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Gestational diabetes mellitus - A metabolic and reproductive disorder

Abbas Alam Choudhury, V. Devi Rajeswari *

Department of Bio-Medical Sciences, School of Biosciences and Technology, VIT University, Vellore 632 014, Tamil Nadu, India

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ABSTRACT

Maternal health associated with Gestational Diabetes Mellitus (GDM) has been gaining significant research attention due to its severe risk and adverse health effects. GDM is the leading health disease in pregnant women. It is the most common metabolic disease and it can affect up to 25% of women during pregnancy. Pregnancy is a sensitive period that impacts both pregnant women and their unborn children's long-term health. It is a well-known fact that the leading causes of disease and mortality worldwide are diabetes mellitus and cancer, and specifically, women with diabetes mellitus are at a higher risk of developing breast cancer (BC). Women who have diabetes are equally vulnerable to reproductive diseases. Reproductive dysfunctions with diabetes are mainly attributed to coexisting polycystic ovarian syndrome (PCOS), obesity, and hyperinsulinemia, etc. Moreover, India has long been recognized as the world's diabetic capital, and it is widely acknowledged that particularly pregnant and lactating women are among the most affected by diabetes. In India, one-third (33%) of women with GDM had a history of maternal diabetes. Nevertheless, the latest research suggests that gestational diabetes is also a risk factor for cardiometabolic diseases of the mother and offspring. Therefore, in the 21st century, GDM imposes a major challenge for healthcare professionals. We intend to explore the role of diabetes on female reproductive function throughout various stages of life in the perspective of the changing prognosis, prevalence, and prevention of GDM.

1. Introduction

Diabetes is defined as high blood glucose levels caused by failure of insulin secretion or due to abnormalities of biological function [1]. It is one of the most prevalent metabolic diseases in the world. Diabetes has become the world's third "silent killer" after cancer and cardiovascular disease due to its increasing morbidity, and fatality rates among the human race [2]. Diabetes has previously been treated as a single disease, however, health care professionals today found that diabetes includes a variety of heterogeneous diseases and leading to a broader range of diseases [3]. International Diabetes Federation (IDF) estimates, over 425 million individuals worldwide were diagnosed with diabetes in 2017, with the number projected to increase to 629 million by 2045 (World Health Organization, 2006) [4]. It is currently projected that 1 in 3 adults will have DM by 2025 in the United States (USA). The increasing prevalence of type 2 diabetes is significantly increased in adults, particularly more young women who are getting diagnosed during reproductive years [5]. Worldwide, the prevalence of GDM ranges from 5% to 25.5% and is dependent on race, ethnicity, age, body composition, as well as screening and diagnostic criteria [6]. In the United States of American, around 1 in every 10 pregnant women is affected and nearly 90% of diabetes occurrences during pregnancy are GDM [7]. The prevalence of GDM in Asian women is higher [8] than the US women [9]. India has the second-highest populace with diabetes mellitus worldwide and is one of the global epicenters for the DM epidemic [10]. Diabetes is categorized into three types: (1) Type 1 diabetes, (2) Type 2 diabetes (T2DM), and (3) Gestational Diabetes Mellitus (GDM) [11]. 90–95% of adult diabetes cases were identified as T2DM [4]. Diabetes during pregnancy causes recurrent interference in both maternal health as well as fetal growth [8]. Diabetic mothers are more prone to abortions and miscarriage. It is the leading cause of premature births or even infant mortality [12]. The majority of complications were treated with a variety of drugs. However, some medicines are known to have a direct or indirect impact on a developing fetus. So, in order to ameliorate the

Abbreviations: DM, Diabetes Mellitus; GMD, Gestational Diabetes Mellitus; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; IADPSG, International Association of Diabetes and Pregnancy Study Groups; OGTT, Oral Glucose Tolerance Test; PCOS, Polycystic Ovary Syndrome; BC, Breast Cancer; IGF-1, Insulin-Like Growth Factor 1; LGA, Large Gestational Age.

* Corresponding author.
E-mail address: vdevirajeswari@vit.ac.in (V. Devi Rajeswari).

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treatment of GDM, phytochemical-based drugs are machinated which envisage lack of side effects [8]. Hence, In spite of significant advances in drug discovery, diabetes still poses as an epidemic medical challenge throughout the world.

2. Diabetes mellitus (DM)

Diabetes mellitus is a multiple etiological and metabolic disease defined by chronic hyperglycemia with alteration of carbohydrate, lipid, and protein metabolism resulting from abnormalities in insulin production [13]. Since 1500 BCE, diabetes mellitus has been recognized as a health problem [14]. The prevalence of DM is 8.5% worldwide and every 1 in 10 adults is presumed to have DM globally by 2035 [15]. DM affects around 451 million people globally, with a forecast increase to over 693 million by 2045 [16]. In the United States, 9.4% (or 30 million) of adults have type 2 diabetes. More than 90% of persons with T2DM are overweight or obese, with obesity being the biggest independent risk factor for developing type 2 diabetes. Those with pre-DM have a 50% chance of developing T2DM within the next 10 years [17]. DM is now one of the most common chronic diseases affecting people's lives in developing countries [18]. T2DM prevalence is quickly growing in middle and low-income countries. Moreover, DM is a prominent cause of mortality around the world [19].

Diabetes mellitus is a set of disorders defined by hyperglycemia caused by insulin deficiency or disruptions in signaling pathways. Type 1 and T2DM are the most frequent types of diabetes. Type 1 diabetes mellitus is an autoimmune disease that causes insulin shortage, whereas T2DM is defined by peripheral insulin resistance, which is commonly associated with defective insulin production [20]. Pancreatic β-cell assist in balancing the demand for and supply of insulin [9] (Fig. 1). Therefore, DM is characterized by total or relative insulin deficiency, resulting in hyperglycemia [12]. T2DM is defined as a progressive condition characterized by insulin resistance and pancreatic β-cell dysfunction, resulting in a persistent hyperglycemic state. T2DM develops in people who have a genetic or acquired predisposition to insulin resistance and β-cell malfunction. The other factors are exposure to variables such as high caloric intake, lack of exercise, and other environmental factors [16].

Diabetes is life-threatening mainly due to vascular complications caused by T2DM, such as neuropathy, nephropathy, retinopathy, cardiac diseases, peripheral arterial disease, and stroke [15]. Obesity, hypertension, hyperlipidemia, cardiovascular disease (CVD), and chronic renal disease are common co-morbidities and consequences of T2DM [4]. T2DM has been associated with several risk factors, including genetic, lifestyle, and environmental factors. Unhealthy eating habits, physical inactivity, and air pollution have all been linked to T2DM. Many studies around the world have been reported a connection between air pollution and the development of diabetes. Furthermore, the climate crisis including air pollution and severe temperatures may contribute to an upsurge in the prevalence and incidence of diabetes, particularly GDM [21]. These individuals are especially vulnerable to heat waves due to defective thermoregulatory mechanisms, reduced autonomous nervous system responses at high temperatures, electrolyte imbalances, and fast degradation of kidney function. Furthermore, exposure to cold temperatures is connected with an increased risk of acute myocardial infarction as well as poor glycemic control, while studies on cold-related mortality in diabetic individuals are ambiguous [21].

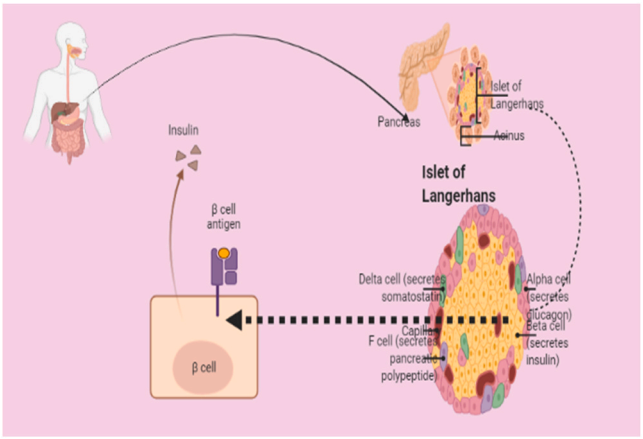

Fig. 1. Pancreatic β cells secrete insulin.

During pregnancy, DM may be either T1DM, T2DM, or GDM [22]. Pregnancy with T2DM has skyrocketed from 28% to 46% over the last 10 years, additionally, in some metropolitan areas, women with T2DM have increased significantly more than that of type 1 diabetes [23]. Pregnancy in diabetic women is associated with an elevated risk of severe adverse effects [24], including a two-to-fivefold increased risk of congenital anomaly, stillbirth, and neonatal mortality as compared to the general maternity population [23]. Moreover, GDM women are around 10 times more likely to suffer T2DM later in life, and up to half of them develop T2DM 10 years after their childbirth [25]. The increasing prevalence of T2DM among women in Asia would seem to be a major factor in GDM. 10–31% of parous female diabetes cases are thought to be related to GDM. The chance of acquiring diabetes after 30 years has grown by 2.3 fold in comparison with a younger mother within 10 years [26]. There is substantial evidence that, regardless of the type of maternal diabetes, intrauterine exposure to diabetes increases the risk of type 2 diabetes and obesity in the offspring [27]. Hence, GDM poses a severe global health concern because of its metabolic and reproductive complications which must be addressed.

2.1. Gestational Diabetes Mellitus (GDM)

As early as 1824, German researchers reported the first incidence of gestational diabetes occurring in a pregnant woman. Lambie reported for the first time about the signs of diabetes to appear in the fifth or sixth month of pregnancy in 1926 [14]. However, the term "gestational diabetes" was coined by Carrington in 1957 however it further received attention in 1961 and 1964 after John O'Sullivan's publications [28]. GDM is defined as intolerance of glucose which starts or first becomes detectable during pregnancy [29,30,28]. GDM is the most common metabolic disease and it can affect up to 25% of women during pregnancy [25], [31]. In 2017, the global prevalence of hyperglycemia in pregnancy adversely affected 16.2% of all live births, with GDM accounting for 86.4% [32]. The World Health Organization (WHO) defines GDM as "any level of the early or first detection of glucose intolerance in pregnancy" [33]. In Europe, the prevalence of GDM reported varies significantly and in some populations, more than 20% of pregnancies have been documented [34]. Prevalence rates for GDM climbed to 14% of the pregnancies among U.S. women [35]. The International Diabetes Federation (IDF) reports that the global prevalence of GDM ranges from 1% to 14%. in 2014 [36]. GDM affects 1–14% of all pregnancies, depending on the ethnicity of the patient population explored and the diagnostic criteria [37,20]. The American Diabetes Association describes gestational diabetes as "any degree of glucose sensitivity with onset or first detection during pregnancy,"[38,20] while pre-gestational diabetes includes type 1 and T2DM that occurs before pregnancy [38].

GDM occurs during pregnancy and is a serious health complication [27]. It is one of the most frequent pregnancy complications is GDM [29, 7,28,39] which is associated with a significant increase in the risk of maternal and neonatal outcomes [39]. GDM is a type of diabetes that first manifests itself during the second trimester [40] or the third trimester of pregnancy [41]. During pregnancy, the metabolic state changes significantly, affecting insulin action and sensitivity. This effect is amplified in the second half of pregnancy due to insulin resistance and consequent hyperglycemia [20]. The progression of GDM increases if

women are more than 25 years old, and have GDM since the last pregnancy, and have a history of T2DM and PCOS [42]. While the etiology of GDM is not entirely understood, obesity increased maternal age, and women of particular ethnic groups were found to be at high risk [25] (Fig. 2). Hence, GDM is a temporary form of glucose intolerance caused by insulin resistance and pancreatic β-cell malfunction during pregnancy [43].

