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CHARLES UNIVERSITY IN PRAGUE
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Department of Pharmacology and Toxicology

CURRENT APPROACHES IN THE TREATMENT OF DIABETES IN PREGNANCY

Diploma thesis

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DECLARATION

I, Pınar Küçük , declare that this work is my own work and that all the information resources are presented in the list of references.

Hradec Kralove, 2010 Pinar Kucuk

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1. LIST OF ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
CI	Confidence interval
GAD	Glutamic acid decarboxylase
GCK	Glucokinase
GDM	Gestational Diabetes Mellitus
GI	Glycemic Index
HAPO	Hyperglycemia and Adverse Pregnancy Outcome
HI	Human Insulin
IAsp	Insulin Aspart
LGI	Low glycaemic index diets
MBL	Mannose-binding lectin
MDI	Multiple Daily Injection
NICE	National Institute for Health and Clinical Excellence
OGTT	Oral Glucose Tolerance Test
PCOS	Polycystic Ovarian Syndrome
RR	Relative Risk
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TNF-α	Tumor necrosis factor
WHO	World Health Organization

2. ABSTRACT

The management of pregestational diabetes requires tight metabolic control to reduce maternal and perinatal morbidity and mortality. It has been suggested that type I diabetes is a disorder characterized by insulin deficiency and type II diabetes is characterized by insulin resistance. If patient is having type II diabetes, they require higher doses of insulin in pregnancy and limited use of oral hypoglycemic agents; moreover, both type I and type II diabetes mellitus appear to have a necessity of administering different doses of insulin in each trimester.

Gestational diabetes mellitus (GDM) is characterized by glucose intolerance of variable severity that begins or is first diagnosed during pregnancy and which shares the same pathophysiology and clinical signs as diabetes mellitus type 2. As well as for a diabetic pregnancy, the therapeutic management of gestational diabetes mellitus must be instituted early and must be intensive.

Risk factors for the development of GDM include obesity, older age, family history, previous history of GDM or poor obstetric outcomes, ethnicity, polycystic ovary syndrome and as more recently noted, hypertension. GDM may also be caused by genetic variation that predisposes women to autoimmune T1DM or late autoimmune diabetes of adulthood. The key symptom of GDM is the development of diabetic fetopathy.

GDMis diagnosed by an oral glucose tolerance test coupled with a fasting blood glucose test. Many clinicians support the concept that all pregnant women should be screened between 24 and 28 weeks or sooner on the basis of low-or high risk factors.

The cornerstone of therapy for GDM is extremely tight glycemic control. Medical nutritional therapy and exercise are generally initiated for newly diagnosed women prior to medical intervention, but diet therapy over a longer period may predispose the patient to increased risk for preeclampsia. Pharmacological management of gestational diabetes mellitus may include oral antidiabetic agents, among which glyburide and metformin, are the most often used ones. Insulin therapy is applied to treat GDM only in women with contraindication of antidiabetic agents. Insuline analogues are generally considered safe for use in pregnancy.

3. AIMS OF THE STUDY

The principal aim of this thesis is to summarize the current knowledge about diabetes mellitus in pregnancy with a special focus on gestational diabetes. We discuss here the up to date information regarding the pharmacological treatment as well as the non-pharmacological management of diabetes mellitus in pregnant women and mention the novel approaches which are recently used in the treatment of DM in pregnancy.

4. METHODOLOGY

This diploma thesis is based on the literature searches of websites and different scientific databases gaining publications in the form of journals, books, published articles or guideline manuals.

The approach used in the first introduction section is:

General description of diabetes mellitus and as a special subject gestational diabetes using books and literature from several websites, including the World Health Organization (WHO) and the National Institute for Health and Clinical Excellence (NICE) and special studies of gestational diabetes American Diabetes Association.

The approach used in the second section of the results is:

American Diabetes Association: Gestational diabetes mellitus guidelines and recommendations for management and pharmacotherapy of gestational diabetes mellitus including the newer agents in the market, and using non pharmacological techniques using the official website of American Diabetes Association.

Published articles used mostly PubMed and Medline databases (English - Turkish language), Obstetrics & Gynecology concerning the epidemiology of pregnant women with diabetes mellitus, using keywords as: Diabetes mellitus, gestational diabetes mellitus, Type 1 diabetes and Type 2 diabetes in general.

General description of gestational diabetes mellitus was found using data from the Obstetrics & Gynecology, and some websites concerning gestational diabetes mellitus in Turkey. Situation about diabetes was found using literature in electronic form from several websites.

Tables and figures were found after searching in the official website of the World Health Organization (WHO), and the Obstetrics & Gynecology.

I. BACKGROUND

5. INTRODUCTION TO DIABETES MELLITUS

Diabetes mellitus (DM) is a syndrome characterized by hyperglycemia resulting from absolute or relative impairment of insulin secretion and/or insulin action [1].

The assortment of diabetes mellitus and the tests used for its diagnosis were brought into order by the National Diabetes Data Group of the USA and the second World Health Organization (WHO) Expert Committee on DM in 1979 and 1980. Besides, modifications by WHO in 1985, little has been changed since that time [2].

The International Diabetes Federation has indicated with signs that the number of individuals suffering from diabetes will increase from 240 million in 2007 to 380 million in 2025, with 80% of the disease burden in low and middle income countries [3].

Even worse is the fact that this incidence is estimated to increase by another 165 percent to 2050. To put this into perspective, the lifetime risk of diabetes in individuals born in 2000 is 33 percent of males and 39 percent of females. This increase is primarily due to type 2 diabetes, which is also referred to as diabesity, because of the strong relationship with the current epidemic of obesity in the United States and other countries [4, 5].

5.0 CLASIFICATION OF DM

The two main forms of diabetes should be appointed only as type 1 and type 2 DM with a respect to etiology and pathogenesis (Table 1 and Table 2).

Deficiency of insulin secretion, which is called type 1 diabetes mellitus (T1DM) leads to destruction of beta cells of islet of Langerhans [6]. The therapy of T1DM is based on multi daily injections of insulin such as rapid acting insulin, intermediate acting or slow insulin. Furthermore, doses are usually regulated according to capillary blood glucose self monitoring [7]. The necessity of life therapy of T1DM may lead to some complications; such as, nephropathy and retinopathy especially in women of childbearing age [7].

Table1: Disorders of Glycaemia: Etiological types and clinical stages. Adopted From [9]

	Normoglycaemia		Hyperglycemia		
…Stages / Types…	Normal Glucose Tolerance	Impaired Glucose Regulation IGT and/or IFG	Diabetes Mellitus		
			Not Insulin Requiring	Insulin Requiring for Control	Insulin Requiring for Survival
Type 1 Autoimmune Idiopathic	<<<<<<<<	<<<<<<<<<	>>>>>>>>	>>>>>>>>	>>>>>>>>
Type 2* Predominantly Insulin Resistance Predominantly Insulin Secretory Defects	<<<<<<<<	<<<<<<<<<	>>>>>>>>	>>>>>>…	…….>>
Other specific Types*	<<<<<<<<	<<<<<<<<<	>>>>>>>>	>>>>>>…	……..>>
Gestational Diabetes Mellitus*	<<<<<<<<	<<<<<<<<<	>>>>>>>>	>>>>>>>…	……>>

*In rare instances patients in these categories may require insulin for survival.

In addition, T1DM was subdivided into an autoimmune mediated and into an idiopathic form as shown in Table 2.

