T.C.
YEDITEPE UNIVERSITY
INSTITUTE OF HEALTH SCIENCES
DEPARTMENT OF NUTRITION AND DIETETICS

THE COMPARISON OF THE EFFECTIVENESS OF TREATMENT OPTIONS IN GESTASTIONAL DIABETES: DIET VS. INSULIN TREATMENT

MASTER'S THESIS

Nazlı Şişik

SUPERVISOR
Prof. Dr. B. Serdar ÖZTEZCAN

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Jüri Başkanı:	Prof.Dr. Serdar ÖZTEZCAN Yeditepe Üniversitesi	(İmza)
Tez danışmanı:	Prof.Dr. Serdar ÖZTEZCAN Yeditepe Üniversitesi	(İmza)
Üye:	Yrd.Doç.Dr. Binnur OKAN BAKIR Yeditepe Üniversitesi	(İmza)
Üye:	Yrd.Doç.Dr. Can ERGUN Bahçeşehir Üniversitesi	(İmza)

ONAY

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CONTENTS

LIST of TABLES

LIST of FIGURES

LIST of SYMBOLS and ABBREVIATIONS

GDM	Gestastional Diabetes Mellitus
MNT	Medical Nutrition Therapy
BMI	Body Mass Index
OGTT	Oral Glucose Tolerance Test
GLT	Glucose Tolerance Test
ADA	American Diabetes Association
CC	Carpenter-Coustan
CDA	Canadian Diabetes Association
WHO	World Health Organization
IADPSG	International Association of the Diabetes and Pregnacy Study Groups
NDDG	National Diabetes Data Group
IDF	International Diabetes Federation
FDA	U.S. Food and Drug Administration
HAPO	Hyperglycemia and Adverse Pregnancy Outcome
ACOG	The American College of Obstetricians and Gynecologists
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
FPG	Fasting Plasma Glucose
PG	Plasma Glucose
LADA	Latent autoimmune diabetes of adult
DKA	Diabetic Ketoacidosis
PGDM	Pregestational Diabetes Mellitus
HPL	Human Placental Lactogen
HCS	Human Chorionic Somatomamotropin
HCG	Human Chorionic Gonadotropin
GH	Growth Hormon
LGA	Large For Gestastional Age

ABSTRACT

Şişik, N. (2016). The Comparison Of The Effectıveness Of Treatment Options In Gestastıonal Diabetes: Diet Vs. Insulin Treatment. Yeditepe University, Institute of Health Sciences, Department of Nutrition and Dietetics, MSc thesis. İstanbul.

Gestational diabetes mellitus (GDM) is a severe condition which progresses with maternal obstetric and fetal complications if a well glycemic control cannot be provided. The basic principal of the therapy is medical nutrition therapy (MNT) and exercise. In cases where the foregoing is inadequate, glycemic control is provided with insulin therapy. The aim of this study is to compare those who are monitored with MNT with those who receive insulin in women who are diagnosed with GDM in terms of complication growth.147 pregnant women who were diagnosed with GDM during the pregnancy for the first time but had no previously known diabetes and glucose intolerance were recruited into this study. In all pregnant women, 24kcal/kg standard diet was applied in obese diabetes, 30kcal/kg in non-obese diabetes in the 1st trimester and 35kcal/kg in the 2nd trimester as from the diagnosis establishment. In the presence of uncontrolled glycemia with two weeks of SMBG (capillary blood glucose profile), insulin was started. Fasting blood glucose targeted was determined as < 95 mg /dl and 1st hour postprandial blood glucose as <140mg/dl during the pregnancy. At least 2 days 7 points blood glucose measurement was requested from all pregnant women in a week. Data collected were compared at the end of pregnancy.105 of pregnant women (71,4%) were monitored by starting medical nutrition therapy (MNT group), 42 (28,6%) were monitored with insulin therapy in addition to medical nutrition therapy (MNT+insulin group). Age average of pregnant women in MNT group was found higher than the average age of pregnant women in MNT+insülin group. (32,4+/-3,8 vs. 34,1+/-3,9 p= 0,018). When BMI values were compared between groups, a difference was not observed. No difference was found between groups in terms of weight gained in the pregnancy and birth week. A difference was not observed between groups in terms of GDM risk factors (DM history in the family, BMI, GDM history, fat infant history). No difference was found between groups in terms of maternal (preeclampsia, birth complications) and fetal (infant weight, prematurity, APGAR score) complications.