Pregnancy is a sensitive period that impacts both pregnant women and their unborn children's long-term health [44]. The first trimester is an important phase as the main organs of the fetus are developed during this period of pregnancy [45]. During pregnancy, the developing fetus is completely reliant on the maternal environment for nourishment [46]. GDM develops as a result of hormonal changes during pregnancy. The placenta secretes hormones that make cells less responsive to the effects of insulin [42]. Therefore, GDM is defined as the first detected glucose intolerance during pregnancy [47,48]. It is a type of insulin resistance, which first occurs in the second or third trimester of pregnancy [49]. However, GDM may develop at any stage during the pregnancy [50]. The reasons for GDM are complicated and not entirely understood but are nevertheless prevalent in pregnancies, with major consequences for the child and maternal morbidity and mortality [51].

Pregnancy itself induces maternal glucose metabolism and insulin sensitivity. The demand for the production of insulin on the mother's pancreas increases with pregnancy [33] (Fig. 3). During pregnancy, several physiological changes occur in the women's body to satisfy the energy demands of the fetus. Insulin resistance increases in order to enhance the fetus's glucose supply. The increased demand for glucose is compensated for by pancreatic β-cell, and a normoglycemic nature is originated. In contrast, women who had previously experience GDM are having an insufficient β-cell response that leads to reduced insulin secretion and consequently to hyperglycemia. Therefore, glucose sensitivity can occur when β-cell are no longer able to regulate insulin resistance [52].

GDM is linked to insulin resistance as well as decreased insulin production, and it shares the same risk factors as T2DM. The prevalence of GDM in a population is closely similar to that of T2DM [26]. Globally, the prevalence of GDM has increased during the previous two decades, posing a serious health risk to upcoming generations [53], GDM is caused due to the disturbance in glucose regulation during pregnancy, has severe short-term and long-term health effects for both mother and child [54] including preterm delivery, cesarean delivery, excessive fetal development, newborn hyperinsulinemia, hypoglycemia, and hyperbilirubinemia, etc [55]. There is evidence that GDM is a precursor to T2DM in women who are susceptible and undergo the metabolic demands of pregnancy [26]. Pregnant, non-diabetic women with high blood glucose levels are presumed to experience GDM throughout pregnancy [51]. Many patients with GDM develop impaired glucose tolerance (IGT) or T2DM after giving birth. Furthermore, GDM during

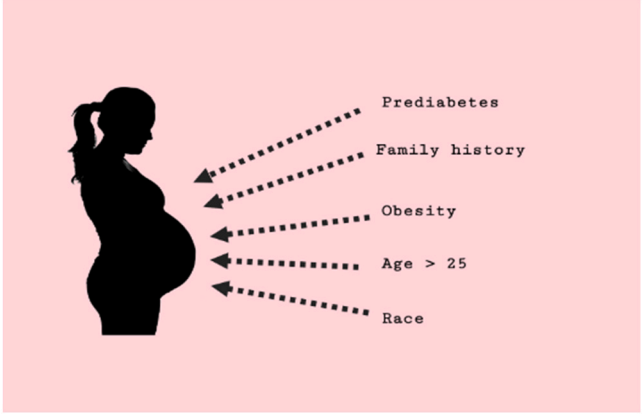

Fig. 2. Etiology of Gestational Diabetes Mellitus.

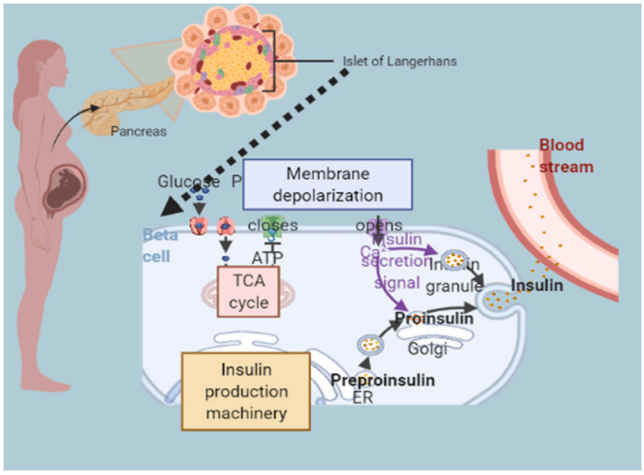

Fig. 3. Mechanism of Insulin secretion in the pancreas of GDM woman.

pregnancy considerably raises the chance of postpartum DM development [20]. GDM has a 7 times higher chance of manifest T2D with normoglycemic pregnancy [56]. In addition, both mothers and infants are more likely to develop T2DM and have increased short-term fetal outcomes and long-term obesity [36].

GDM is associated not only during fetal development, such as death from birth, visceromegaly, and fetal macrosomia but also later in life is linked to a higher risk of metabolic disorders for recurrent maternal as well as in children [48]. As a result of GDM, women are more likely to develop pregnancy-induced hypertension, increased incidence of cesarean delivery, and as well as a higher risk of developing obesity, diabetes, and other metabolic disorders in the future. GDM is linked to an increased risk of pregnancy complications as well as long-term metabolic risks for both the mother and her offspring [57,56]. Nevertheless, in addition to type 2 diabetes, the latest research suggests that GDMis also a risk factor for cardiometabolic diseases of the mother and offspring [57,20] reported that GDM patients have considerably lower levels of IL-1Ra in their plasma than healthy pregnant controls in their research. Furthermore, they reveal that GDM patients with postpartum IGT or T2DM have ever-lower levels of IL-1Ra [20]. While it is well known that women with GDM are at a high risk of developing T2DM [58,33]. GDM has significant consequences for maternal health, including an increased risk of developing T2DM [59,60,33], in addition to the increased risk of adverse neonatal outcomes [59].

GDM and metabolic syndrome are two major metabolic illnesses that affect women all over the world. The occurrence of GDM among pregnant women is strongly associated with early manifestations of metabolic syndrome components particularly hyperglycemia and hypertriglyceridemia. Pregnancy-related hypertriglyceridemia is known to generate hormonal changes that impact lipid metabolism. Regardless of GDM status, maternal triglyceride levels, particularly in the third trimester, were found to be strong predictors of birth weight [55]. GDM is characterized by resistance to insulin and tolerance to glucose, which may persist after delivery [61,62] results exhibit a high frequency of early postpartum glucose abnormalities, for both early and typical GDM. [48] illustrated that even brief exposure to maternal diabetes during early development is enough to induce permanent changes in DNA methylation and expression of genes that control insulin secretion, implying a methylation-mediated epigenetic mechanism for GDM-induced intergenerational glucose intolerance. Furthermore, their findings provide experimental evidence for the long-term health effects of GDM insulin therapy on the offspring, which shows that these offspring still have the tendency to get affected with metabolic diseases, particularly in an unfavorable post-natal environment [48,39] detected that as the pregnancy progressed, an increase in the estimated metabolic pathways associated with the breakdown from polysaccharides was

found which could be related to increased insulin resistance with the course of the pregnancy [39].

Despite the fact that normal glucose regulation normally recovers quickly after delivery, women with GDM have a sevenfold greater risk of developing T2DM in the future. T2DM is a growing public health concern linked to a range of major health problems that diminish the life expectancy of patients and their quality of life [63]. GDM risk factors include advanced age, obesity, excessive GWG, ethnicity, family history of diabetes, history of GDM, PCOS, and previous LGA deliveries [32]. Moreover, apart from food and lifestyle factors, recent findings reveal that the risk of developing GDM is due to environmental and psychosocial factors [28]. Normal aging is related to a decrease in endocrine processes such as β-cell function and insulin sensitivity. In addition, the declining ability of an individual to secrete insulin has a significant influence on the development of GDM. Earlier studies were well-documented that older pregnant women are more likely to acquire GDM, confirming that advanced maternal age is a risk factor for GDM. Furthermore, older women are at a higher risk of both acute and chronic cardiovascular problems, such as coronary artery disease, atherosclerosis, heart failure, and stroke [32].

GDM is a major predictor of diabetes development. The risk of diabetes developing within 10 years has increased by 2.3-fold being treated with insulin during pregnancy compared with a woman not being treated with insulin. Similarly, having a baby weighing more than 3.5 kg increased the risk of developing diabetes by 2.4 fold [26,64] reported that women with GDM had an almost 5 times higher risk of PPH than women without GDM [64]. Furthermore, women with GDM had a 10 fold increased chance of acquiring T2DM throughout a ten-year follow-up period when compared to those without GDM [26]. This increase is linked to the rise in metabolic disease among women of reproductive age [14]. However, there is still much to understand about the entire etiology and pathophysiological mechanisms of GDM [27]. Some of the reported etiologies of GDM are tabulated in Table 1. Nevertheless, there is strong evidence that GDM is a chronic disease that has a significant impact on pregnancy outcomes [65]. When it comes Indian scenario, there are various cultural plethora that plays a significant role in preventing GDM even though it affects many pregnant women in the country. Patients with type 2 diabetes mellitus (T2DM) have been evaluated in several studies, but knowledge and awareness of GDM in women is limited [66].

In order to avoid these life-threatening obstetrical problems and improve pregnancy outcomes, there is an urgent need for modifications in maternal care and intervention approaches for women with GDM.

Table 1
Etiology of GDM.

#	Etiology	Consequence	Study group
1	Overweight or obesity	Maternal obesity is one of the most significant risk factors for GDM	[30]
2	Family history of diabetes	Familial history of diabetes is one of the key risk factors for GDM	[64]
3	Age	Women who are older than 25 are at a greater risk for developing GDM	[42]
4	Race	Women who are African-American, American Indian, Asian American, Hispanic or Latino, or Pacific Islander have a higher risk of GDM	[41]
5	LGA	Previous large-for-gestational increased risk of GDM	[32]
6	PCOS	PCOS women are at an elevated risk of GDM during pregnancy	[67]
7	Prediabetes	Pre-diabetes are connected with the increased risk of GDM	[68]

2.2. Hyperglycaemia in GDM

GDM is a hyperglycaemic condition that arises during pregnancy and is neither T1DM nor T2DM [69]. It is characterized as the first detected level of glucose intolerance that develops for the first time during pregnancy [70,36]. The GDM is the most common health condition in pregnancy characterized as glucose intolerance leading to hyperglycemia that starts or is diagnosed during pregnancy [57,71]. Hyperglycemia is typically developed during the second half of pregnancy as insulin resistance increases [72]. Worldwide around 85% of hyperglycemia symptoms in women during pregnancy are caused by GDM at age 20–49 years [73]. GDM and overt diabetes (OD), generally known as “diabetes in pregnancy,” are both manifestations of hyperglycemia in pregnancy [72]. According to the International Diabetes Federation, hyperglycemia was widespread in 16.2% or 20.9 million pregnant women in 2015, with GDM accounting for 85.1% of those cases [37]. Insulin resistance and increased concentrations of estrogen in women with GDM can cause typical pregnancy-related lipid metabolism fluctuations to exceed physiological homeostasis. In women with GDM, they reported substantially higher TG levels compared to women without GDM. Hence, there is convincing evidence that the biologically plausible association between hyperglycemia and dyslipidemia [25]. Pregnancy with hyperglycemia is divided into two types: GDM and Pre-Gestational Diabetes Mellitus [74].