MODY (maturity-onset type diabetes in young people) was characterized to be mainly associated with primary defects of insulin secretion. It was distinguished from type 2 diabetes according to the category of genetic defects of beta-cell function, related to mitochondrial diabetes (maternally inherited diabetes and deafness) [7].

In the case of type 2 diabetes mellitus (T2DM) pancreatic insulin production continues, but it may be insufficient for control of blood sugar levels. Moreover, most patients of this group can be treated with diet and exercise together or with peroral antidiabetics. Therefore, people with T2DM whose blood glucose levels exceed 17mmol per liter will need insulin therapy for control of blood glucose [8].

Table 2: Classification of DM Adapted from [9]

T1DM	Immune-mediated nature, where beta cell loss is a T-cell mediated autoimmune attack
	An idiopathic form
T2DM	May range from predominantly insulin resistance to predominantly an insulin secretory defect with insulin resistance
GDM	Any degree of glucose intolerance with onset or first recognition during pregnancy"
Genetic mutations in beta beta-cell function	• MODY
	• Mitochondrial DNA mutation depended Diabetes
	Hyperglycemia usually diagnosed before age 25 yr
	Absence of insulin therapy at least 5 yr after diagnosis
	Autosomal-dominant pattern of inheritance
	Overweight or obesity is rarely associated
Genetic defects in insulin action	• Defects in proinsulin conversion
	• Insulin gene mutations
	• Insulin receptor mutations
Genetic syndromes	• Down, Klinefelter, Turner
Endocrinopathies	• Cushing syndrome, pheochromocytoma, others
Drug or chemical induced	• glucocorticosteroids, thiazides, beta-adrenergic agonists, others
Infections	• congenital rubella, cytomegalovirus, coxsackievirus

6. INTRODUCTION TO GESTATIONAL DIABETES MELLITUS

The need to treat women in pregnancy for diabetes arises either from the T1DM, T2DM or MODY, which has been pre-diagnosed before the conception, or from the occurrence of gestational diabetes. Gestational diabetes mellitus (GDM) is any carbohydrate intolerance with onset or first recognition in pregnancy [10]. According to this definition, GDM includes women whose glucose intolerance develops during pregnancy and also those, which had not been diagnosed before pregnancy.

Somewhat more than 131,000 American women had pregnancies complicated due to diabetes representing 3.3 percent of all live births in 2002. Also, more than 90 percent of these women had GDM, and are likely to have T2DM that has previously gone undiagnosed [11].

The most important thing is that women with childbearing may be complicated by DM, and it may be lead to serious complications including mother and her fetus.

6.0 HISTORY of GDM

Gestational diabetes a term that applied until the 1950s to what was considered to be a transient condition that influenced the fetal outcomes reversing and then minimizing them after delivery. In the 1960s, O'Sullivan found that the degree of glucose intolerance during pregnancy was related to the risk of developing diabetes after pregnancy [12].

O'Sullivan mentioned that the degree of glucose intolerance during pregnancy was associated to the risk of developing diabetes after pregnancy in the 1960s [13]. He proposed criteria for the explanation of oral glucose tolerance tests (OGTTs) during pregnancy that were essentially statistical, determining cut-off values; which means that a new diagnostic test for classifying cases as positive or negative; may be determined utilizing some statistical techniques. In addition, approximately 2 standard deviations are used for diagnosing glucose intolerance during pregnancy, which results by distinguishing infected individuals from uninfected individuals [7, 12,13]. In the 1980s those cut-off points were adapted to modern methods for measuring glucose and applied to the modern definition of GDM; glucose intolerance with onset or first recognition during pregnancy [14].

6.1 DEFINITION OF GDM

GDM is the impaired carbohydrate metabolism first diagnosed in pregnancy, which may lead to serious health problems for the mother and her fetus [14]. Among those complications are shoulder dystocia, birth injuries, neonatal hyperbilirubinaemia, hypoglycaemia, and respiratory distress syndrome. Furthermore, the complications may lead to the necessity of caesarean section, and pre-eclampsia which is characterized by hypertension and fluid retention and albuminuria [14, 15]. Insulin secretion and insulin resistance increase in normal pregnancy [16]. If the insulin secretory capacity becomes insufficient to overcome this progressive insulin resistance [16], GDM is evident. Additionally, pancreatic β cells are no longer able to compensate for the increased insulin resistance during pregnancy [10], which induces the GDM. Furthermore, the maintenance of glucose tolerance in pregnancy requires a two to three fold increase in postprandial maternal insulin secretion. Glucose intolerance leads to imbalance of metabolic process when it is not cured.

Additionally, fewer features of insulin resistance are reported in women, who have got autoimmune GDM; therefore, more frequent insulin therapy is required than in negative women, and apparently had presymptomatic T1DM. Nevertheless, among many reports that women with GDM and with or without GADA positivity at follow up; display similar clinical characteristics with the exception of body mass index (BMI) [44].

No specific disease modifying therapies are currently available for autoimmune GDM.

6.2 PATHOPHYSIOLOGY OF GDM

GDM is characterized by insulin levels that are insufficient to meet insulin demands. The causes of pancreatic β-cell dysfunction that lead to insulin insufficiency in GDM are not fully defined. The first and second phase insulin responses supply for the result of reducing in insulin sensitivity [17].

Three general categories have been identified [17]:

1) Autoimmune β-cell dysfunction,

2) Highly penetrable genetic abnormalities that lead to impaired insulin secretion,

3) β-cell dysfunction that is associated with chronic insulin resistance.

When pregnancy is over, insulin resistance may persist.

One potential pathophysiological explanation of GDM is the limitation in pancreatic β cell reserve that shows clearly as hyperglycemia only when insulin secretion does not increase to match the increased insulin needs of late pregnancy [20]. When pregnancy is over, it appears an increase in insulin resistance which can lead to development of T2DM in some women [21].

Euglycemia is a condition of having a normal concentration of glucose in the blood, which is maintained through an equivalent in value increasing the insulin secretion. The key factor which results in the development of GDM appears to be a failure to compensate with increased insulin secretion [21].

6.3 COMPLICATIONS OF GDM

GDM

Fetal complications, including fetal death in utero, macrosomia and\or lung immaturity, have been seen in all types of DM. In addition, untreated diabetes lead to fetal death in utero. The preterm birth is associated due to excessive production of lactate by anaerobic glycolysis, decompensation of hypertropic cardiomyopathy. Therefore, prevention from those complications should have good control of blood glucose levels [24]. The American Diabetes Association has announced that, fasting hyperglycemia determined as more than 105 mg/dl may be connected to a raised, risk of fetal death during the last 4 to 8 weeks of gestation. Adverse maternal effects include an increased frequency of hypertension and cesarean delivery [9].

Macrosomia is declared as birth weight more than 4000 to 4500 grams; besides, moderate macrosomia has been defined as birth weight between the 90th and 97.7th percentile and severe macrosomia as birth weight greater than 97.7th percentile [25].

The characteristic of macrosomia, mainly result on the upper end of the trunk with a significant raise in the shoulder area; hence the macrosomic children have approximately 4cm difference between shoulder and head. When nondiabetic pregnancies compared to diabetic ones, the differences between them are shown clearly [24]. The American College of Obstetricians and Gynecologists (ACOG) has stated that the perinatal focal point is forbearance of difficult delivery. Difficult delivery is due to macrosomia, which has as a natural result birth trauma associated with shoulder dystocia [26].