Glycemic control is essential in pregnant women who are followed due to GDM. Monitoring only with nutrition or starting insulin therapy does not increase the complication risk.

Key words: Gestastional diabates mellitus, GDM, insulin, medical nutrition therapy

ÖZET

Şişik, N. (2016). Gestasyonel Diyabette Tedavi Etkinliklerinin Karşılaştırılması: Diyet ve İnsülin Tedavisi. Yeditepe Üniversitesi, Sağlık Bilimleri Enstitüsü, Beslenme ve Diyetetik ABD, Master Tezi. İstanbul.

Gestasyonel diyabet (GDM) iyi glisemik kontrol sağlanamadığında maternal obstretik ve fetal komplikasyonlarla seyreden ciddi bir durumdur. Tedavinin temel prensibi medikal nütrisyon tedavisi (MNT) ve egzersizdir. Yetersiz kaldığı durumlarda glisemik kontrol insulin tedavisi ile sağlanır. Bu çalışmanın amacı GDM tanısı almış kadınlarda MNT ile izlenenleri insülin verilenlere kıyasla komplikasyon gelişimi açısından karşılaştırmaktır. Bu çalışmaya daha önceden bilinen diyabet ve glukoz intoleransı olmayan ilk kez gebelik sırasında GDM tanısı almış 147 gebe kadın dahil edilmiştir. Tüm gebelere tanı anından itibaren, obez diyabetlerde 24kkal/kg, obez olmayan diyabetlerde 1.trimestarda 30kkal/kg 2.trimestarda 35kkal/kg'lık standard diyet uygulanmıştır. İki haftalık SMBG(kapiller kan şekeri profili) ile kontrolsüz glisemi varlığında insülin başlanmıştır. Gebelik boyunca hedef açlık kan şekeri < 95 mg /dl, 1.saat tokluk kan şekeri ise <140mg/dl olacak şekilde belirlenmiştir. Tüm gebelerden haftada en az 2 gün 7 nokta kan şekeri ölçümü istenmiştir. Gebelik sonunda toplanan veriler karşılaştırılmıştır. Gebelerin 105'i (%71,4) medikal nütrisyon tedavisi ile (MNT grubu), 42'si (%28,6) medikal nütrisyon tedavisine ek olarak insülin tedavisi (MNT+ insülin grubu) başlanarak izlenmiştir. MNT grubundaki gebelerin yaş ortalaması MNT+insülin grubundaki gebelere göre daha yüksek bulunmuştur. (32,4 +/- 3,8 vs. 34,1+/-3,9 p= 0,018).Gruplar arasında VKİ değerlerleri karşılaştırıldığında bir fark gözlenmemiştir. Gebelikte alınan kilo, doğum haftası açısından gruplar arasında fark yoktu. GDM risk faktörleri açısından (ailede DM öyküsü, VKİ, GDM öyküsü, iri bebek öyküsü) gruplar arasında fark bulunmamıştır. Maternal (preeklemsi, doğum komplikasyonları) ve fetal (bebek ağırlığı, prematürite, APGAR skoru) komplikasyonlar yönünden gruplar arasında fark bulunmamıştır. GDM nedeniyle takip edilen gebelerde glisemik kontrol esastır. Sadece beslenme ile izlem veya insulin tedavisi başlanması komplikasyon riskini artırmamaktadır.

Anahtar kelimeler: Gestasyonel diabates mellitus, GDM, insülin, medikal nütrisyon tedavisi

1 INTRODUCTION AND AIM

Gestational diabetes mellitus (GDM) is defined as glucose intolerance disorder developed in the pregnancy for the first time[1]. Having gestational diabetes mellitus increases the complication risk for both mother and infant before and after the delivery. Its most common complications are represented by maternal (pre-eclampsia, hypertension, caesarean section) and fetal morbidity (macrosomia, birth trauma, hypoglycemia, hyperbilirubinemia, respiratory distress syndrome)[2].

