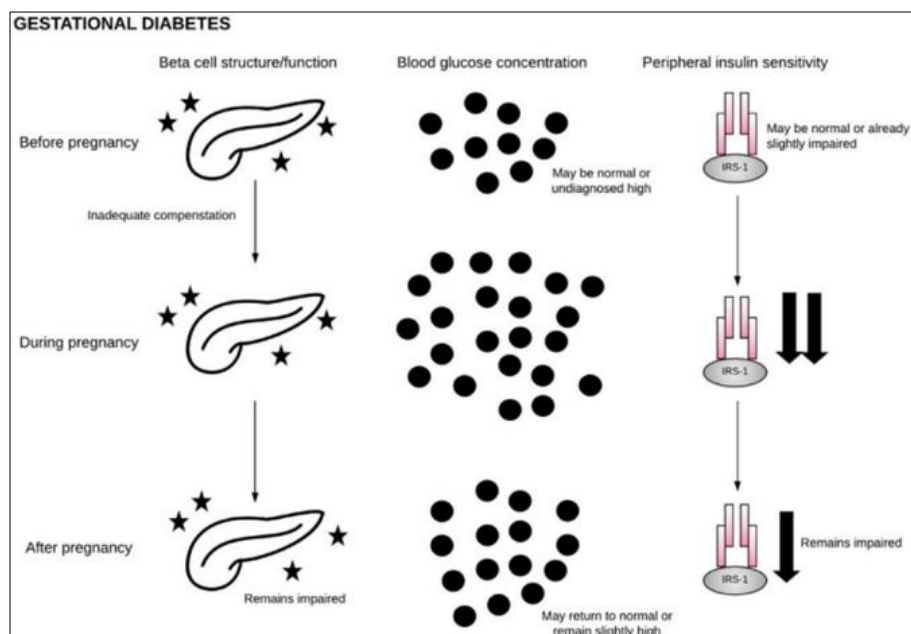


Fig 4: Function of B cells during GDM pregnancy (Plows *et al.*, 2018) [38]

Effect of Gestational Diabetes on mother and children

Different causes of gestational diabetes have been reported in different studies, these factors include environmental factors, lack of nutrition, unhealthy diet, psychological stress, pollutants in the environment and along with these elements some people suffering from diseases or immunocompromised, smokers and alcohol consumers are at the high risk of diabetes (Hernandez-Aguilera *et al.*, 2016) [28]. These all elements change the metabolic pathways occurring in mother and child both and may lead to chronic and long lasting effects on both of them (van Dijk *et al.*, 2015) [49].

Examination of epigenetic modification that took place in the gestational period i.e. pregnancy revealed that these external elements alter the internal metabolism and programming of the fetus (Ma *et al.*, 2015) [34]. Gestational diabetes (GDM) is very short time diabetes that took place during the pregnancy and retrogresses after delivery. But it has been reported in literature that there is a close relationship between gestational diabetes and diabetes mellitus type 2 (T2DM), so in some cases GDM is converted to TDM (Hod *et al.*, 2015) [29].

Effects of Gestational Diabetes on mother

Some of the complications observed in mother due to GDM are:

- Hypertension
- Several heart diseases (cardiovascular diseases)
- Alterations in vascular functions (vascular dysfunction)
- Uncontrolled level of lipids in the body regarded as (dyslipidemia)
- Development of plaque in the arteries such as atherosclerosis (Rayanagoudar *et al.*, 2016) ^[39].

Effects on offspring due to GDM

Following are the short-term effects of GDM

- Prematurity
- Birth injury
- Macrosomia (a condition which is characterized by excess weight of the offspring at the time of birth)
- One of the serious short term complication is a condition at the delivery time during which the baby stuck, his umbilical cord squeezes and baby fails to breath properly it is called as shoulder dystocia, this may also damage some vital body parts of the baby including collarbone or nerve damage that may influence the functioning of the shoulder, arms or brain or may also causes speech difficulty (Burlina *et al.*, 2019) ^[23].