6.4 DIAGNOSIS OF GDM

Diagnosis is made with an Oral Glucose Tolerance Test (OGTT); although, the criteria diverse all over the world [15]. According to scientific studies GDM occurs in 2.2%–8.8% of pregnancies, which is depending upon the ethnic mix of the population and the criteria used for diagnosis [15].

The necessity for diagnosis may be according to symptoms which are shown in Table 3.

Table 3: Symptoms of GDM. Adapted according to [22,23]

Blurred vision
Fatigue
Frequent infections, including those of the bladder, vagina, and skin
Increased thirst
Increased urination
Nausea and vomiting

Woman with GDM is diagnosed to determine high plasma glucose levels, glucosuria, and ketoacidosis. Similarly, women with a random plasma glucose level greater than 200 mg/dl plus classic signs and symptoms such as polydipsia, polyuria, and unexplained weight loss or a fasting glucose exceeding 125 mg/dl are considered to have overt diabetes by the American Diabetes Association.

100-g three hours OGTT carried out after an overnight fast remains the standard in United States [26, 27] as shown in Table 4. On the contrary the National Institutes of Health (NIH) has funded a multicenter international trial called Hyperglycemia and Adverse Pregnancy Outcome (HAPO). This trial intends to blind caregivers as to results to a 75 g oral glucose tolerance test. Then, the infant outcome can be related to degrees of hyperglycemia without the confounding problems that are due to treatment [28].

So far the best way is to comply with the guidelines of the American Diabetes Association, until the hyperglycemia and HAPO results are completed [26]. Whether universal or selective screening should be used and in which plasma glucose level after a 50-g glucose test threshold is the best to identify women at risk for gestational diabetes. Moreover a 50-g oral glucose challenge test can be followed by a diagnostic 100-g OGTT, if results exceed a predetermined plasma glucose concentration [29], and if the screening test is positive, after 1 hour the results may be over 140 mg/dL .

Table 4: Determination of GDM, According to 100-g OGTT. Adapted According to [27].

	Plasma/Serum Carpenter and Coustan		National Diabetes Plasma Data Group	
Status	*mg/dL*	*mmol/L*	*mg/dL*	*mmol/L*
Fasting	95	5.3	105	5.8
1 hr	180	10.0	190	10.6
2 hr	155	8.6	165	9.2
3 hr	140	7.8	145	8.0

The main changes proposed to the diagnostic fasting plasma (blood) glucose value, which has been either lowered or more or equal to 7.0 mmol/L (6.1 mmol/).

New diagnostic criteria and classification of DM are recently proposed by WHO. A major change in diagnostic criteria is lowering the diagnostic fasting plasma glucose level; for instance, level of 7.0mmol/L/l or more in two separate samples is sufficient for the diagnosis. Diagnostic criteria for plasma glucose in 120 min of OGTT are unchanged. Recently, it is recommended that fasting glycemia level seems to correlate better within 120 min [30].

An addition, WHO declared that screening of mild GDM at 16 to 30 weeks' of gestation for a singleton or twin pregnancy gives a positive result with a 75 g OGTT for 2-hour glucose level, 7.8 to 11.0 mmol/L [140 to 200 mg/dL] and fasting plasma glucose level <7.8 mmol/L [<140 mg/dL]) [30]. See Table 5.

Table 5: Glucose tolerance test values (mmol/L). Adapted according to [30] .

	Glucose load	Fasting	1 hour	2 hours	3 hour	Abnormal values for diagnosis
ADA	75 g	5.3	10	8.6		Two or more
	100 g	5.3	10	8.6	7.8	Two or more
ADIPS	75 g	5.5		8.0		One
CDA	75 g	5.3	10.6	8.9		Two or more GDM
						One value IGT of pregnancy
WHO	75 g	7.0		11.1		One

6.5 SCREENING of GDM

ACOG has determined that it may be available to use selective screening in some clinical settings and universal screening in others.

The participants at the 4th International Workshop Conference on Gestational Diabetes recommend that women who met certain characteristics, such as member of low risk ethnic group, no known diabetes in first-degree relatives, age <25 years, normal weight, no history of abnormal glucose tolerance, and no history of poor obstetric outcomes did not have to be screened routinely. However, this recommendation has not been universally accepted [14, 31].

Although the American Diabetes Association, ACOG, and the WHO suggested screening most pregnant women for GDM between 24^{th} and 28^{th} weeks of gestation and screening high risk pregnant women; for example, those with a personal history of GDM or marked obesity at the first antenatal visit. As shown in the Table 6 which declares the Screening Strategy Based on The Risk Assessment for Detecting GDM [32]. The researches have shown that the raise in insulin resistance is the greatest in the third trimester, GDM usually develops going into this period. Therefore, as mentioned previously, screening for GDM usually occurs around 24–28 weeks into the pregnancy [15].

In Turkey, screening of glucose tolerance in the postpartum state for GDM management and monitoring diagnosed carefully from the first visit of childbearing women. On the other hand, it is seen the availability of GCK mutational screening of Czech diabetic, and the methods are used; such as Temperature Gradient Gel Electrophoresis (TGGE) and Single-stranded Conformation Polymorphism (SSCP), those which can used to screen a large number of exons or other DNA fragments. Therefore the screening for GCK mutations and polymorphisms are not commonly used to determine patients with GDM and T2DM in European populations [33].

On the other hand, the screening combined with therapy for GDM could reduce fetal macrosomia; however, there are no enough evidence that tell us about other health benefits for mothers and infants [34]. Potential benefits include reduction in maternal preeclampsia, stillbirth, brachial plexus injuries, and clavicular fractures due to macrosomia.

In addition, the evidences show the importance of diagnosing of GDM, to understand the evidence for the benefits and harms of GDM, it is better to compare the range of adverse maternal and neonatal outcomes that results with untreated GDM [27].

Table 6: The Estimation of Risk Factors for Detecting GDM. Adopted from [32].

Low Risk
Blood glucose testing not routinely required if all of the following characteristics are present:
Member of an ethnic group with a low prevalence of gestational diabetes
No known diabetes in first-degree relatives
Age less than 25 years
Weight normal before pregnancy
No history of abnormal glucose metabolism
No history of poor obstetrical outcome
Average Risk
Perform blood glucose testing at 24–28 weeks using one of the following:
Average risk—women of Hispanic, African, Native American, South or East Asian origins
High risk—women with marked obesity, strong family history of type 2 diabetes, prior gestational diabetes, or glucosuria
High Risk
Perform blood glucose testing as soon as feasible. If gestational diabetes is not diagnosed, blood glucose testing should be repeated at 24–28 weeks or at any time a patient has symptoms or signs suggestive of hyperglycemia

6.6 RISK FACTORS

GDM has some risk factors, which includes obesity, older age, family history, previous history of GDM or poor obstetric outcomes, ethnicity, polycystic ovary syndrome (PCOS), and as more recently noted, hypertension [15]. As shown in Table 7. In addition, GDM is considered to result from interaction between genetic and environmental risk factors [17], such as mutations in maturity onset diabetes of the young (MODY) genes [18], dysfunction, and/ or mutation in glucokinase (GCK) gene [19].

According to a cross sectional data, GDM is developed in 722 women from 14 613 women. Those 14 613 women who are without previous GDM or other known diabetes who reported singleton pregnancy between 1990 and 1994 were used to measure risk factors for gestational diabetes. From the review, have seen that maternal age more than 40 years had a two times increased risk of GDM compared with women aged 25–29 years [35].

A recent systematic review examined the rates and factors associated with recurrence of GDM among women with a history of GDM [38] Recurrence rates for GDM varied from 30% to 84%. The probability of GDM is given insulin treated GDM in a previous pregnancy is approximately 75%.