The actual incidence is not clear since data in literature vary by the community where studies are conducted and criteria. American Diabetes Association reported that GDM is found in about 135.000 women yearly that is 4% of pregnant women[3]. While prevalence is less than 2% in low-risk populations like Sweden, it varies between 4,9% and 12,8% in high-risk populations like Native American, North Californian Hispanic and North Californian Asia.

Diabetes history in first degree relatives, previous macrosomia (birth weight >4000 g) / polyhydramnios, polycystic ovary syndrome, age of mother (>25), obesity (BMI >28 kg/m2), essential or pregnancy-related hypertension, unexplained abortions as well as ethnic factors of the society constitute risk factors for diabetes[4].

A consensus could not been reached in diagnosis of gestational diabetes mellitus. While many association and organizations use different screening/diagnosis test, threshold values of these tests are different from each other[5]. There are two approaches for diagnosis in diabetes. ***One-step approach***; particularly in high risk individual and communities, oral glucose tolerance test is performed regardless of plasma and serum glucose. ***Two-step approach***; diagnostic oral glucose tolerance test (OGTT) is performed for those who exceed threshold value as a result of 50 g oral glucose loading (plasma glucose >140 mg/dl in the first hour). Oral glucose tolerance test (OGTT) may be performed with 10 g or 75 g glucose[6].

The basic principles of therapy is medical nutrition, glucose monitoring and exercise. In cases which cannot be controlled with diet, oral-antidiabetic or insulin therapy may be started[7].

The aim of this study is to compare those who are monitored with MNT with those who take insulin in women who are diagnosed with GDM in terms of complication development.

2 GENERAL INFORMATION

2.1 DEFINITION, DIAGNOSIS AND CLASSIFICATION OF DIABETES MELLITUS

DEFINITION

Diabetes Mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels[8].

DIAGNOSIS

Changes have been made in diagnosis and classification of other disorders of diabetes and glucose metabolism In 1997, an International Expert Committee was convened to review to Classification and Diagnosis criteria of diabetes which based on the 1979 publication of the National Diabetes Data Group and subsequent WHO study group. And right after, World Health Organization (WHO) accepted these criteria with minor revisions in 1999.

A minor revision was made for impaired fasting glucose (IFG) diagnosis by American Diabetes Association in 2003. On the other hand, protection of 1999 criteria was adopted in the report published by WHO and International Diabetes Federation (IDF) in 2006[9].

Current diagnosis criteria for other disorders of diabetes and glucose metabolism are seen in Table 1[9].

Table 1: Diagnosis criteria in other disorders of Diabetes mellitus and glucose metabolism (*)[9]

	Apparent DM	Isolated IFG(**)	Isolated IGT	IFG + IGT	High DM Risk
FPG	≥126 mg/dl	100-125 mg/dl	<100 mg/dl	100-125 mg/dl	
OGTT 2-H PG (75 g glucose)	≥200 mg/dl	<140 mg/dl	140-199 mg/dl	140-199 mg/dl	
Random PG	≥200 mg/dl + Diabetes symptoms				
A1C(***)	≥%6.5 (≥48 mmol/mol)				%5.7-6.4 (39-46mmol/mol)

(*)Glycemia is measured as 'mg/dl' with glucose oxidase method in venous plasma. While any one of four diagnosis criteria is sufficient for 'Apparent DM' diagnosis, two criteria are compulsory for 'Isolated IFG', 'Isolated IGT' and 'IFG + IGT'.

(**) In 2006 Report of WHO/IDF, it was adopted to protect normal APG cut-off as 110 mg/dl and IFG as 110-125 mg/dl.

(***) It should be measured with Standardized methods.

DM: Diabetes mellitus, FPG: Fasting plasma glucose, 2h PG: 2nd hour plasma glucose, OGTT: Oral glucose tolerance test, A1C: Glycated hemoglobin A1c, IFG: impaired fasting glucose, IGT: impaired glucose tolerance, WHO: World Health Organization, IDF: International Diabetes Federation.

CLASSIFICATION

It is recommended for ideal diabetes classification to contain both diabetes stages based on clinical descriptive criteria and etiological grouping. Accordingly, changes suggested by “American Diabetes Association (ADA) Experts' Group” were reviewed by World Health Organization (WHO). According to the new diabetes classification defined by WHO in 1998; "insulin dependent diabetes mellitus" and non-insulin dependent diabetes mellitus" definitions are not used since they reflect a classification based on therapy and lead to confusion. Instead, Type 1 and Type 2 diabetes mellitus definitions are used[10].