According to the International Prospective Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study group, maternal hyperglycemia is attributed to many adverse pregnancy outcomes, such as high birth weight, cesarean section, premature birth, and pre-eclampsia [75]. Pre-eclampsia is a gestational disease characterized by the start of hypertension after 20 weeks of gestation [76]. Proteinuria, edema, and early-onset hypertension are all signs and symptoms of preeclampsia, which develops in the second half of pregnancy [77]. Pre-eclampsia is associated with placental malfunction and therefore a fetal restriction of growth. The placenta is the main route of hormones during pregnancy [78]. It is well-known fact that GDM is characterized by increased insulin resistance and decreased beta-cell function [79]. The glucose levels of pregnant women play a crucial role in GDM if it is not adequately regulated which can cause fetal hyperinsulinemia, neonatal hyperglycemia, and excess fetal growth, known as macrosomia [80,49]. According to [79] research, maternal hyperglycemia stimulates the fetal pancreas to secrete excessive insulin. Subsequently, an increase in fetal insulin secretion leads to the accumulation of fat tissues and protein in the fetus, which causes macrosomia [79].

Hyperglycaemia in pregnancy is common in 1 in 4 women in Southeast Asia. Women with a GDM history have a 7 times higher T2DM risk later than women without GDM. During early pregnancy, there is an enhanced insulin secretion and insulin sensitivity, that enables storing fat and glycogen in mothers [26]. GDM has long-term negative consequences for children, including an increased risk of T2DM and obesity [80]. Moreover, hyperglycemia during pregnancy could produce macrosomia (excessive growth in fetus $\geq$ 4 kg) [81,33], fetal birth trauma, neonatal hypoglycemia, large for gestational age, delayed lung growth as well as fetal hypoxia [7,81]. GDM involves short-term and long-term complications impacting mother and child, such as macrosomia [54] and T2DM [82,83] (Figs. 4, 5).

Hyperglycaemic exposure of the mother during fetal development is also associated with short-term complications such as macrosomia and neonatal hypoglycemia and also increased the chance of developing T2DM and other metabolic diabetes in long term [84]. Thus, women with GDM are more prone to develop Pre-eclampsia, preterm birth, and macrosomia [85] as well as T2DM after childbirth [84]. The early prenatal screening for hyperglycemia would enable earlier hyperglycemia therapy, and hence improve the pregnancy outcomes [72].

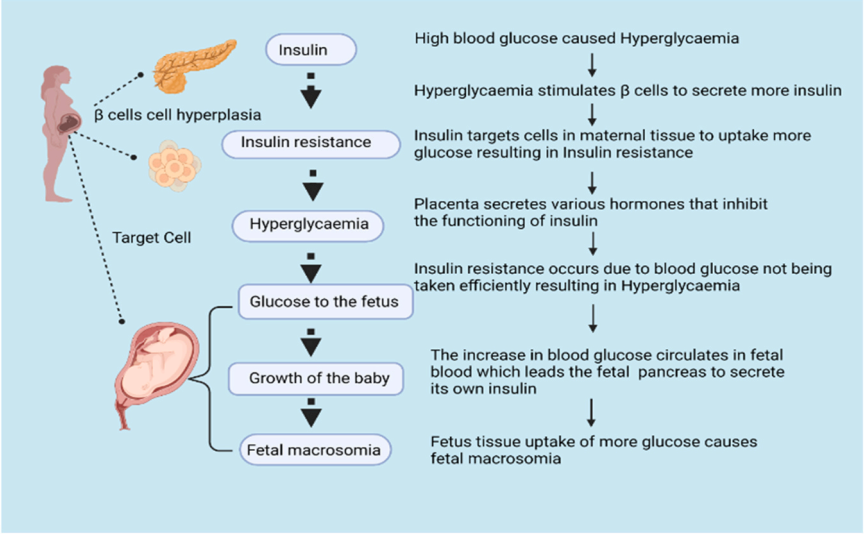

Fig. 4. Pancreatic β cell hyperplasia.

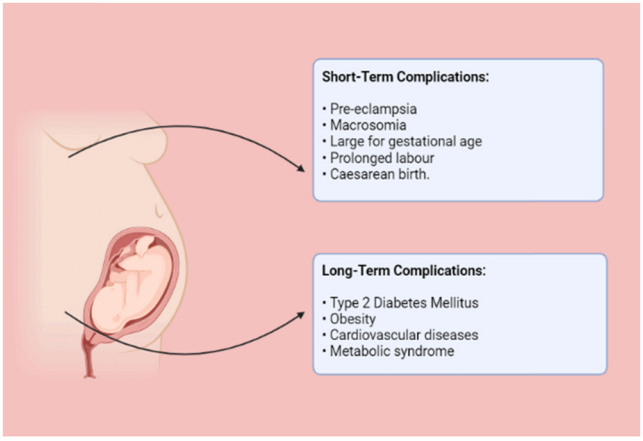

Fig. 5. Maternal risk factors associated with gestational diabetes mellitus.

2.3. Role of insulin in GDM

Insulin is a hormone secreted by the pancreas that allows the body to efficiently utilize glucose. In diabetics, however, the pancreas produces inadequate insulin, leading blood sugar levels to rise [86]. During natural pregnancy, the pancreas produces high amounts of insulin at post-prandial is called β-cell hyperplasia [60] (Figs. 4, 5), particularly during the third trimester, increasing placental hormone release leads to an increase in insulin resistance. Hence, GDM develops as a result of insulin resistance not being overcome by β cell activity [60]. Thus, pregnancy induces insulin resistance [71,87]. Insulin resistance during pregnancy can be caused by a combination of increased maternal adiposity and placental products that have insulin-dependent effects, such as placental human lactogen, estrogen, and prolactin. However, during pregnancy, an increase in insulin resistance is normally compensated by insulin secretion by pancreatic islet β-cell [71].

Maternal insulin resistance is a physiological phenomenon that develops to maintain the supply of fetal energy throughout gestation. Although this metabolic adaption is tackled by most, however, some women develop GDM [40]. Hyperinsulinemia develops when β cell pancreatic accelerate insulin synthesis in order to maintain adequate blood glucose levels [64]. Growth hormone, corticotropin-releasing hormone, placental lactogen, and progesterone are all secreted by the placenta and act to create insulin resistance in the mother, providing an adequate supply of nutrients to the developing fetus. Diabetes develops when the mother's pancreatic activity is insufficient to respond to the developing insulin resistance [87]. GDM develops when the pancreatic function fails to overcome insulin resistance. Insulin resistance develops during pregnancy as a result of elevated levels of growth hormone and cortisol, the presence of human placental lactogen (HPL), insulinase release from the placenta, and high levels of estrogen and progesterone [88].

Insulin resistance is also regarded to be a pathophysiological factor underlying metabolic syndrome. Furthermore, it has been reported that GDM is one of the first metabolic abnormalities to be detected during the development of metabolic syndrome [37]. Serum chemerin during pregnancy is known to increase with gestational age as the sensitivity of insulin reduces. Normal pregnancy is associated with significantly greater levels of chemerin in the blood, which can help lower insulin resistance and prevent glucose intolerance throughout pregnancy. Women with GDM, on the other hand, have much-decreased chemerin levels that remain low after childbirth, which can lead to insulin resistance, glucose intolerance, and an increased risk of T2DM and GDM [89]. Resistin is a cysteine-rich hormone released mostly by adipose tissue that plays an important role in insulin sensitivity. Resistin concentrations during pregnancy are increased in comparison with the non-pregnant women and are even more increased in the third trimester. Resistin levels rise with increasing gestational age. Several studies have found that women with GDM have lower insulin sensitivity and higher insulin resistance. Resistin raises insulin resistance, lowers insulin sensitivity, and promotes postprandial hyperglycemia during pregnancy, leading to GDM [37]. Metabolic stress could accelerate β-cell depletion and lead to insulin shortage during pregnancy and a rise in blood glucose [9].

Furthermore, GDM may occur when a hereditary propensity to pancreatic islet β-cell dysfunction is manifested by increased insulin resistance during pregnancy. Six of the most widely researched GDM genes (TCF7L2, GCK, KCNJ11, CDKAL1, IGF2BP2, and MTNR1B) are hypothesized to affect pancreatic islet β-cell function and all were found to be strongly linked with GDM [71]. Women who have developed GDM are less sensitive to insulin and their insulin secretion is not good enough to sustain euglycemia and hence lead to intolerance to glucose. However, during the later stages of pregnancy, lower insulin sensitivity is considered beneficial to promote fetal growth and enhanced nutritional absorption even if it is associated with metabolic impairment and inflammation [39]. Therefore, it is conclusive that GDM is caused by insulin resistance [8] and reduced pancreatic insulin production similar

to T2DM. In addition, while the metabolism of glucose returns to normal shortly after delivery, studies have shown that GDM mothers are at higher risk for T2DM and their children are at a higher risk of obese infancy [55,53]. Women with GDM have increased levels of glucose and C-reactive protein, lower levels of sex hormone-binding globulin, and an increased chance of hyperinsulinemia when compared to pregnant women who do not have GDM [68].

2.4. Role of Glycated hemoglobin (HbA1c) in GDM

Glycated hemoglobin (HbA1c) is a potential technique that helps to detect pregnant women who are more likely to have or develop GDM and adverse pregnancy outcomes. The average blood glucose of (HbA1c) is represented between 2 and 3 months, depending on the lifetime of the red blood cell. Their findings show that HbA1c has a low sensitivity during early pregnancy while identifying GDM [65]. As gestational age increased, the levels of estrogen, progesterone, cortisol, and other hormones in pregnant women, along with insulin resistance gradually increased, and therefore the risk of GDM [90]. GDM is considered the first diagnosis of glucose intolerance that occurs during pregnancy. Polycystic ovarian syndrome, maternal obesity or overweight, a familial history of T2DM, prediabetes, a previous history of fetal death, and higher maternal age are the key risk factors for GDM [68].

During pregnancy, the levels of various steroids, such as prolactin, placental lactogen, estrogen, progesterone, and glucocorticoid, began to increase rapidly during the 24–28 weeks of gestation, maximum at 32–34 weeks of gestation, and decreased the sensitivity of insulin and thereby produce a remarkable resistance to insulin. In such circumstances, the mother secretes extra insulin to maintain the normal level of blood glucose. When the secreted insulin cannot balance properly for the resistance of insulin, blood glucose increases, which leads to GDM. Hence, GDM is defined as any degree of glucose intolerance that begins or appears for the first time during pregnancy [90]. In 2010 the American Diabetes Association recommended the HbA1c test for diagnosis of DM for the citizens. The World Health Organization (WHO) in 2011 evaluated their suggestion and endorsed the cut-off of as HbA1c $\geq$ 48 mmol/mol for the diagnosis [85].

2.5. Etiology of GDM and maternal obesity

GDM and maternal obesity are both common metabolic complications during pregnancy [91]. It is reported that obesity has been linked to an increase in the number of T2DM [22] and GDM which are related to excess body weight [92]. According to The International Association of Diabetes and Pregnancy Study Groups (IADPSG) guidelines for diagnosing GDM have reported a substantial increase in GDM prevalence [91]. Maternal obesity is one of the most significant risk factors for GDM [93]. It is reported that 21.7% of pregnant women had overweight and obesity and the prevalence of GDM have increased parallel to the rise in obesity in India [91]. GDM raises the severe risk in pregnancy, including premature delivery, hypertensive disorders, and also induces excessive fetal development, which leads to cesarean delivery, or even the baby's shoulders may get stuck inside the mother's pelvis during labor and neonatal hypoglycemia. Moreover, GDM is also responsible for long-term complications of diabetes and cardiovascular diseases for both mother and their offspring [91]. Overweight and obesity are also closely connected later in life to GDM and T2DM [78]. Based on the fact that fetal abdominal obesity occurs predominantly during late pregnancy, screening for GDM at 24–28 weeks of gestation is currently the most commonly used approach. Maternal obesity increases the chances of fetal abdominal obesity and LGA delivery. GDM is more prevalent in elderly (>35 years) and overweight (BMI > 29 kg/m2) pregnant women [30]. Moreover, maternal obesity is a key risk factor for GDM, and more women of childbearing age are overweight or obese, the prevalence is rising exponentially. GDM, in addition to hyperglycemia, is related to increased oxidative stress and inflammation in the placenta and fetus. Neonates from GDM pregnancies are more likely to be macrosomic, have higher fat depositions, and are at a higher risk of developing T2DM later in life [40].