Table 7: Risk factors that lead to GDM Adopted from [5].

Risk category	Clinical characteristics	Recommended screening
High risk (presence of any is sufficient)	Marked obesity	Blood glucose screening at antepartum visit or as soon as possible thereafter; repeat at 24–28 wk if not already diagnosed with GDM by that time
	Diabetes in first-degree relative(s)	
	Personal history of glucose intolerance	
	Prior delivery of macrosomic infant	
	Current glycosuria	
Average risk	Fits neither low- nor high-risk profile	Blood glucose screening between 24 and 28 wk gestation
Low risk (all required)	Age <25	Blood glucose screening not required
	Low-risk ethnicity	
	No diabetes in first-degree relatives	
	Normal prepregnancy weight and pregnancy weight gain	
	No personal history of abnormal glucose levels	
	No prior poor obstetrical outcomes	

6.7 GENETICS OF GDM

GDM is a heterogeneous disorder; according to some researches, it is considered to result from interactions of several factors such as environmental and genetic factors [36]. These factors provide to the abnormal glucose metabolism [36] including fetal macrosomia and risk of stillbirth. On one side, some new mediators have been implicated in the pathogenesis of insulin resistance; for example, TNF-α (Tumor necrosis factor) and other proinflammatory cytokines lead to insulin resistance in pregnancy [36].

Mannose-binding lectin (MBL) is a plasma protein synthesized in the liver, which is studied by Research Department, University Hospital of Tarragona, and the researchers found that deficiency in 10% of the population makes it the most frequent immunodeficiency [36]. According to MBL deficiency, there are more than three risk factors such as recurrent infections, recurrent miscarriage, T1DM, and etc. [36].

Insulin resistance is the result of a low-grade chronic inflammatory state, and any inflammatory response will favor the decrease of insulin sensitivity [36]. Beside, MBL is a factor known to influence the inflammatory response which is able to enhance phagocytosis and to inhibit TNF-α release [36]. This cytokine has been repeatedly strongly associated with the degree of insulin resistance. Consequently, down-regulation of the insulin sensitivity could contribute to the appearance of GDM.

Women with mutations in MODY genes often suffer from GDM. Also, It has been shown that several candidate genes such as, potassium inwardly rectifying channel subfamily J, member 11 [KCNJ11], glucokinase [GCK], Hepatocyte nuclear factor-1alpha [HNF1A], and etc. [18].

On the other hand, VNTR polymorphism in the promoter region of the insulin gene (INS-VNTR) affects transcription rate [37]. The widely known VNTR type includes 0–40 repeats (0–600 bp, class I), and the less common allele involve 157 repeats (1600–2400 bp, class III). Although those polymergic sequences control the rate of transcription of insulin gene and may interact with transcription factors, the longer (classIII) polymorphic allele has been associated with less efficient gene transcription in the pancreas [18].

Some researchers emphasis distribution of the insulin gene VNTRs in women with GDM, which investigate possible associations of this polymorphism with features of β- cell function and glycaemic control in population of GDM [37].

The most important fact is that the permutation test shows an indeed effect of the VNTR-III allele on the expression of GDM giving a significant increase in risk [37].

There is a difference between patients homozygous for the wild type allele and patients with the mutant allele. Insulin therapy shows that patients homozygous for the wild type allele were less frequently insulinized when it compares patients with the mutant allele [18]. Consequently, more severe metabolic disturbance in these patients [18] who are in mutated group need frequent insulin therapy during pregnancy in GDM [18].

G*CK* is a rate-limiting enzyme for glucose sensing in β-cells. GCK changes mild fasting hyperglycemia and glucose intolerance decreased sensitivity of insulin secretion for MODY [19].

The G6PC2 FG raising allele is combined by an above normal insulinogenic index, which catalyzes glucose-6-phosphate dephosphorylation, thereby opposing the action of GCK in the β-cell. Furthermore, an above normal insulinogenic index leads to a flat-to-slightly protective effect on T2DM. To normalize the signaling between the pancreas and insulin sensitive tissue need to balance both GCK and G6PC2; for example, GCK and G6PC2 control the rate-limiting step of glycolysis; therefore, they regulate insulin secretion in vitro.

II. EXISTING AND NEW APPROACHES TO TREATMENT OF DIABETES IN PREGNANCY

7. PHARMACOLOGICAL MANAGEMENT for T1DM and T2DM in pregnancy

According to study results of American Journal of Obstetrics Gynecology, women with pregestational diabetes are three to four times more probably to have a child with one or multiple birth defects compared with mothers with no diabetes [38]; in addition, in the women with T1DM and T2DM have an increased risk of undesirable pregnancy outcomes, including miscarriage, fetal congenital anomaly and perinatal death [38].

7.0 Pregnant women with T1DM

The immune markers directed against pancreatic islets such as anti islet cell antibodies or β-cell antigens such as glutamic acid decarboxylase [GAD] lead to T1DM. Accordingto studies of women with GDM, it is found that they have less than 10% of the same markers present in their circulation [21], which makes us to call GDM as a heterogeneous condition.

When hyperglycemia in pregnancy is associated with the absence of insulin release it is called T1DM with anti islet or anti GAD antibodies. Women with T1DMs who become pregnant need to be monitored exceptionally in pregnancy through routine glucose screening during pregnancy. It is necessary to diagnosed and treat the women with hyperglycemia in pregnancy properly as early as possible, because it may lead to severe complications for both mother and fetus including poor fetal health, excess fetal growth. Furthermore, those complications may lead to interfere with vaginal delivery, and diabetic ketoacidosis, and they can have a rapidly progressive course to overt diabetes after pregnancy [39]. Whether pregnancy can actually initiate or accelerate islet directed autoimmunity is unknown, and should not start any new exercise or continue physical activities without evidently and clearance by a physician [40]. However, exercise together with diet is good for treatment of diabetes.

Additionally, the first efficacy question is whether the drug has been shown to help the condition for which the mother is being treated. If the mother has diabetes, and it has been suggested to take an oral antidiabetic drugs. However, this will not always be the case. When the case with patients T1DM; a medication whose mechanism of action is to stimulate pancreatic insulin secretion and/or release would not be helpful. In the case of postprandial hyperglycemia for pregnant women with T1DM, the blood glucose levels may be controlled by using of rapid acting insulin analogue such as insulin aspart rather than insulin lispro; therefore, the process prevents both mother and fetus from severe complications; moreover, insulin aspart is more effective and well tolerated [41]. Table 8 shows the work of insulin analogs.

Furthermore, the treatment with insulin aspart was used for 322 pregnant women with T1DM who underwent to randomized controlled study. In this study it is found that insulin aspart helped to reduce postprandial hyperglycemia, as well as it was associated with a fewer fetal losses and preterm deliveries than treatment with human insulin [87]. Consequently, insulin treatment in pregnant women with pre-existing T1DM is safe and beneficial [87].