GDM lead to Type 2DM in mother

A very close association has been noticed in these two types of diabetes, it has been demonstrated that some genes are associated with both of these types of diabetes and this is the reason that lead to the transformation of diabetes during pregnancy to type 2 diabetes mellitus (Lowe *et al.*, 2016) ^[33]. The genes TCF7L2, GCK, KCNJ11, CDKAL1, IGF2BP2 and MTNR1B participated in the release of insulin and IRS1 is involved in insulin resistance, so these six-insulin secretions and one insulin resistance gene also participated in the T2DM. Hence, abnormalities in the pancreatic cells alter all the metabolic pathways and alterations in these genes may lead to both GDM and T2DM in pregnant women (Stover *et al.*, 2018) ^[44].

Epigenetic alterations in placenta

Changes in the Deoxyribonucleic acid (DNA) but not in the

sequence of DNA are referred as epigenetic alterations. Epigenetic changes are observed in the placenta during the GDM. In this case methyl groups are introduced or eliminated from the structure of the DNA that led to changes in the DNA. In some cases, the alterations in the major proteins such as histone proteins also occurred and disturb the functioning of placenta. GDM influences the structure of placenta and disrupts the supply of nutrients to the fetus (Nelissen *et al.*, 2011) ^[37]. As a result, the growth of fetus retarded. The experimental evidence in mouse model declared that up-regulation and down-regulation of some genes take place due to GDM including reduction in Dlk1 gene and over-expression of Gtl2 is reported. Dlk1 stimulates insulin signaling pathway and accumulation of adipose tissues take place, while, Gtl2 gene participated in maintaining notch signaling pathway and TGF- β (Liyanage *et al.*, 2014) ^[32].

Low level of methylated DNA has been reported in placenta and the main reason behind this is the damage of MEST gene in case of GDM women as compared to non-GDM women. This study suggested that if the women are suffering from GDM then impairment of MEST gene may cause obesity throughout the life (El Hajj *et al.*, 2013) ^[24].

MIRNAS and GDM

Disturbance in the regulation of miRNA has been noticed in GDM firstly increased level of 330-3p miRNA (performs multiple functions in the body like act as a tumor suppressor, controls metastasis and cell development) was identified in women suffering from GDM (Sebastiani *et al.*, 2017). Some other miRNAs like miR132, miR29a, miR222 and miR195-p these all are expressed in GDM (Tagoma *et al.*, 2018).

GDM and Gender (male/female)

A female carrying male fetus is at a higher risk of getting GDM as compared to female fetus because in case of male fetus abnormal functioning of β -cells along with postprandial glycemia is observed this adversely affect the maternal glucose metabolism (Retnakaran *et al.*, 2015) ^[15]. On the other hand if the mother is carrying a female then the risk of GDM lowers but the risk of getting T2DM increases (Retnakaran & Shah, 2016) ^[41].

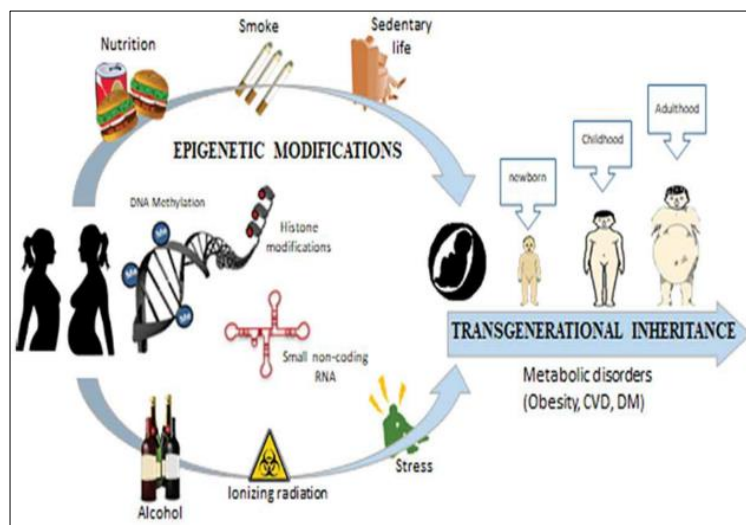


Fig 5: Epigenetic alterations (Franzago *et al.*, 2019) ^[26]