The worldwide prevalence of GDM is rising in parallel with the rise in the prevalence of overweight and obesity among pregnant women, and it is linked to physical inactivity, food habits advanced maternal age, and ethnicity. Inappropriate GWG, including excessive or insufficient GWGs, are linked to an increased risk of adverse pregnancy outcomes [41]. Overweight/obese women had a considerably higher risk of GDM than normal-weight women. Obese pregnant women may be at a higher risk of homeostatic dysregulation during pregnancy due to metabolic changes that occur during pregnancy, including decreasing insulin sensitivity in late pregnancy. In their study, Insulin resistance is approximately 40% higher in obese women than in normal-weight women. Hence, maternal age and early pregnancy BMI are more important risk factors for GDM than GWG [32]. Pre-eclampsia, large--for-gestational-age infants, and preterm birth are all connected with excessive gestational weight gain, which also increases the risk of postpartum weight retention [94].

Recently, there has been increasing attention to the role of maternal mental health in developing GDM. The development of GDM is thought to be influenced by several factors, including maternal age and pre-pregnancy body weight status. Moreover, the development of GDM was also reported to be significantly associated with an increase in early GWG [95]. It is widely established that maternal food patterns during late pregnancy can put infants at risk of obesity later in life. Moreover, the risk of obesity is elevated in the offspring of women with GDM [96]. Dietary fat consumption in particular has been linked to increased GDM risk. Apart from a fat-rich diet, milk products were the only food group that has been recognized as significantly related to an increase in GDM. The primary GDM predictors appear to be woman age and pre-pregnancy BMI. There it illuminates that the most powerful modulator of GDM risk before conception is presumably normalizing body weight [95]. It has been demonstrated that children born to women who have GDM were at an elevated risk of neonatal adiposity and childhood obesity [97]. Despite the fact that women who have GDM are typically overweight, more likely to have T2DM other hypersensitive diseases, and produce large kids who will also have a higher risk of obesity and metabolic diseases later in their lives [96]. However, diabetes during pregnancy can be treated if it is regularly monitored. Both conditions are distinguished by increased insulin resistance and hyperinsulinemia, and they are normally diagnosed at the same time [91].

2.6. Pathophysiology of GDM and Polycystic Ovary Syndrome (PCOS)

Polycystic ovary syndrome is a reproductive and genetic disorder characterized by a variety of symptoms such as ovulatory dysfunction, polycystic ovaries, and excess androgen secretions, etc. [98,99]. PCOS is an ovulatory syndrome in women caused by hyperandrogenism, infertility, and anovulation during reproductive age. Pathophysiology of PCOS involves insulin resistance, diabetes, and hypertension [100]. GDM is the most frequent pregnancy concern in women with PCOS [67, 98]. Women with PCOS who become pregnant are more likely to develop GDM, which is defined as glucose intolerance that begins or is recognized for the first time during pregnancy. Moreover, it is reported that the risk of GDM is higher in women with PCOS; however, this increase is primarily due to obesity. As a result, Insulin resistance and hyperinsulinemia are widely considered as the most plausible explanations for the mechanisms underlying the development of PCOS [88].

PCOS is colloquially known as a syndrome with metabolic complications that may have an impact on women's health at various phases of reproductive age. Pregnant women with PCOS have been identified to suffer insulin resistance and impaired β-cell function [98]. Moreover, PCOS is also a major cause of infertility in women [101], who might need Assisted Reproductive Technology (ART) to get pregnant [98]. PCOS women are at an elevated risk of GDM during pregnancy

irrespective of assisted reproduction technology [98]. In both type 1 and type 2 diabetes, insulin resistance and hyperglycemia can both lead to ovarian dysfunction. In type 2 diabetes, endogenous insulin resistance and hyperinsulinemia lead to stimulation of ovarian granulosa cells raise the risk of small follicle growth. These multiple small follicles with enlarged ovaries increased the prevalence of polycystic ovarian syndrome in type 2 diabetes. The most common endocrinopathy in women of reproductive age is PCOS, affecting up to 8–13% of women. PCOS is a heterogeneous disease that has various reproductive, cardiometabolic, psychological implications largely dependent on insulin resistance and obesity [102]. Women with PCOS, including many teenagers, have been found to have reduced β-cell function and poor glucose tolerance, resulting in non-insulin-dependent diabetes (NIDDM) [99]. Women who have T2DM are equally vulnerable to reproductive diseases, though literature is insufficient in this field. Reproductive dysfunctions with T2DM are mainly attributed to coexisting obesity, polycystic ovarian syndrome, and hyperinsulinemia [102]. The prevalence of PCOS was found to be significantly higher in women with a history of GDM in the retrospective analysis. PCOS was independently related to a greater risk of GDM in a large community-based cohort of reproductive-aged women, regardless of body mass index (BMI). The similarities in the metabolic conditions that support GDM and PCOS may indicate that common causes may play a role in the etiopathogenesis of these two disorders [88]. According to [99], pregnant women with PCOS are more likely to acquire GDM. The [88] study attempted to establish a relationship between PCOS and GDM, as well as the associated maternal and fetal outcomes. Subsequently, they concluded that PCOS combined with GDM raises the risk of pregnancy-induced hypertension by 2.4-fold and pre-eclampsia by 2-fold [88].

PCOS contributes significantly to the rising burden of women with diabetes type 2 and dysglycaemia. PCOS is not only common in women with type 2 diabetes, but it also tends to influence the development of T2DM in women without PCOS. In ethnographic type 2 diabetes, polycystic ovarian morphology (a characteristic feature of PCOS), with a frequency up to 61% in Indian women and 34% in Turkey, has been reportedly more common. It is worth noting that in women with Type 1 diabetes, the biochemical and clinical complications of PCOS can be different than in women who have PCOS alone [102]. Previous research has demonstrated that GDM has a greater incidence of PCOS among women than without PCOS. Decreased insulin sensitivity and β-cell disorder predispose women with PCOS to glucose intolerance that increases the risk of GDM during pregnancy. Hence, It is well established that GDM has been associated with PCOS [103]. The Japan Society of Obstetrics and Gynecology Reproductive Endocrine Committee has published recommendations for PCOS that if clomiphene does not ovulate patients with PCOS then the choice of treatment is clomiphene plus metformin [100].

2.7. Epidemiology GDM and Breast Cancer (BC)

Pregnancy itself causes a long-term implication on the development of breast cancer and thus it is considered that pregnancy can temporarily increase the risk of BC [104]. BC risk is increased during pregnancy with diabetes. In 1990, Trichopoulos stated that BC was caused in prenatal environments by changes in hormone concentration [78]. Diabetes mellitus and breast cancer are both widespread chronic diseases in women, and they frequently coexist [105]. BC risk is also increased by lifestyle factors [106]. It is a well-known fact that the leading causes of disease and mortality worldwide are diabetes mellitus and cancer, and specifically, women with DM are at a higher risk of developing breast cancer. It is reported that 8–32% of BC patients had DM [18]. BC is the world's second most prevalent cancer and the most common disease among women [104]. Type I and type II diabetes are connected with the increased risk of different types of cancers [68].

Cancer and diabetes mellitus are the leading causes of death worldwide. It is reported that patients who have been diagnosed with DM are more likely to develop cancers such as pancreatic, colon, liver, kidney, bladder, or BC [3]. GDM has T2DM-like characteristics and is a predictor for subsequent substantial T2DM. Hence, it is plausible to presume that GDM can also be linked with a higher risk of cancer in women. Prevention of GDM can therefore play an essential part in preventing the future development of several forms of cancer [68]. The connection between T2DM and BC has already been reported. Furthermore, women who had several GDM pregnancies were found to be more likely to develop BC [61]. Women suffering from DM have a moderate but statistically elevated risk of postmenopausal BC associated with changed insulin levels, IGF, and/or endogenous sex hormones [78]. Cancer cells usually increased their metabolism after undergoing a complex pathway to become malignant. Cancer cells can undergo significant cell survival, proliferation, mitogenesis, and metastasis through rapid insulin and IGF-1 receptors. Glucose intake is relatively high in cancer cells. Furthermore, numerous strategies of cell proliferation, evasion of apoptosis, and progression from cancer are stimulated. Hyperglycemia, hyperinsulinemia, and chronic inflammation may be caused by DM. A high blood glucose level causes hyperglycemia. Furthermore, hyperinsulinemia raises IGF-1 levels, which promotes carcinogenesis [3].

BC detected during pregnancy or the postpartum period is referred to as pregnancy-associated breast cancer (PABC) [104]. Furthermore, around 18% of BC patients have been reported to have diabetes. Diabetic mastopathy is an unusual development of fibrous tissue in the breast that looks like a tumor. It was first documented in premenopausal women with long-standing type 1 diabetes mellitus to affect one breast. It was later described in elderly women with type 2 diabetes, and it may affect both breasts. Insulin resistance and increased circulating insulin decrease levels of sex hormone-binding globulin (SHBG), which enhance the bioavailability of endogenous estrogens and androgens associated with higher postmenopausal BC risk [105]. Insulin and IGF-1 receptors are both overexpressed in cancer cells. It has been hypothesized to have a potential association between diabetes and cancer, including BC are metabolic (hyperglycemia) or hormonal (insulin and IGF-1) factors which have been attributed as diabetes characteristics [18]. It is reported that the use of metformin has resulted in a lower risk of BC [106]. Abnormal pregnancy and long-lasting undesirable health problems like T2DM are also related to GDM [61]. GDM is further distinguished by hyperglycemia, insulin resistance, and hyperinsulinemia, all of which have been linked to uncontrolled cell proliferation and cancer. Furthermore, it is reported that GDM has been linked to an increased risk of breast, thyroid, stomach, and liver cancer in women [68].

[61] reported that an elevated risk of BC has been connected with a history of several GDM pregnancies in parous women, which suggests that the improper metabolism of blood glucose can be an etiology for BC. Therefore, GDM is a sign for women at risk of alterations in glucose metabolism that may affect the long-term disease risk. Furthermore, their research has a biological plausibility that women with multiple GDM pregnancies were impaired with glucose tolerance during their pregnancy. Thus, it is conclusive that there is a significant relationship between type 2 diabetes, GDM, and BC [61].

2.8. Impact of diabetes on female reproductive functions

Diabetes-related reproductive dysfunction is a widespread, however, coexisting complication of both disorders has received limited attention. As a result, diabetes patients face a wide range of reproductive health complications [102]. According to [9], menarche at a young age is an independent risk factor for GDM. Menarche, or the beginning of first menstruation, marks the beginning of ovarian and other reproductive endocrine processes. It is reported that menarche at a young age has been linked to an increase in the risk of developing type 2 diabetes. The development of GDM characterizes chronic insulin resistance and pancreatic β-cell dysfunction and early menarche age is linked to an increase in insulin resistance. Their study not only explored the

correlation of menarche age with GDM risk but also validated the findings of the relation between menarche and plasma glucose [9]. Women with type 1 diabetes have previously been reported associated with puberty delays. Furthermore, women with type 1 diabetes have significantly more menstrual abnormalities than non-diabetic women [102].