Table 8: Work of Insulin Preparations in Human Body. Adopted From [42, 88]

Insulin Preperations	Generic Name	Onset	Peak	Usually Effective Duration	Comments
Rapid –Acting	Insulin Aspart	5-10 min	1-3 hrs	3-5 hrs	Eat within 5-10 min of injection
	Insulin Lispro	<15 min	30 min - 90 min	2-4 hrs	Eat within 5-10 min of injection
	Insulin Glulisine	<15 min	30 min – 90 min		Take from 15 min before to 20 min after starting meal. May only mix with NPH.
Short - Acting	Regular (Humulin* R)	30 min – 1 hr	2 – 3 hrs	3 – 6 hrs	Duration is up to 24 hrs.
Intermediate-Acting	NPH	2 -4 hrs	4 – 10 hrs	10 – 16 hrs	Given once or twice daily.
Long - Acting	Insulin Glargine	1 hr	No peak	24hrs	Do not use the same syringe or another insulin. Given once daily.
	İnsulin Detemir	1 – 2 hrs	No peak	6 -23 hrs depending on dose.	May be given once or twice daily.

Onset, peak, and duration may vary depending upon the insulin dose, physical activity, site of injection, & temperature.

Women in the more advanced classes of overt diabetes increasingly developed preeclampsia, which is associated with significant amounts of protein in the urine, and known as hypertension that arises in pregnancy [43].

7.1 Pregnant women with T2DMs

The condition for women with GDM is somewhat different than it is for women with T2DM who aren't pregnant. Moreover, pregnancies are becoming complicated with women who has T2DM, including severe complications and placing both mother and fetus at higher risk.

Though, complications are sorted with association of high risk of miscarriage, pre-eclampsia, preterm labour and high rates of fetal malformation, neural tube defect, urinary tract disorders, macrosomia, birth injury and perinatal mortality [41].

According to ACOG and the American Diabetes Association, prevention from those risk factors are suggested to control blood glucose levels, both prior or throughout the pregnancy, and the best achieved through comprehensive preconception care where other issues such as genetic risks, health status, reproductive history, exposure to environment toxins, immunization, and lifestyle risk factors management is the best and which modifiable risk factors can be identified and reduced [45, 46].

It is preferred to choose the rapid-acting insulin analogues; such as, insulin aspart and insulin lispro for the therapy. Because they reduce postprandial hyperglycemia without increasing the risk for hypoglycemia, and even provide a small improvement in HbA1c compared with regular human insulin. It is need to use of multiple insulin injection regimens, which process may offer more benefits with respect to postprandial glycemic control [40, 45]. In addition, open label trials of insulin aspart, women with GDM have similar effects to those women who have pre-existing type 1 or 2 diabetes, so may also be used in pregnancy [24, 87].

Also women with preexisting diabetes may use insulin lispro which does not lead to any adverse maternal or fetal effects during pregnancy, and also that its use in these women lead to improved glycemic control, fewer hypoglycemic episodes, and improved patient satisfaction.

It is recommended to stop such medications like angiotensin converting enzyme inhibitors (ACEIs), statins, beta- blokers, diuretics, and angiotensin receptor blockers (ARBs) for diabetic women before getting pregnant [46].

The Centre for Maternal and Child Enquiries (CEMACH) received information from researches including comparison of women with T1DM and T2DM; reported that 38% (32/84) of women with T2DM and 40% (50/121) of women with T1DMs were documented as having not planned their last pregnancy compared with 42% in the general maternity population. Contraceptive use in the 12 months prior to pregnancy was lower in women with T2DM (32%) compared with women with T1DM (59%, $P = 0.001$) [47].

As a conclusion, when we compare, glycemic disturbance in T1DM and T2DM in pregnant women, we have seen that with T2DM has less severe conditions than in those with T1DM if they are well controlled [48].

8. NON-PHARMACOLOGICAL MANAGEMENT of DM in PREGNANCY

NICE has announced guidelines on the management of DM before, during and after pregnancy [22].

Women who were diagnosed with GDM should be offered lifestyle advice and offered a fasting plasma glucose measurement at the 6 week postnatal check and annually thereafter; however, not an OGTT. Treatment consists of glucose monitoring, dietary modification, exercise, and when necessary, pharmacotherapy to maintain euglycemia. Insulin therapy is the mainstay of treatment, although glyburide and metformin may become more widely used.

According to The Fourth International Workshop Conference on Gestational Diabetes recommended that maternal capillary glucose levels be kept at 95 mg/dL or less in the fasting state [43].

Insulin therapy is usually suggested when standard dietary management does not consistently maintain the fasting plasma glucose at less than 95 mg/dL or the 2-hour postprandial plasma glucose at less than 120 mg/dL (ACOG).

During pregnancy, women with T1DM who become unwell should have diabetic ketoacidosis excluded as a matter of urgency.

8.0 DIET

The basic approach is nutrition interposition for women with GDM; therefore it has an important role for the therapy [49].

According to significant affect of carbohydrates to blood sugar levels, it is important to control intake of carbohydrates; therefore, a healthy diet can be reached for women with GDM. Moreover, diet may play a significant part in the control of diabetes, with whole grain carbohydrates and low glycaemic index diets (LGI) being helpful; even more, carbohydrate should be limited to 35%–40% of calories. Dietary advice; such as, low carbohydrate diets in pregnancy, and for the carbohydrate to be of low glycemic index, in pregnancy may reduce the number of women who get GDM and its effects. The outcomes relevant to the review in the trial on high fiber diets were inconclusive.

Dietary prescriptions should include personal preference, body weight and type and level of exercise, blood glucose levels, ketone levels and any medications taken for the DM. However the association acknowledges that the most appropriate diet for women with GDM has not been established, this should be monitored with weekly tests for ketonuria, because metarnal ketonemia has been linked with impaired psychomotor development in the offspring [53].

16 women with newly diagnosed GDM are compared to 24 pregnant women who are healthy via case control study. The women with GDM consumed significantly fewer carbohydrate foods with LGI values ($P < 0.05$) [55]. The results on the LGI diet suggested that this may be advantage, to the mother and child. However, the evidence was not strong enough to be confident of these effects [43].

Eventually; the diet of woman with GDM needs to provide sufficient nutriment for both mother and her fetus without leading to either excess weight gain or hyperglycemia. Therefore the American Diabetes Association has recommended nutritional counseling with personalization based on height and weight and a diet that provides an average of 30kcal/kg/d based on prepregnant body weight for non obese women. Significance is given to spreading the dietary intake over six meals daily, which also regulates the metabolism; with three main meals and three snacks, in order to avoid large carbohydrate loads at any time moderation.

8.1 EXERCISE

It is know that exercise is an important activity for all people. Moderate exercise has been found to improve blood glucose control in women with GDM [36].

The American College of Obstetricians and Gynecologists reviewed three randomized trials of exercise in women with GDM. One trial has been given a result that exercise improved cardio respiratory fitness without improving pregnancy outcome [27]. On the other hand, it was found that physical activity during pregnancy reduced the risk of GDM. The third trial; reported that resistance exercise helped escape insulin therapy in overweight women with GDM [43, 49].

Considering, a retrospective study with the women who had been diagnosed with GDM in a recent pregnancy that the perceived advantage of exercise during pregnancy was controlling blood glucose and during that postnatal period it was controlling weight [50].

On the other hand, cochrane systematic review aimed to evaluate the effect of exercise programmer's alone or in conjunction with other therapies such as diet, compared with no specific programmer or with other therapies, in pregnant women with diabetes on perinatal and maternal morbidity and mortality. As a result, the review found no significant difference between exercise and the other regimens in any of the outcomes evaluated [51].

The exercise may prevent and/or reduce risk for women with GDM from T2DM in later life. However the women with GDM should be carefully watch by physician, and do not start or stop the exercise during pregnancy without any recommendation of physician.