GDM causes hypertension in mother

It has been reported in literature that almost 55% females face the problem of GDM during pregnancy and this GDM causes hypertension. GDM stimulates the NIDDM and this NIDDM is responsible for hypertension for hypertension in the females and this hypertension not only adversely affect the health of the mother but also have bad effects on the health of the fetus as well (Jones *et al.*, 2019) [30].

GDM and cardiovascular disease (CVDs)

There are two cases for females' one case is in which the mother has a genetic history of diabetes and other one is that in which the females do not have any history of diabetes. It is observed by different experiments that females having genetic history of diabetes are at the higher risk of getting GDM during pregnancy almost 29% females face GDM and in some cases GDM may turn into T2DM. Whereas, in the second case there are 14% chances of getting GDM. The heart diseases may transfer to next generation and may appear at any stage of their life may be active during childhood or may be in the adulthood or at the age of 40. Different heart disorders may occur involving heart failure, pulmonary embolism, thrombosis (Yu *et al.*, 2019) [50].

GDM prevalence and their effects in Pakistan

Hyperglycemia has severe effects on those cells of body that cannot compete with the increased glucose level due to insufficient glucose regulatory mechanism. The major cells that are more susceptible to glucose dysfunction are neural cells, vascular endothelial cells and pancreatic β -cells. Thus increased level of glucose can affect many parts of body such as kidneys, eyes, heart and bones and severe diseases such as neuropathy, nephropathy, myocardial infarction and retinopathy (Gray *et al.*, 2017) [27].

Gestational diabetes mellitus survey was conducted at the small scale in the hospitals of Pakistan. According to the survey, 3.3% - 8% prevalence of GDM were observed in the Pakistan. In this survey, the total 11,430 participants were involved and majority of the diabetes are found in the age group of 27 years with the aggregation of 18.8% and 23.1% (Riaz *et al.*, 2019) [42].

Obesity is increasing with the time and the vicious cycle of this gestational diabetic is repeating. If we want to stop this cycle then we should treat polycystic ovary syndrome properly and control the increase of obesity in the young generation. Last but not least is the control of hyperglycemia during the pregnancy of women (Alejandro *et al.*, 2020) [20].

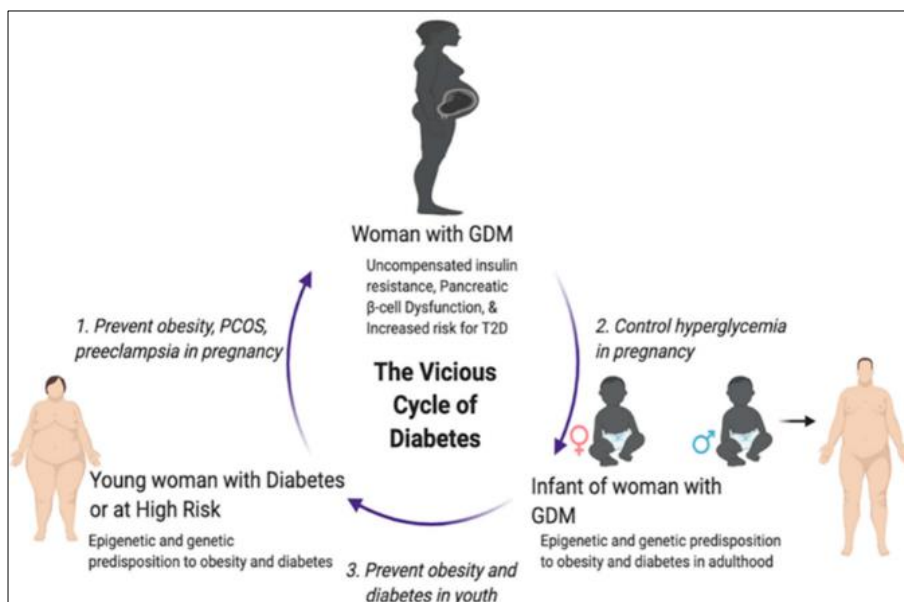


Fig 6: Vicious Cycle of GDM (Alejandro *et al.*, 2020) [20]