Diabetes can have an impact on female sexual function through a variety of pathways, including vascular abnormalities in the urogenital tissues that impact genital lubrication and neuropathy-mediated changes in vaginal arousal response [107]. While previous evidence suggested the benefits of vaginal delivery, however, most diabetic pregnant women preferred cesarean section (CS) due to the risk of fetal macrosomia and the fear of rupture of the uterus. Fetal microsomal is an etiology of GDM may be the predominant indicator of CS. Hence, there is rising concern over unnecessary CS, which increases the risk of maternal morbidity and infant death. Furthermore, recent research in Uganda revealed that while the procedures of delivery were similar, genital injuries were more prevalent in women with GDM [64].

Furthermore, GDM has a profound impact on the sex of offspring. It is also reported that there are metabolic variations between the male and the female fetuses due to different maternal hyperglycemia sensitivities which have later on lead to risks of sex-specific illnesses. Evidence from epidemiological research has shown that as far as long-term health is concerned, GDM therapy can impact offspring during their infancy and adolescence [48]. GDM is the leading health disease in pregnant women, with substantial short- and long-term complications for maternal morbidity. GDM also increases the cesarean delivery rate by up to 57.4% and has a significant impact in cases of obesity and/or previous cesarean section history [64,91] explored the impact of GDM and its combination on adverse pregnancy outcomes in Saudi women using the International Association of Diabetes and Pregnancy Study (IADP SG) guidelines. According to their research reports, the primary outcomes were birth weight and macrosomia and the secondary consequence was Caesarean delivery [91].

In addition, the association between early menarche and GDM risk may be caused by hormonal changes. Hence, the metabolic milieu of menarche women of early age may activate GDM-related pathophysiologic phenomena. Evidence of epidemiological studies has shown the harmful effects of early age in menarche including T2DM, and cardiovascular disease [9]. Hence, Diabetes has harmful consequences on the reproductive function of women [86]. Type 2 diabetes, insulin resistance, hyperinsulinemia, obesity, and PCOS all have an impact on fertility. However, due to the research is limited in this area, the evidence is insufficient to determine the relative contribution of each disorder to reproductive dysfunction. Therefore, long-term cohort studies are required to better understand these relationships. With a rising number of young women living with diabetes, utmost care should be given to face the challenges of handling the reproductive health issues of women.

2.9. GDM-related comorbidities

There has been evidence that GDM is associated with a variety of endocrine risk factors, including obesity, high blood glucose resistance, and insulin resistance. Maternal diabetes or chronic hypertension is linked to an elevated risk of hypertensive disorders of pregnancy in nulliparous women at all gestational ages [11]. In recent studies, maternal depression is a risk factor for several adverse effects of pregnancy and is associated with GDM. Inadequate health and poor dietary intake were linked with limited social support to pregnant women, which could adversely affect pregnancy issues such as GDM [51]. Women who have GDM are more likely to develop type 2 diabetes. Increased weight and adiposity are two more risk factors for T2DM [73]. It has also been established that depression has an adverse health effect on pregnant women having GDM. Psychophysiological factors have been proven to influence diabetes regulation. Emerging evidence suggests that hyperglycemia has been linked to depression [51,51] findings underscore the involvement of both psychosocial and biological factors in the development of GDM. Hence, this illuminates that depression and diabetes are likely to have a two-way link, both physiological and psychological [51]. GDM has been implicated in the pathophysiology of pre-eclampsia, the cesarean section of the mother, as well as macrosomia [33], hypoglycemia, shoulder dystocia, and neonatal jaundice in the baby [67]. Macrosomia is caused by excessive fetal growth, which is fuelled by maternal hyperglycemia. In addition, macrosomia appears to have been ignored in most nations. With the explosion of T2DM and obesity, macrosomia will become an important concern in maternal and child health and should be recognized and monitored as a marker for GDM [33].

GDM increases the risk of pregnancy hypertension, pre-eclampsia, cesarean birth, amniotic fluid excess, preterm membrane rupture, and ketoacidosis as short-term side effects. Furthermore, the long-term detrimental effects of GDM on the mother include cardiovascular disease and metabolic syndrome in addition to T2DM [73,80]. Moreover, GDM raises the danger of neonatal complications such as birth injuries, respiratory distress syndrome, hyperbilirubinemia, and hypoglycemia [80]. Gestational Diabetes Insipidus (GDI) is a kind of diabetes that can arise during pregnancy, however, it is extremely rare, occurring in 1 in 30,000 pregnancies and having the highest prevalence in multiparous women. Diabetes insipidus (DI) during pregnancy was originally identified in 1942 and is caused by an increase in the breakdown of the hormone arginine vasopressin (AVP) by the placental enzyme vasopressinase. Gestational Diabetes Insipidus (GDI) occurs near the end of the second or early third trimester and is associated with an increased risk of pre-eclampsia. Due to the rarity of gestational DI, there is no specific diagnostic test for it [108]. The epidemiological, and research reveal that GDM may interfere with intrauterine brain development and which can alter behavior in a future life [49]. The independent and additional risk factors for fetal macrosomia include maternal obesity, excess gestational weight gains, and GDM [60]. The increased adiposity of the fetus ($\geq$ 4 kg) is called macrosomia, a serious fetal consequence of GDM that can be minimized by 50% when treated properly [30]. Excessive stress can cause DM, and it can also deteriorate the patient's condition [19]. Additionally, smoking increases the risk of perinatal mortality particularly among pregnant women who have pre-gestational diabetes [109].

Excessive gestational weight gain has been reported to link with the negative consequences of pregnancy [47]. GWG is one of the main indicators for physiological and somatic changes, which affect fetal development and growth during pregnancy. Furthermore, inadequate or excessive GWG can harm mother and infant's health and lead to unwanted gestational consequences, particularly in high-risk pregnant women [110]. The major risk factors for GDM that are widely documented in women undergoing ART are advanced maternal age, obesity, multiple pregnancies, and PCOS, implying a probable link between GDM and ART [67]. The increased risk of pregnancy-induced hypertension is connected to GDM [6]. The pregnancy-induced hypertension is classified as the pregnant woman having a systolic blood pressure of $\geq$ 140 mmHg and/or diastolic blood pressure of $\geq$ 90 mmHg after 20 weeks of pregnancy. While proper antenatal treatment and appropriate lifestyle changes might improve the adverse maternal outcomes of women with GDM. The complications of one or more of these outcomes such as cesarean birth, pregnancy-induced hypertension, induced labor, premature rupture of membranes (PROM), antepartum hemorrhage (APH), and/or postpartum hemorrhage (PPH) have been recognized as the composite adverse maternal outcome [64].

Gestational hypertension is a metabolic disease caused by hormonal changes during pregnancy [8]. It is one of the most prevalent pregnancy problems which is most likely to occur in the middle and late stages of pregnancy. During pregnancy, blood pressure exceeds the normal maximum level, which causes more damage to different organs of pregnant women [111]. Gestational hypertension can cause liver and

kidney damage, as well as pre-eclampsia, fetal macrosomia, and other pregnancy complications that may necessitate a cesarean section [8]. It can result in several negative pregnancy outcomes as well as substantial damage to the health of mothers and children [111].

Nevertheless, GDM is a major risk factor for adverse maternal outcomes [24,64] revealed that GDM can contribute to higher maternal morbidity. When compared to their counterparts, women with GDM were three times more likely to develop pregnancy-induced hypertension. The findings were consistent with those of several previous research. Likewise, another study in Eastern Ethiopia indicated that women with GDM had three times the risk of pre-eclampsia. The link could be attributed to the type of common risk factors, like obesity, late motherhood, and family history of diabetes and hypertension [64]. It is also claimed that women who achieve singleton pregnancy with ART have a higher risk of GDM than those who achieve pregnancy naturally [67]. During pregnancy, the level of blood lipids will rise physiologically in order to meet the normal demand of the pregnancy. The blood lipid level rises to maintain homeostasis throughout pregnancy. Some studies have revealed that the level of TG fluctuates dramatically during the first trimester, which may be related to the influence of progesterone and estrogen in the body, as well as the preferential intake of high-calorie foods to prepare for pregnancy [80,64] concluded that GDM is a chronic disorder with a major effect on maternal outcomes. Thus, access to standard preventive measures must be strengthened in order to alleviate the plight of GDM women [64].

GDM is a common pregnancy disorder that is connected with antenatal, postnatal depression, and post-traumatic stress disorder [43]. Moreover, researchers found a link between GDM and Premature Rupture of Membranes. Their research also revealed that mothers with GDM had a higher incidence of Premature Rupture of Membranes than women without GDM. This could be related to the secondary complications of polyhydramnios and macrosomic infants induced by GDM, which causes the fetus' head to be blocked at the pelvic inlet and the full force exerted by the uterus to be directed to the area of membranes in touch with the internal os. As a result, membrane rupture is more likely to occur early. Furthermore, this research showed that the risk of APH was two times higher in women with GDM than in women without GDM. This could be because GDM has a disastrous effect on placenta previa and abruption placentae that leads to APH [64]. GDM has also been identified as a risk factor for a newborn due to excessive adiposity as evaluated by skinfold thickness at birth [112]. As a result, it is important to intervene before pregnancy to detect hyperglycemia as well as maternal obesity to prevent any adverse effects by controlling glucose levels to provide a healthy lifestyle.

3. Prognosis and prevalence of diabetes in India

India has long been recognized as the world's diabetic capital, and GDM is a serious concern in India than in other parts of the world. It is widely acknowledged that particularly pregnant and lactating women are among the most affected by diabetes [113]. India is the world's largest democratic nation, accounting for 16% of the worldwide population. Unfortunately, India has the highest number of maternal mortality in the world, with 45,000 deaths in 2015. It is one of six countries that account for 50% of all maternal mortality worldwide [114]. When compared to other Asian countries, the prevalence of GDM in the Indian population is significantly higher [54,115]. Diabetes is a major disease in India with prevalence rates ranging from 14% in urban areas to 13.2% in rural areas. T2DM affects an estimated 62 million people in India, with that figure projected to rise to 79.4 million by 2025. It is not surprising that there is a growing incidence of GDM (GDM) simultaneously increasing along with diabetes prevalence [116]. In India, 6 million pregnant women were reported to have some form of hyperglycemia, with GDM accounting for 90% of the cases in the year 2013. GDM is typically asymptomatic and is most frequently detected during pregnancy by routine screening. In the year 2010, The International Association of Diabetes and Pregnancy Study Group (IADPSG) guidelines were implemented and have since achieved widespread acceptance. However, some research suggests that it could lead to increased GDM risk factors [117]. In India, GDM affects approximately five million women per year. According to existing literature, pre-diabetes and diabetes affect approximately six million births in India alone with GDM responsible for 90% of the cases [118].