8.2 BLOOD GLUCOSE MONITORING

The main goal of DM management is to control glucose together with blood pressure and lipid management [52]. Many evidence have been shown that self monitoring of blood glucose levels is postulated to have a beneficial effect on glucose levels in patients who are not taking insulin [52].

Blood glucose targets during pregnancy for women with diabetes; also for GDM, are a preprandial value of 3.5–5.9 mmol/L and a 1 hour postprandial value of less than 7.8mmol/L. The recommendations for self-monitoring of blood glucose during pregnancy are to test fasting blood glucose (FBG) levels and to test blood glucose 1 hour after eating [53].

A retrospective study showed that there was a significant improvement in all diabetes self-management behaviours; accordingly, the study the effect of an intensive diabetes management programme during pregnancy on women's long-term self-management behaviours and glycaemic control; including the frequency of self-monitoring of blood glucose, frequency of insulin injections, and frequency and complexity of insulin dose adjustment from entry to the programme to the baby's birth. There was also a significant improvement in HbA1c from entry to the baby's birth [53].

Finally, in the generality of women glycemia is sufficently controlled with diet and exercise, those patients who are not under insulin therapy and promoting dietary and lifestyle changes that a patient may make as a response to feedback provided by blood glucose results [53]. From the other point of view, approximately 30% to 40% of them recommended to have a pharmacological treatment. Traditional management of women with GDM in whom diet therapy fails involves the subcutaneous insulin administration [54].

9. PHARMACOTHERAPY of GDM

In the case of GDM, treatment options show similarities to those for other forms of diabetes. However, treatment of GDM needs to have tight glucose control to reduce the risk of increased fetal growth and other adverse effects; such as teratogenicity [87].

Therefore, the main subjects treatment focuses on are safety and efficacy. The traditional treatment goal for GDM was by achieving "normal" range values for maternal glucose by diet and/or insulin therapy. It should be carefully monitored so that a drug would not cross the placenta and be helpful to the fetus without causing any harm, it could then be considered to be both safe and efficacious [27].

However; the fetus indirectly may be influenced from the treatment of the mother. The second efficacy question is whether the drug's effect on the mother will be beneficial and not harmful to the fetus. It is discussed that any medication that given to normalize maternal glycemic levels should benefit the fetus as well. The third efficacy question is whether the drug crosses the placenta and has a direct benefit to the fetus [21].

The woman, who has GDM, should be carefully inspected and the necessity to use set pharmacotherapy should be evaluated carefully.

9.0 INSULIN THERAPY of GDM

The choice of therapy for GDM depends on the efficacy and safety for mother and her fetus. Since insulin is effective and safe, its therapy is considered the gold standard of pharmacotherapy for GDM, against other treatments [15].

Insulin therapy is introduced to women with GDM, if fasting glucose levels exceed 105 mg/dL, even though on diet therapy [86]. Different approaches are mentioned for insulin therapy in GDM by experts. A total dose of 20 to 30 units given once daily, before breakfast, is commonly used to initiate therapy. The total dose is usually divided into two thirds intermediate acting insulin and a third short-acting insulin [14].

The Major Types of Insulin:

Short-Acting Insulin: Regular insulin has a delay in onset of action of 30 to 60 minutes. Therefore patients who are starting to use short acting insulin should be informed that insulin should be injected regularly 20 to 30 minutes before meals to match insulin availability and carbohydrate absorption. Regular insulin acts almost immediately when administered via intravenously [55].

Intermediate-Acting Insulin: There are two basic reasons why to suggest use of insulin; when the fasting blood glucose concentration is becoming higher than 90 mg/dL on 2 or more times during a two weeks of period, or when the one hour postprandial blood glucose concentration is greater than 120 mg/dL [56].

The main insulin types most commonly used in GDM are neutral protamine Hagedorn (NPH) and regular insulin. In addition, NPH insulin is slowly absorbed due to the addition of protamine to regular insulin [55]; thus, NPH is intermediate acting insulin, and which is typically used when the fasting glucose is high.

The onset of action is 2 to 4 hours, the peak effect is at 6 to 12 hours, and the duration of action is 10 to 16 hours which was mentioned previously in the table8. Regular insulin has an onset of action within 30 to 60 minutes, a peak effect at 2 to 3 hours, and duration of 3 to 6 hours. Among women with GDM, 15% will require insulin [56].

Human insulin is the least immunogenic available preparations, which does not normally cross the placenta, in spite of antibody bound animal insulin, which has been reported to do so. However, it has been shown that it is maternal glucose control, rather than maternal anti insulin antibody levels which influence birth weight. Besides, human insulin is considered safe in pregnancy as years of experience has not suggested an increase in fetal complications as a result of its use [57].

On the other hand, the two rapid acting insulin analogs, lispro and aspart (IAsp) have been examined in pregnancy. According to those examinations, they have shown clinical effectiveness, minimal transfer across the placenta, and no evidence of teratogenesis [57].

The doses may be higher than those required in non pregnant subjects and should be reviewed frequently so that adequate glycemic control is achieved rapidly. Regular insulin bound to zinc, lente insulin, has a slightly longer effective duration than NPH. In addition it is preferred to use insulin preparations of low antigenicity; therefore, prevention and/or minimizing the transplacental transport of insulin antibodies. Even more, low antigenicity insulin is used to prevent fetus from adverse effects of medicine used in the therapy. On the other site when human regular insulin is compared to the rapid acting insulin analogs, lispro and aspart, it has seen that they develop antibodies at rates and titers [57].

Earlier studies have shown that insulin antibody complexes may cross the placenta and be associated with the development of macrosomia in the infant. The presence of IAsp in the cord blood sample of this subject may have occurred as a result of the disruption in the uterine placental barrier during delivery. Since the sample was collected during delivery, it is not possible to determine whether IAsp crosses the placenta during development of the fetus. Overall, IAsp appeared to be of low immunogenicity in women with GDM [58, 83]. It is known that insulin lispro, did not cross the human placenta in an in vitro perfusion study [66]. Additionally, it is necessary to have close screening of both mother and her fetus [58], to minimize the risk factors; such as of hypoglycemia and especially nocturnal episodes.

On the studies the efficacy and safety of IAsp, a rapid acting human insulin analogue, were compared with regular human insulin (HI) for therapy of GDM**,** in which GDM is diagnosed at 18-28 weeks to 6 weeks postpartum. When IAsp compared to HI, the results have shown that IAsp is more effective than regular HI in providing postprandial glycaemic control in women with GDM.

According to study, endogenous insulin, measured by the C-peptide response, showed that the demand for endogenous insulin was lower after IAsp injection than after HI injection, even though the fact that the same dose of insulin was used. Therefore, less demand was placed upon the β-cells after IAsp injection than after HI injection. The pharmacokinetics of IAsp may lead to this observation and IAsp provides mealtime coverage of glycaemic needs by achieving higher peak insulin concentrations in less time and with a shorter duration of action than HI, thereby reducing the demand for endogenous insulin secretion during the meal test [59].

Moreover, Insulin lispro shows significant effect to reduce postprandial hyperglycemia and some neonatal features related to hyperglycemia in women with GDM; thus, stressing its usefulness in this condition [60].

Correspondingly, a RCT randomly allocated 42 women with insulin requiring GDM to either insulin lispro or regular insulin. The women receiving insulin lispro had significantly lower glucose excursions after a test meal and experienced fewer episodes of hypoglycaemia. There was no difference in obstetric or fetal outcomes [61].