GDM is measured by the different diagnosis test such as blood glucose random, blood glucose fasting and HbA1c test. The normal values of Gestational diabetes can be

measured by the indication of glucose level in the blood streams. The values are mentioned in the given table;

	Fasting plasma glucose 2-h	plasma glucose on 75-g, 2-h OGTT	HbA1c	Random plasma glucose
Diabetes	≥ 126 mg/dLb	≥ 200 mg/dLb	$\geq 6.5\%$	≥ 200 mg/dLc
Pre-diabetes				
Impaired fasting glucose	100–125 mg/dL	—		
Impaired glucose tolerance	—	140–199 mg/dL		

Discussion

Diabetes mellitus is lifelong disease in which body is unable to produce insulin or sometimes it is not properly responding to the molecules of glucose. The glucose molecules are not properly utilizing into the substrates and thus their glucose level is increases in the blood streams. Pancreas is an organ that are involve in the releasing of insulin and the insulin function is to control the increased

glucose level. B cells are involved in the releasing of insulin, insulin is natural hormones that play an essential role in the control of level of glucose.

Gestational diabetic mellitus is one of the prevailing diseases of Pakistan and it usually occur after the three months of pregnancy. Their prevalence has been observed in the different countries of Europe such as Australia, America, United Kingdom, Belgium and Canada. According to figure

1, the majority of prevalence is observed in the east and central Asia of the world which is above 15%. The glucose level increases due to the pregnancy and insulin sensitivity fall down. Insulin molecules are not properly attached with the insulin receptor substrate and thus glucose will not break down into glycogen, pyruvate and fatty acids. Thus, it cause hyperglycemia in the body that can also effect the fetus and mother as well (Szmuiłowicz *et al.*, 2019) ^[49]. The hyperplasia of glucose can cause severe diseases such as nephropathy, neuropathy, cardiovascular diseases and many bones disorder.

Gestational diabetes can also cause epigenetic alteration in the children that can cause variations in the genetic system. GDM can produce damages in the placenta that can lead to the disruption in the supply of food from mother to the fetus. Gestational diabetes is also a major reason of cause stress, mood swings and hypertension in the mother. Cardiovascular disease such as stroke, heart beat disruption can occur due to GDM.

Hyperglycemia can affect the fetus in the womb of mother and can cause severe complications such as urgent C section for the delivery of baby. The high level of glucose causes broad shoulder of fetus and cause complication during delivery. Metformin, insulin therapy and many other drugs are using for the control of glucose level in the blood. Exercise, fresh air, no stress and tension and balanced diet can also control the increase of glucose level. Further studies can be performed to study the effect of high glucose level on the heart, eyes and brain of fetus.

Conclusion

Gestational diabetes is hyperglycemic that can occur during the trimester of pregnancy. Their major prevalence is observed in Asian countries. The outbreak of gestational diabetes had also been seen in European countries such as Australia, America and Canada. In Pakistan, women in the age group of twenty-seven years of age are more susceptible to gestational diabetic mellitus. Hyperglycemia in pregnancy happened due to the malfunction of B cells of pancreas and glucose molecules will not convert into their substrates. The main reasons for GD are obesity, polycystic syndrome pregnancy at a late age. GDM has severe effects on mothers and children. In mother, it can cause neuropathy, nephropathy and cardiovascular disease. Insulin therapy and metformin are common treatments for the control of high levels of glucose.

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