Diabetes prevalence is rising globally, particularly in the developing countries, with China and India suffering a significant share of the blame. The fact that India is likely to have the world's largest diabetic population by 2030 is a major area of concern. According to a study in India, women with GDM have a threefold greater lifetime chance of acquiring T2DM when compared to pregnant women without GDM 16 years after the index pregnancy. In India, one-third (33%) of women with GDM had a history of maternal diabetes [119]. In India, it was in the mid-20th century when the first scientific investigation was conducted on DM. In the late 1960 s, there were seven prevalence articles published [10]. DM is becoming more prevalent worldwide, especially in developing countries such as India. In addition, the prevalence of GDM is also increasing along with the upsurge of the current diabetes epidemic. GDM increased the potential of abnormalities in both the mother and baby, but early diagnosis and treatment can improve better health outcomes for both [117]. The short- and long-term impacts of GDM on both maternal and neonatal health are detrimental and cause major financial and health implications [9].

DM is a group of diseases that make a huge impact on increased health and financial burdens in many countries worldwide [33]. In rural India, financial problems are a significant barrier to accessing maternal health services. Similarly, poor nutritional status, Vitamin A deficiency in pregnant women lead to chronic disorders such as eclampsia, pre-eclampsia, and post-partum hemorrhage are the contributing factors to maternal mortality. However, The Indian government has successfully adopted several cash transfer programs in order to remove financial barriers, boost utilization of maternal health services, and promote institutional deliveries. Although in recent years, India is making progress and has seen a significant decrease in maternal mortality, more intensive measures are required [114]. As the number of people with diabetes increases worldwide, so does the prevalence of GDM, especially in less developed countries such as India. During pregnancy, Indians are eleven times more likely to develop DM [113]. The other major concern is that India's government health budget remains insufficient at 1.28% of total GDP. This is one of the lowest government health expenditures, in that region compared with Nepal, Sri Lanka, Thailand, and Indonesia [114]. In Indian communities, several social taboos and myths existing which prevent effective GDM management. As a result, particularly in rural areas of the country, the conflict is spreading among families because of the misunderstanding of GDM diagnosis. Furthermore, a lack of knowledge about the myth of insulin-related use poses a severe threat to GDM care. Many women are unaware of the importance and consequence of GDM for both maternal and fetal health. Increased GDM knowledge among pregnant women eventually leads to a better lifestyle, better health care, and self-care practices. Studies suggest that the diagnosis and management of GDM must be cost-effective, evidence--based as well as patient-friendly, and thus early detection and early diagnosis can be helpful to prevent GDM [66]. Hence, it is imperative to understand the prevalence of GDM and then attempting to reduce it to accomplish mother and child health care services in underdeveloped country.

3.1. Screening and diagnosis of GDM

O'Sullivan et al. proposed in 1964 that "screening, diagnosis, and treatment of hyperglycemia in women without diabetes improves outcomes" [14]. The fact is that majority of pregnant women are unaware that they have GDM until it is detected during regular prenatal screening, implying that the fetus has already been exposed to the

harmful intrauterine environment [48]. Hence, the universal screening program should be made available to all pregnant women which help to detect the presence of diseases [14]. The GDM screening determines if a pregnant woman is at a higher or lower risk of having GDM based on a predetermined glucose threshold. The words "screening" and "diagnostic" are commonly used interchangeably [120]. Several diagnostic criteria for GDM are currently available [69] although their accuracy in detecting GDM is questionable [65]. Unfortunately, the concern of universal GDM screening remains unresolved for decades despite several attempts have been made to find an accurate universal GDM screening [121,30]. Although the best GDM screening test is contentious, the American Diabetes Association recommends an OGTT for pregnant women during 24–28 weeks of gestation [25]. According to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations, GDM screening and diagnosis can be performed on a routine basis during the pregnancy between 24 and 28 weeks of gestation [36]. The American College of Obstetricians and Gynecologists recommends that antenatal testing should be done at 32–34 weeks of gestation with twice-weekly nonstress tests or weekly modified biophysical profiles [60]. A Primary screening approach for the identification of women with the risk of GDM is given in (Fig. 6). Moreover, it's a known fact that Asians have a high frequency of DM and a genetic susceptibility to metabolic syndrome, which puts them at risk of developing GDM and associated complications. As a result, universal screening is required in South East Asia, where Type II diabetes is prevalent and genetic predisposition is strong, especially in Indian women. A cost-effective universal screening and diagnostic procedure are therefore needed [122].

In Germany, The German Diabetes Association has proposed a two-step screening technique for GDM diagnosis based on IADPSG since 2011 [123]. Since 2012 all pregnant women in Germany are tested with a two-step test following the German Maternity Directive [56]. The risk of GDM is higher for women living in poor locations in Germany [93]. Hence, all pregnant women who have had no previous diabetes in Germany are offered GDM screening free of charge between the 24th and 27th gestational week since 2012 [29,109,93]. Moreover, the two-step screening for GDM diagnosis went into effect in July 2013 in Germany [123]. Screening, diagnosis, and treatment for GDM not only prevents adverse maternal and perinatal outcomes, but also future diabetes in both mother and child. Hence, Universal screening is essential, regardless of the method used. A list of GDM symptoms during various phases of pregnancy are summarised in Table 2.

The risk of future T2DM and metabolic anomalies for women who have GDM and their offspring is increasing. This risk should be reduced by early diagnosis and adequate management of GDM and post-partite monitoring and preventative care [119]. Detection of GDM is extremely important, not only for pregnancy and delivery, but also for the long-term consequences for both mother and child, such as obesity,

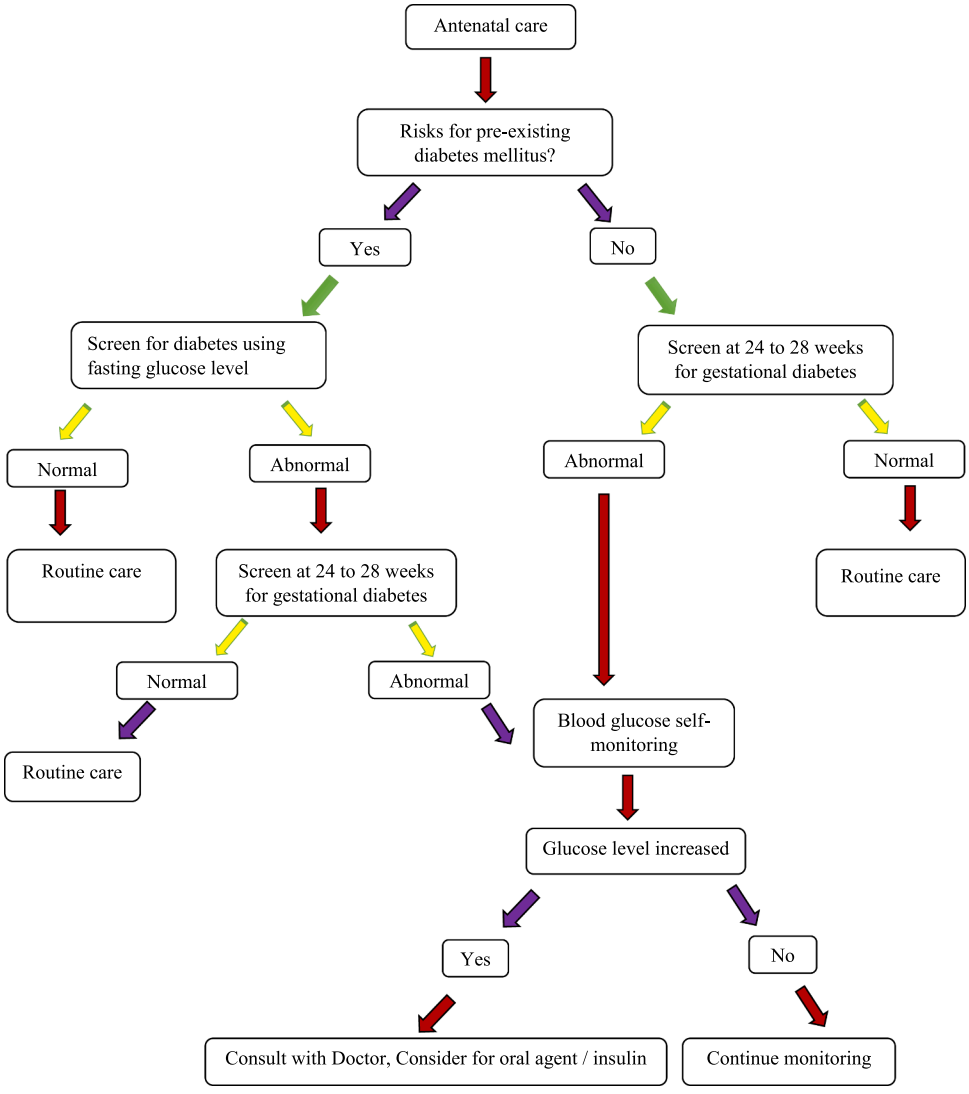

Fig. 6. Screening & Diagnosis of GDM.

Table 2
A list of GDM symptoms during various phases of pregnancy.

#	Phase	Symptoms	Study Group/First author
1	Preconception	• Family history • Advanced age • Overweight /obese	[64]
2	Prenatal	• Early diagnosis of GDM • HbA1c (glycated hemoglobin). • High insulin requirement • Multiparity • Obstetric complications • Induced hypertension	[11] [19] [72]
3	Neonatal	• Neonatal hypoglycemia	[50]
4	Postnatal	• Non-lactation • Prolonged insulin requirement post-delivery	[96]

T2DM, and a variety of metabolic and cardiovascular problems [124]. Therefore, it is important to identify women at risk for GDM who benefit from early preventive measures.

3.2. Oral Glucose Tolerance Test (OGTT) - based diagnostic criteria for GDM

The OGTT has been first described by Conn and used in clinical practice for more than 100 years [14]. It has been a matter of contention ever since O'Sullivan and Mahan conducted the first systematic evaluation of the OGTT in 1964 in regards to find the appropriate screening and diagnostic criteria for the detection of GDM [28,120]. Unanimous recommendations on GDM diagnosis criteria remain elusive despite several decades of attempts to achieve international consensus [28]. Thus, screening and diagnosis guidelines for GDM vary amongst countries and major global communities [120]. A lot of controversies have been involved regarding fundamental aspects of GDM screening such as why and how to screen for GDM, universal screening versus selective screening [30,120] one-step versus two-step criteria, early (first trimester) versus second-trimester screening [120]. As a result of the lack of agreement on screening and diagnostic criteria for GDM, different women are diagnosed using different criteria [120]. Consequently, the screening and diagnostic techniques of GDM are not uniform across the world, which insinuates both underdiagnosis and undermanagement of GDM [125]. Henceforth, there is no universally accepted diagnostic technique for GDM, making worldwide comparisons problematic [28]. Notwithstanding, scientists have raised concerns about the accuracy and precision of the OGTT, but it remains the "gold standard" test available for diagnosing T2DM and GDM [14].

GDM only affects pregnant women with abnormal glucose tolerance. It is therefore necessary to carry out an OGTT in order to identify this disease [7]. For decades, the OGTT has been the gold standard for diagnosing gestational diabetes [14]. OGTT has been used to detect GDM between the 24 and 28 weeks of pregnancy. Generally, during the second trimester, pregnant women should undertake an OGTT for the screening of GDM on a regular basis in accordance with risk factor screening guidelines [36]. The American College of Obstetricians and Gynecologists advises universal screening for all pregnant women. The "diabetogenic condition' of pregnancy is normally checked between 24 and 28 weeks of pregnancy [7]. Hence, most guidelines prescribe an OGTT during 24–28 gestational weeks for GDM diagnosis [50]. However, [36] research reveals that risks for GDM can be identified with a combination of numerous maternal demographic characteristics during the first trimester of pregnancy [36].