Additionally, no significant differences were found in perinatal outcomes between CSII and MDI including perinatal mortality, including stillbirths from 24 weeks of gestation and neonatal deaths up to 7 days of life, RR 2.00, 95% CI 0.20 to 19 fetal anomaly, RR 1.07, 95% CI 0.07 to 15.54; gestational age at birth, WMD 0.63, 95% CI −4.87 to 6.13; neonatal hypoglycaemia, RR 1.00, 95% CI 0.07 to 14.64; and SGA, RR 1.55, 95% CI 0.27 to 9.00. Also there were not any significant differences in maternal outcomes between CSII and MDI; such as caesarean section rate, RR 1.03, 95% CI 0.57 to 1.84; mean maternal HbA1c; 24 hour mean blood glucose level in each trimester; hypoglycaemia; or hyperglycaemia [62].

Long-Acting Insulin: Ultralente insulin which means insulin zinc extended that is absorbed slowly due to its zinc crystalline form [55]. Insulin glargine, modified human insulin, the NICE guideline for the management of T1DMs recommends the long-acting insulin analogue glargine for use outside of pregnancy. However, no clinical trials have as yet been published for their use in pregnancy [63].

In brief, specific treatment is including dietary advice and insulin for mild GDM reduces the risk of maternal and perinatal morbidity. However, it is associated with higher risk of labour induction [27].

9.1 ORAL HYPOGLYCEMIC AGENTS

ACOG has not recommended the usage of oral hypoglycemic agents during pregnancy. However, there are randomized controlled trials which have demonstrated efficacy of the oral agents glyburide and metformin. According to whilst short term data, there are many adverse effects of glyburide and metformin on the fetus, and they are increasingly used in pregnancy; besides, long term therapy concerns regarding their potential for harm [43].

9.1.0 SULFONYLUREAS

The sulfonylureas are known to be as effective as insulin in controlling hyperglycemia in pregnant women; even more they have a refractory effect to caloric restriction [15]. The sulfonylureas lower plasma glucose primarily by stimulating insulin secretion. The classification according to FDA; secondary effects on improving peripheral and hepatic insulin sensitivity may be due to the decrease in both glucose toxicity and insulin clearance; therefore, sulfonylureas therapy is used as an alternative to insulin therapy for the treatment of GDM. Its primary action is to enhance insulin secretion. On the other hand, most sulfonylureas cross the placenta and enter breast milk, which mean then not all the sulfonylureas are available for GDM; such as Cholorpropamide and tolbutamid [64].

Glyburide (Glibenclamide): Glyburide is currently classified as Category B by the FDA for use in pregnancy, which means that there is no evidence of risk in humans; which are called second generation sulfonylureas.

Glibenclamide has been demonstrated to have minimal transfer across the human placenta (4% ex vivo), and it has not been associated with excess neonatal hypoglycemia in clinical studies [65]. Furthermore, if increasing the glibenclamide concentration to one hundred times the therapeutic level did not alter transport significantly. Because of glibenclamide is highly bound to plasma proteins like albumin (99.8%), the therapeutic level of drug plasma levels exceed ten times so it was neither metabolized nor appropriated by the placenta [65].

The pharmacokinetics and pharmacodynamics of Glyburide shows clearly large individual variations [65], besides the drug is extensively metabolized by human hepatic microsomes to form its two major metabolites, 4 Tran- and 3-Cis-hydroxycyclohexyl glyburide, which are excreted in bile and urine to equal extent [66].

In addition because of its low half life time which is about 4hr, and rapid elimination (1,3 ± 0.5 mL / kg / min) also play role in its limited transplacental passage [66]. On the other site, Tolbutamide was found to diffuse across the placenta freely. Glipizide, on the other hand, although a second generation sulphonylurea like glibenclamide, was found to cross the placenta in small amounts that were significantly higher than glibenclamide [15].

Glyburide action must be carefully balanced with meals and snacks to prevent maternal hypoglycemia, as with insulin therapy. There is some evidence that glyburide may be less successful in obese patients or those with marked hyperglycemia earlier in pregnancy [15].

In 2004, the ACOG reported that 13% of 1400 American obstetricians used glyburide as first-line therapy in the case of failure of dietary intervention in women diagnosed with GDM [65].

According to Langer and colleagues, the randomize study of 257 women with GDM exposed to insulin or glyburide therapy, near normoglycemic levels were achieved equally well with either regimen. Moreover, there were no apparent neonatal complications describable to the glyburide [67]. Several studies have confirmed that the observation of glyburide does not appear to adversely affect the fetus [68], so it appears to be safe by measures obstetric and neonatal outcomes [53], or by an evaluation of neonatal body composition which precisely reflects individual effects of maternal environment on fetal growth and better estimates fetal effects of various methods of metarnal glycemic control [69].

On the other hand, Conway and coworkers found that women with fasting glucose levels greater than 110 mg/dL did not adequately respond to glyburide therapy [65].

A crosscheck was made on the use of glibenclamide and insulin in women with GDM, those who were unable to achieve adequate metabolic control with diet and exercise alone [65]. In this study, four hundred and four women were randomly assigned to take either of the two treatments.

According to results, it is found that 82% of the glibenclamide group and 88% of the insulin group achieved good glycaemic control, but there was less maternal hypoglycaemia in the glibenclamide group (2%) as compared to the insulin group (20%). Finally, there were no significant differences between the 2 groups in the incidence of pre-eclampsia, macrosomia, neonatal hypoglycaemia, congenital anomalies, perinatal mortality, cord serum insulin concentrations and the rate of caesarean section. Moreover, glibenclamide was not detected in the cord serum of any infant in the glibenclamide group. It is a very significant study which gives a well conducted randomised, controlled trial involving a large number of subjects [65].

On one another study, it is shown that glyburide is an acceptable alternative to insulin, whose results are summarized in Table 9.

Table 9: Comparison of glyburide therapy to the insulin. Adopted from [14].

Selected neonatal outcome variables				
Required number per group	Glyburide	Insulin	Difference	Percent difference
LGA 17,277	24 (12%)	26 (13%)	-1%	-8%
Birth weight 1,281	3,256 +- 543	3,194 +- 598	62	-2 %
Ponderal index >2.85 1,646	18 (9%)	24 (12%)	-3%	- 25
Birth weight >4 kg 909	14 (7%)	9 (4%)	3%	75%
Intravenous glucose 1,916	28 (14%)	22 (11%)	3%	27%
Hypoglycemia 1,214	18 (9%)	12 (6%)	3%	50%

In conclusion, insulin and glyburide shows similar effectiveness but glyburide shows less adverse effects when compared to insulin (such as maternal hypoglycemia). Therefore glyburide may be the drug of choice in the therapy of GDM to prevent from unwanted conditions.

9.1.1 BIGUANIDES

Biguanides perform their action through two mechanisms, first, reducing serum glucose levels by reducing hepatic gluconeogenesis and the second, sensitizing peripheral tissues to insulin action [70, 71].

Metformin: According to FDA, metformin is in Pregnancy Category B [72]. Metformin may be safe and may reduce risk of miscarriage and development of GDM when used for the entire pregnancy, in spite of the fact that freely crosses the placenta to the fetus reaching concentrations similar to maternal plasma [15]. Altough, drug during pregnancy decreases insulin, insulin resistance, insulin secretion, weight, testosterone, preventing androgen excess in women with PCOS and development of GDM [73].

Additionally, its use in GDM seems suitable, because it has not shown a significant effect on fetal glucose transport, glucose uptake being at least placenta, no teratogenic effects and not causing neonatal hypoglycemia. On the other side, if metformin is used during the second half of pregnancy it would lead to an increased prevalence of preeclampsia and high perinatal mortality [15].