Notwithstanding, the OGTT has always been considered as the test of choice for GDM [85]. In 2010, new diagnostic criteria based on the study of Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) were proposed by the International Association of the Diabetes and Pregnancy Studies Group (IADPSG). These guidelines have proposed a 2-hour 75 g OGTT for universal GDM test [121,30], [24]. Moreover, IADPSG announced updated diagnostic criteria for GDM in 2010 based on risks of LGA. Fasting blood glucose (FBG), 1-h, and 2-h OGTT plasma glucose concentrations of 4.5, 7.4, and 6.2 mmol/l have been used as standards respectively [12].

The IADPSG and WHO criteria are currently the most widely accepted screening and diagnostic criteria for the detection of GDM [28, 120]. The World Health Organization (WHO) has approved the standard diagnostic test for glucose intolerance outside pregnancy as the 2 h 75 g OGTT [126]. The International Federation of Gynecology and Obstetrics, in collaboration with the European Board and College of Obstetrics and Gynecology, and the European Association of Perinatal Medicine, recently accepted the IADPSG's one-step universal screening approach for hyperglycemia in pregnancy [30]. However, In the United States and Canada, IADPSG criteria are not widely used [28]. The National Institutes of Health (NIH) in the United States and the National Institute for Health and Care Excellence (NICE) in the United Kingdom have not approved these recommendations [121]. Moreover, in the past recent years, 3-h and 100 g OGTT was carried out by the American Diabetes Association [126]. Different protocols are employed in Germany, which conducts a 75 g OGTT of the IADPSG criteria after a 50 g glucose challenge test (GCT). While simplified guidelines have been recommended by Diabetes in Pregnancy Study Group of India (DIPSI) that an OGTT can be conducted using a 75 gm glucose load, regardless of whether the woman is fasting or not, and a 2-h venous plasma glucose (VPG) value of 140 mg/dl as a single-step screening and diagnostic test for GDM. The Women in India with GDM Strategy (WINGS) initiative, which was recently completed in Chennai, India, attempted to develop a Model of Care for GDM. The WINGS project recommends a single-step 75 g OGTT in the fasting state utilizing the IADPSG criteria, and that VPG is considered as the gold standard [120].

Nonetheless, The IADPSG recommendations were adopted as the standard diagnostic criteria by several national and international organizations. In Europe and around the world, the International Federation of Gynecology and Obstetrics (FIGO) and the International Diabetes Federation (IDF) have endorsed the IADPSG criteria used [28]. Table 3.

However, the OGTT's diagnostic criteria differ from country to country and have been the subject of much debate in recent years. Hence, it's a race against time as scientists try to find a biomarker/test that can detect this at-risk maternal population easily, accurately, reproducibly and economically [14]. For the time being, the IADPSG criteria appear to be the most effective for screening and diagnosing GDM [120]. Furthermore, early detection and treatment of GDM have been shown to improve unfavorable pregnancy outcomes [75].

3.3. Prevention of GDM using biomedicine and pharmacotherapy

It is universally acknowledged that Biomedicine has a profound impact on human existence and is well-documented. Biomedicine is a branch of medical research that integrates biological and physiological concepts into clinical practice. It is an indispensable aspect of modern medicine and plays a significant role in the advancement of modern medicine [127]. Both in modern medicine and traditional medicine, medicinal plants provide valuable and safe therapeutic chemicals [53]. Therefore, the importance of biomedicine in modern society cannot be underestimated [127]. Similarly, DM is a popular therapeutic subject for investigation in natural product research. DM is treated with up to 800 plants, according to global ethnobotanical information on medicinal plants [3]. Moreover, there is mounting evidence that early and extensive pharmaceutical management of diabetes is extremely important. The most recent American Diabetes Association guidelines emphasize pharmacological treatment for diabetes prevention and several patient groups have benefited significantly [16].

Traditional medicine provides a viable alternative to the global diabetes conundrum. Plants including *Momordica charantia* and *Eugenia jambolana* have been identified to improve diabetes repercussions such

Table 3
OGTT-based diagnostic criteria for GDM.

#	Criteria	Step	Glucose (gm)	Hour (h)	Glucose threshold mg/dl				Author/Refs.
					Fasting	1 h	2 h	3 h	
1	O'Sullivan & Mahan - 1964	2 step	100 g	3 h	90	165	145	125	[24,28,120]
2	WHO - 1999	1 step	75 g	2 h	126	–	140	–	[120,126]
3	ADA - 2004	2 step	100 g	3 h	95	180	155	140	[126,120,125]
4	IADPSG – 2010	1 step	75 g	2 h	92	180	153	–	[24,30],[120,121]
5	WHO - 2013 (revised)	1 step	75 g	2 h	92	180	153	–	[120,126]
6	NICE - 2015	1 step	75 g	2 h	101	–	140	–	[120,121]

as neuropathy, nephropathy, insulin-induced fructose resistance, and cataracts using animals experiment methods [3]. Furthermore, it has been reported that *Strobilanthes crispus* is another medicinal plant that has antibacterial properties and is used in traditional medicine to treat diabetes, cancer, and hypertension, etc. [124]. Diabetes is strongly linked to bodyweight loss, which is one of the most prominent symptoms of the disease. Different botanical species in traditional medicine exhibit anti-diabetic properties. Moreover, the use of herbal antioxidants is recognized as an alternate approach for the treatment of diabetic oxidative damage [128].

Pregnancy is a critical time in which pregnant women's health literacy is also important not only for their own health but also for the health of their innocent babies. Proper public health encourages pregnant women in making decisions about the use of alternative medications [44]. Oral medications are the ideal first-line treatment, while insulin has traditionally been recommended for women with uncontrolled GDM as first-line therapy [60]. Nanomedicine systems play an important role in overcoming certain constraints through present therapeutic choices. Over the past two decades, significant progress has been made in exploring molecular mechanisms of pregnancy-related diseases. Nanoparticles may provide non-invasive approaches for the treatment of various reproductive complications [45].

Pharmacotherapy is required for almost 1 out of 4 women and Insulin is considered as the first-line pharmacotherapy [7]. Insulin therapy has been the cornerstone of treating hyperglycaemic patients for the past 15 years [129], The prevalence of GDM varies depending on various factors of the mother [130]. T2DM occurs when the β cells are unable to secrete enough insulin to combat insulin resistance [131]. Therefore, It is necessary for DM patients to take insulin when other medications fail to keep blood sugar levels within acceptable ranges [131]. For women with GDM, insulin is the recommended first-line treatment in the case of diet failure [7,130]. The endogenous hormone insulin is recommended by the American Diabetes Association, the American College of Obstetricians and Gynecologists, and the Canadian Diabetes Association (CDA) [31]. Since insulin has an excellent safety profile for developing fetuses, several organizations continue to recommend it as the first-line therapy for GDM [132,83]. However, there is also limited international agreement about the best possible first-line pharmacological agents for the management of GDM [31]. In the USA and Canada, insulin therapy is common but not a universal practice [129].

In spite of the fact that diet and insulin therapy can normalize maternal and newborn glycemia, GDM continues to have a detrimental influence on placenta function and the neonate metabolic state [133]. A rapid-acting insulin analog, such as lispro or aspart, is routinely administered to women with GDM and pregnant women with type 1 diabetes. It has been shown that insulin therapy for women with GDM has a better maternal and newborn outcome than diet, oral anti-diabetic drugs, or insulin analogs for women with GDM [133]. Moreover, macrosomia incidence is also lower with insulin therapy and the cranial-thoracic circumference ratio is less with insulin therapy than with insulin analogs [133]. The standard therapy for women with gestational diabetes requiring drug treatment is insulin. However oral agents are more attractive than insulin to treat women with gestational diabetes [130,134]. According to [134] findings, Insulin and metformin are better alternatives for women with gestational diabetes who require drug treatment, but glyburide is unsatisfactory compared to both. Hence, glyburide (Glibenclamide) should not be used to treat women with gestational diabetes if metformin or insulin are available [134].

Metformin (N, N-dimethyl biguanide) is prescribed as a first-line medication for GDM in various countries, along with insulin [135]. Metformin was discovered in 1922 and belongs to the biguanide family of drugs. It is developed from guanidine, which is abundant in *Galega officinalis* [136]. Since the 1960s, biguanides like metformin have been used to treat type 2 diabetes and metabolic syndrome [137]. It is one of the most often prescribed medicine that has been used to treat T2DM which is a natural product precursor of metformin [138]. In India, UK, and Israel non-insulin medicines namely metformin and sulfonylureas are is relatively widespread [129]. The Society of Maternal-Fetal Medicine (SMFM) recommends Metformin (N, N-dimethyl biguanide), an oral insulin sensitizer and glucose-lowering drug [31]. Patients with type 2 diabetes are prescribed metformin as a first-line treatment option [139,131]. Metformin can block the mitochondrial shuttle enzyme glycerol-3-phosphate dehydrogenase. As a result of this, liver metabolism is altered, including gluconeogenesis and lactate production, as well as AMP-activated protein-kinase [131]. Hence, In addition to its hypoglycemic effects, metformin also inhibits the production of glucose in the liver [139].

Metformin is classified as a category B pregnancy medication approved by the FDA. However, Lactic acidosis is more likely to occur when metformin is used during pregnancy because it crosses the placenta freely. Metformin was therefore not recommended for pregnant women with gestational diabetes [140]. However, recent studies have reported despite the fact that metformin crosses the placenta, it does not cause teratogenic effects [115]. Moreover, there was no difference in neonatal hypoglycemia rates between metformin-treated and insulin-treated women [140]. A similar report has been published that Metformin is a potential oral hypoglycemic drug commonly utilized to increase insulin sensitivity. In the management of diabetes during pregnancy metformin monotherapy helps maintain glycemic control [13]. Metformin therapy is specifically advised for patients with prediabetes, a BMI of 35 kg/m2 and younger than 60 years, as well as women with a history of GDM [16]. Furthermore, It has been reported that metformin is used to induce ovulation [100].

There are several advantages to using metformin and glyburide instead of insulin. In addition to their route of administration, oral hypoglycemic agents such as metformin and glyburide have proven to be more cost-effective alternatives to insulin [115]. According to research published in Obstetrics and Gynecology, GDM women who take metformin more than twice are more likely to require insulin therapy than those who receive glibenclamide [141]. The results of the [140] study are in concordance with the results of the studies done by [142] which suggested that there was no difference in perinatal complications between women with GDM who took metformin alone and those who took it in combination with insulin. [81] published a similar report, suggesting that women with type 2 diabetes could get benefit from appending metformin to insulin during pregnancy. According to the [115] study, It has been shown that metformin therapy improves maternal and neonatal outcomes, and thus can be recommended as an

option for GDM treatment [115]. Metformin crosses the placenta during pregnancy, and the offspring are exposed to high doses that could affect intrauterine fetal with long-term implications and cardiometabolic health [135]. When it comes to teratogenicity, their study provides convincing evidence that the use of metformin is safe during use pregnancy. According to the [135] study, metformin use in the first trimester of pregnancy is not teratogenic. It is reported that Metformin reduces the postprandial blood glucose (2HPG) level better than insulin [13]. Pre-eclampsia, LGA, newborn hypoglycemia, and maternal weight gain may be reduced using metformin as an alternative to insulin, however, there is some evidence to suggest an increased risk of premature delivery [39]. Furthermore, [137] finding suggests the possibility that metformin could have a beneficial effect on other age-related diseases as a result of its association with lower cancer and cardiovascular disease risk [137]. Moreover, Metformin is also used to help women with PCOS [143] increase their fertility and reduce the risk of pregnancy complications [143,135]. However, the way metformin is increasingly being prescribed to pregnant women with type 2 diabetes, despite a lack of research concerning the short and long-term effects of the medicine [94]. Hence, further studies are required for the effectiveness and safety of metformin [7,129].