The transfer and distubution of metformin in placentas that were obtained from uncomplicated pregnancies was not different from diabetic placentas, and indicates that GDM does not affect the transfer or distribution of metformin, no accumulation of the drug in the placental tissue occurred. Therefore metfomin does not shown any affect on placental glucose uptake or transport [74].

Furthermore, the treatment was acceptable when compared usage of metformin and insulin with women who has GDM. Use of metformin as an adjunct or alternative for diabetes treatment preconceptionally when insulin treatment is refused or a patient develops resistance, and it is recommended by the more recent guidelines [75]. However it is found that metformin has similar effect as insulin for maternal blood glucose control and neonatal outcome [76].

RCT of metformin study for the treatment of GDM (the Metformin in Gestational Diabetes (MIG) trial) a pilot study, submitted for experimental purposes randomly 14 women to insulin and 16 to metformin. There were no differences in perinatal outcomes [77].

In another studies, they have found that metformin is as effective and safe as insulin for glycemic control in GDM. However, one study, a randomised controlled trial, was not have a sufficient evidence to support the effectiveness and safety of metformin in GDM. In another study, a retrospective case control study, subjects treated with insulin had a greater degree of initial glucose intolerance, so the comparison was of limited validity [78].

Another study comprised a retrospective cohort which included a mixture of both GDM and women with T2DM seen from 1966–1991. It was found an increase in stillbirth and perinatal mortality, as well as preeclampsia amongst those treated with metformin, compared to women treated with insulin or sulphonylureas. However, as there was no evaluation of glycemic control early in pregnancy, and more women on metformin had pre-existing T2DM, the groups do not appear to be well matched.

Correspondingly, New Zealand and Australian multicenter study which was mentioned that metformin alone or supplemented with insulin is not associated with increased perinatal complications [78].

In one another study, it is demonstrated that there was a median percentage reduction of 40% in serum insulin at the last preconception visit, when compared the different parameters at the pretreatment and preconception baseline, at the last preconception visit on metformin, and during the first, second and third trimesters on metformin; moreover, which did not increase in the first or second trimester (P >0.05), but only 10% in the third trimester. Also it is found that a 46% median percentage reduction in insulin resistance at the last preconception visit with no significant increase (P >0.05) in the first, second or third trimester [73].

NIHCE suggests the use of metformin as an alternative or complementary treatment to insulin [79].

9.1.2 α-GLUCOSIDASE INHIBITORS

The α-glucosidase inhibitors slow the absorption of sugars in the upper gastrointestinal tract, decreasing postprandial glucose excursions and not depend on the presence of endogenous insulin [66].

Acarbose: Acarbose is an α-glucosidase inhibitor that competitively inhibits hydrolysis of oligo and monosaccharides, and which is poorly absorbed from the gastrointestinal tract, and two preliminary studies have suggested efficacy in reducing postprandial glucose excursions in GDM.

In a small study by Zarate, 6 pregnant women with moderately elevated levels of fasting and postprandial blood glucose were treated with acarbose, after which, the fasting and postprandial glucose levels normalized [80].

In a randomized trial of acarbose, it is found that it was successful to control glucose and HbA_{1C} levels on 91 gestational diabetic women who were failing diet therapy, and only 6% of acarbose treated patients required insulin [66].

On the other hand, women treated with oral hypoglycemic agents were compared with those treated with all types of insulin. Two trials compared insulin to glyburide; one trial compared insulin, glyburide, and acarbose; and one trial compared insulin to metformin. Although, no significant differences were found in maternal glycemic control or cesarean delivery rates between the insulin and glyburide groups. Beside, a meta-analysis showed similar infant birth weights between women treated with glyburide and women treated with insulin. There was a higher proportion of infants with neonatal hypoglycemia in the insulin group (8.1%) compared with the metformin group (3.3%). Therefore, there was no substantial maternal or neonatal outcome differences with the use of glyburide or metformin compared with use of insulin in women with GDM [58, 81].

According to a reference guide to drugs in pregnancy and lactation reported that there were limited data on the use of metformin, acarbose, nateglinide, glimepiride, glipizide and glibenclamide in pregnant women and suggested they present a low risk to the fetus [82].

Insulin was needed to achieve the glycemic goals. In addition, until now there has not been sufficient long-term follow-up data on the safety of metformin use in GDM with respect to the physical and psychological health of the offspring [58, 81].

No data were found on the use of repaglinide or pioglitazone in pregnant women, but it was suggested that they present a moderate risk to the fetus. No comparative studies were found on the use of rosiglitazonein pregnant women, but it was suggested that it presents a risk to the fetus. Evidence suggested that chlorpropamide and tolbutamide present a risk to the fetus if taken by women in the third trimester of pregnancy [82].

The use of thiazolidinediones, glinides, and glucagon like peptide 1 agonists during pregnancy is considered experimental, which means that they are not available for women with pregnancy at the moment.

9.2 STEM CELLS FOR GDM

Specific transcriptional control mechanisms of insulin gene normally affect pancreatic β-cells [83].

According to gene introduction or the administration of different proliferation factors to the body, lead to pancreatic β cells regeneration [83]. Moreover, using a novel multistep process helps to understand better the derivation of human embryonic stem cells to pancreatic β- cells [83, 84].

Pancreatic exocrine cells are normally produce digestive enzymes for release into the gut. Dou Melton and his team at Harvard University gave an evidence of a simple method for producing β- cells in situ the pancreases of diabetic mice. According to their researches, they administered transcription factors to transform pancreatic exocrine cells into cells that imitate beta cells. As a result, the experiment showed that exocrine genes were switched off, and β cell genes activated few days later [85]. However, the normalization of blood glucose levels has not been achieved in this experiment.

Finally, the development of pancreatic β- cell targeting regenerative medicine can lead to the next generation of diabetes treatment, but the stem cell therapies are still very early in their development, may need to see the more forward.

III. CONCLUSION

GDM and T2DM share a similar pathophysiology with increased insulin resistance, poor control of hepatic gluconeogenesis and pancreatic beta-cell response decreased. Therefore it is possible to increase the normal glycemic levels via insulin, glibenclamide, or metformin therapy which are safe, effective, affordable and easy to use by outpatient pregnant women with GDM. The pharmacological therapy is applied when the patient with GDM does not response the diet, and exercise alone.

Pharmacotherapy may include both mother and fetus or mother alone. The choice of therapy depends on the severity of GDM. The major approach includes efficacy and safety during treatment of GDM.

Insulin is the first choice of therapy for GDM with systematic diet. When the patient does not response, then can be suggested to use oral hypoglycaemic agent.

Glyburide (glibenclamide) may be recommended to patient with GDM, mainly because it has been shownthat it has high availability to bind to plasma protein, it cannot cross human placenta and does not cause harm to fetus.

Metformin does cross the placenta and it is not known yet whether it causes long-term metabolic programming effects in the offspring.

Acarbose inhibits carbohydrate absorption from the gastrointestinal tract; serious adverse effects are rare; hypoglycaemia is not a risk; no effects on body weight, so it is safe to use when patients has GDM.

Having established current recommendations for the preconception care of diabetic women, there is now a need to focus on guideline implementation. More work is needed to look at the applicability of the recommendations in the local setting, and to specifically examine what barriers and enabling factors exist to ensure successful implementation.

Stem cell therapy is a novel approach which could provide an efficient and safe alternative to the traditional treatment to GDM.

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