According to [144] reports, the prevalence of GDM was lowered after consuming myoinositol. Insulin sensitivity is increased by myoinositol outside of pregnancy [144]. Orlistat can be used as a second-line therapy to prevent T2DM in obese patients in addition to lifestyle improvement [145]. From a biological perspective, there is abundant evidence that vitamin D may affect non-skeletal health complications such as cardiovascular disease, cancer, and Type 2 diabetes [146]. GDM and pre-eclampsia incidences are presumably reduced by supplementing with vitamin D [144,147] documented that there was a lower risk of cesarean section and hemorrhage after childbirth when vitamin D was supplemented. Further benefits include a reduced risk of neonatal hyperbilirubinemia, giant children, and premature birth. Hence, a significant function for vitamin D in type 2 diabetes seems biologically plausible [146]. Alpha-glucosidase inhibitors (AGIs) are oral diabetic medications used to control diabetes, largely by reducing postprandial glucose levels in the bloodstream [148]. Further, It is reported that studies with AGI medicines provide direct evidence for the favorable effects of decreasing postprandial glucose [149].

3.4. Early treatment and management of GDM

Early detection and treatment of GDM significantly decrease the potential impact on women and infants and it is economical in terms of better results, such as reduced rates for Pre-eclampsia, cesarean sections, newborn hypoglycemia [55]. It is necessary to improve the accuracy of identifying women who are at risk of developing GDM because early diagnosis and treatment improve the outcomes of this common pregnancy disorder. A prognostic model could assist all areas that use selected risk factor-based testing for GDM. It is suggested that prognostic models for GDM be evaluated for incorporation into obstetric recommendations [82]. International Association of Diabetes in Pregnancy Study Groups (IADPSG) 2010 criteria, which were endorsed by the World Health Organization (WHO) in 2013, distinguish between women who are diagnosed with diabetes during pregnancy and women who would be diagnosed with diabetes if hyperglycemia was detected outside of pregnancy. These women have been described by IADPSG as 'overt diabetes,' although the WHO preferred the term 'pregnancy diabetes' [28].

The World Health Organization (WHO) advises the diagnosis of GDM when hyperglycemia is first detected at any pregnancy stage [13]. GDM is a common gynecological and obstetric disease that is associated with abnormal glucose metabolism during pregnancy. It is directly linked to the patients' hereditary characteristics, lifestyle, and dietary habits [80]. Diabetes, obesity, and long-term metabolic disorders are more prevalent in mothers with GDM. However, proper GDM management in pregnant women, including glycemic monitoring, lifestyle adjustments, nutrition counseling, exercise, and insulin administration, can assist to reduce short-term maternal and neonatal complications [50] (Fig. 7). GDM is a type of diabetes that develops or is discovered during pregnancy due to abnormal glucose tolerance. It is one of the most prevalent metabolic problems during pregnancy. Moreover, due to lifestyle and diet pattern changes and lack of understanding of the complications associated with pregnancy have increased the incidence of GDM in pregnant women [80]. GDM increased the potential of adverse pregnancy [24] and childbirth and has an impact on the offspring [80], [34]. GDM-historical women should be screened for overt diabetes every three years [60].

Diet and exercise are the first-line treatments for T2DM and obesity, and they can reduce the risk of developing T2DM by 58%. In fact, when compared to metformin, lifestyle modification was more successful in preventing the onset of T2DM [17]. Diet plays a major impact in preventing T2DM in women with GDM history and obesity. Changes in the quality of food have been strongly and independently associated with long-term changes in weight among women with GDM history [35].

Some of the lifestyle choices of mothers including smoking during the pregnancy and does not allowing breastfeed their infant after the first few months of delivery can have an impact on the health outcomes both of mothers and children [44]. Breastfeeding can minimize the risk for T2DM in women suffering from GDM [60], [144]. Researchers in Germany have found that breastfeeding reduces diabetes risk by more than 40% and appears to delay the progression of T2DM for at least another decade [144]. When compared to women without a GDM history, GDM-historic women have an extremely high chance of developing obesity-related chronic disorders such as T2DM and hypertension in their later life. Women with GDM are usually recommended to avoid gaining weight in order to reduce their risk of developing T2DM especially throughout the postpartum period [35,96] evaluates the effect of a third-trimester diet in women with GDM using a questionnaire. Their findings revealed that the maternal dietary pattern in women with GDM during their third trimester of pregnancy is associated with improved appetitive control. Therefore, a health-conscious dietary pattern in women with GDM may potentially minimize their offspring's risk of developing overweight/obesity [96].

Controlling (HbA1c) levels and maintaining optimal blood glucose levels are considered excellent diabetes management strategies [19]. GDM management is mostly focused on dietary improvements and increased physical exercise also patients can be educated for long-term self-management during the GDM patient training program [56]. Physical activity is beneficial to both the mother and the fetus during pregnancy. It promotes the prevention of GDM, excessive GWG, pre-eclampsia, cesarean deliveries, and the improvement of mental health. Regular cardiovascular exercise throughout pregnancy can help with postpartum recovery as well [150]. The World Health Organization (WHO) emphasizes the importance of patient-centered education for the effective management of chronic diseases. In the field of diabetes awareness, diabetes self-management education is a promising technique for reducing the burden of diabetes [1]. Therefore, the importance of GDM management during pregnancy relies on lifestyle adjustments and/or proper medication to minimize unfavorable pregnancy outcomes.

4. Research gaps in gestational diabetes mellitus

There is much disagreement specifically on the criteria used to diagnose GDM. American Diabetes Association and American College of Obstetricians and Gynecologists currently recognize the criteria for the 2-step procedure (50 g glucose challenge test followed by the 100 g 3 h OGTT. However, Hyperglycemia and Adverse Pregnancy Outcomes Study (HAPO) revealed a single step glucose tolerance test (75 g 2 h OGTT) in the late second and early third trimester which gave a better positive outcome. As a result, the accurate OGTT procedure is a significant area of research gap, and the precise and reliable method for GDM

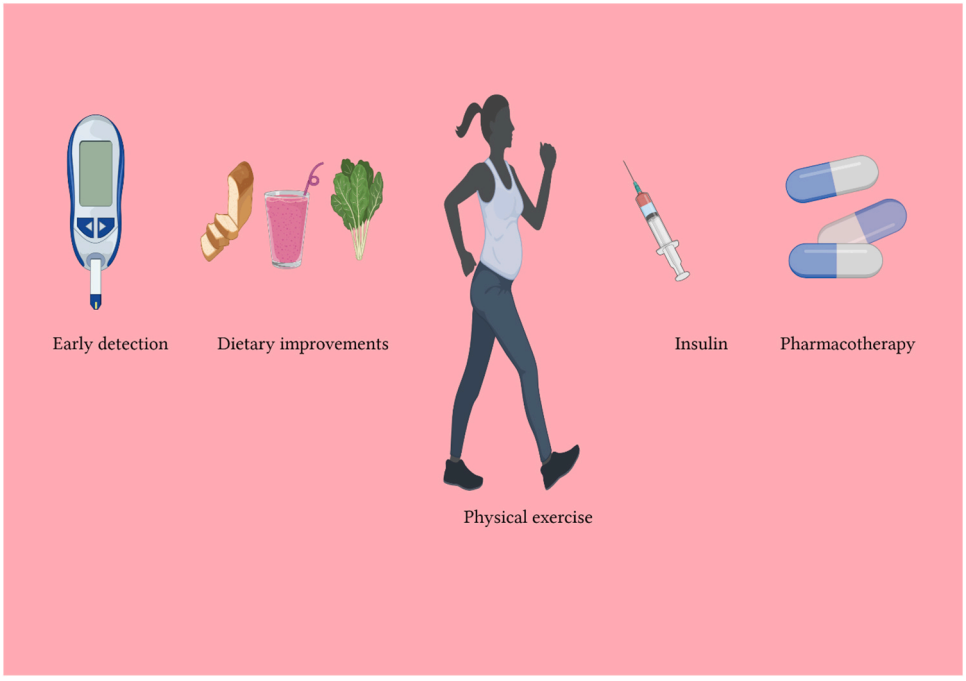

Fig. 7. Management of gestational diabetes mellitus.

diagnosis has yet to be identified. Furthermore, It is unconfirmed whether diagnosing and treating GDM before 20 weeks of gestation improves perinatal outcomes or not. Hence, the critical concerns are related to early vs. late GDM diagnosis procedures yet to be found. Another concern is that glucose tolerance testing was inadequate for early pregnancy. In addition to that, due to the glucose tolerance test are an inadequate indicator for early pregnancy diagnosis. Hence, the quest for alternative Bio-markers for early pregnancy diagnosis needs to be explored.

Another significant research lacuna is in GDM pharmacological therapy. The American Diabetes Association recognizes insulin to be first-line therapy, but metformin has a higher trans-placental fetal exposure than glyburide. According to the 2018 Society for Maternal-Fetal Medicine statement on GDM treatment, both metformin and insulin are suitable first-line therapies for GDM. Metformin is considered second-line therapy by the American College of Obstetricians and Gynecologists in patients who hesitate insulin, and both metformin and insulin are favored above glyburide. The ADA does not recommend one oral drug over the other. These recent contradicting guidelines accentuate the need for extensive further research to compare the efficacy of GDM insulin and oral medicines. The relative effects of insulin versus metformin versus glyburide on safety, tolerability, and long-term results are still obscure and hence there is a huge lacuna. Future research should compare all three drugs and emphasis the perinatal and long-term effects of the mother and infant. For each of these drugs, optimal dose techniques should also be investigated. In the perspective of the unpredictable progression of GDM further research should be carried out in prospects to improve our understanding of the etiology and prevention of GDM both the short-term and long-term prognosis for mothers and their children. A list of research gaps in GDM is summarised in Table 4.

Table 4
A list of research gaps in GDM.

I. Early pregnancy diagnosis and treatment:
A. Diagnostic criteria
B. Alternative markers for diagnosis
C. Effect of early diagnosis and treatment on outcomes
II. Pharmacologic management:
A. Pharmacokinetics and placental transfer of oral glucose-lowering medications
B. Effects of glucose-lowering medications on perinatal outcomes
C. Effects of glucose-lowering medications on long-term outcomes
III. Additional gaps:
A. Phenotypic heterogeneity
B. Novel and individualized treatment

5. Conclusion

In the 21st century, GDM imposes a major challenge for healthcare professionals. GDM is more widespread in the Indian population than in other Asian countries. Changes in lifestyle and dietary patterns, as well as a lack of understanding of pregnancy complications, have increased the occurrence of GDM in pregnant women. Physical activity is beneficial to both the mother and the fetus during pregnancy. Since GDM diagnostic technique is not universally accepted, the World Health Organization (WHO) therefore emphasizes patient-centered education and which is a promising strategy for minimizing the burden of diabetes. In conclusion, our review analysis found that women in poor locations have a higher chance of acquiring GDM and even small expenses are likely to impair their participation in GDM screening. Thus, free-of-cost GDM screening and proper treatment for maternal health care can be a significant step towards diabetes care as well as social prosperity.

CRediT authorship contribution statement

All authors are equally contributed to complete the manuscript and all authors approved the version of the manuscript.

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Conflict of interest

The authors have declared that there is no conflict of interest in publishing this article.

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