Diabetes can be classified into the following general categories:

1. Type 1 diabetes
2. Type 2 diabetes
3. Gestational diabetes mellitus (GDM)
4. Specific types of diabetes

There are four clinical types in diabetes classification summarized in Table 2. Three of which are known as (type 1 diabetes, type 2 diabetes and GDM) primary and the other (specific types of diabetes) known as secondary diabetes forms[11].

Table 2:Etiologic classification of diabetes mellitus[11]

I. Type 1 diabetes (b-cell destruction, usually leading to absolute insulin deficiency)	
A. Immune mediated	
B. Idiopathic	
II.Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)	
III. Other specific types	
A. Genetic defects of b-cell function	E. Drug or chemical induced
1. Chromosome 12, HNF-1a (MODY3)	1. Vacor
2. Chromosome 7, glucokinase (MODY2)	2. Pentamidine
3. Chromosome 20, HNF-4a (MODY1)	3. Nicotinic acid
4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)	4. Glucocorticoids
	5. Thyroid hormone
5. Chromosome 17, HNF-1b (MODY5)	6. Diazoxide
6. Chromosome 2, NeuroD1 (MODY6)	7. b-adrenergic agonists
7. Mitochondrial DNA 8. Others	8. Thiazides
B. Genetic defects in insulin action	9. Dilantin
1. Type A insulin resistance	10. g-Interferon
2. Leprechaunism	11. Others
3. Rabson-Mendenhall syndrome	F. Infections
4. Lipoatrophic diabetes	1. Congenital rubella
5. Others	2. Cytomegalovirus
C. Diseases of the exocrine pancreas	3. Others
1. Pancreatitis	G. Uncommon forms of immune-mediated diabetes
2. Trauma/pancreatectomy	
3. Neoplasia	1. “Stiff-man” syndrome
4. Cystic fibrosis	2. Anti-insulin receptor antibodies
5. Hemochromatosis	3. Others
6. Fibrocalculous pancreatopathy	H. Other genetic syndromes sometimes associated with diabetes
7. Others	
D. Endocrinopathies	1. Down syndrome
1. Acromegaly	2. Klinefelter syndrome
2. Cushing’s syndrome	3. Turner syndrome
3. Glucagonoma	4. Wolfram syndrome
4. Pheochromocytoma	5. Friedreich ataxia
5. Hyperthyroidism	6. Huntington chorea
6. Somatostatinoma	7. Laurence-Moon-Biedl syndrome
7. Aldosteronoma	8. Myotonic dystrophy
8. Others	9. Porphyria
	10. Prader-Willi syndrome
	11. Others
IV. Gestational diabetes mellitus	

2.1.1 TYPE 1 DIABETES MELLITUS

This form, previously called “insulin-dependent diabetes” or “juvenile-onset diabetes,” accounts for 5–10% of diabetes and is due to cellular-mediated autoimmune destruction of the pancreatic b-cells.[6] 90% of patients have autoimmune (Type 1A), 10% have non-autoimmune (Type 1B) b-cells destruction[9].

- **Type 1A Diabetes**

Autoimmunity is stimulated in individuals having genetic predisposition (risk-tissue groups) with the effect of environmental stimulant factors (virus, toxins, emotional stress) and progressive b-cell destruction starts. When b-cell reserve decreased in the rate of 80-90%, clinical diabetes symptoms develop. In Type 1A diabetes, islet auto-antibodies are initially found positive in the blood.

- **Type 1B Diabetes**

It develops as a result of absolute insulin deficiency depending on some reasons apart from the autoimmunity. Islet antibodies are not found in the blood.

PROPERTIES

- It generally starts prior to the age of 30. Three peaks are seen in pre-school (around 6 years old), puberty (around 13 years old) and young adolescent (around 20 years old). However, it has been reported that "Latent autoimmune diabetes" (LADA: Latent autoimmune diabetes of adult) form which can develop in more advanced ages is seen in a rate being close to type 1 childhood diabetes (<15 years old) for the last 20 years.
- Childhood diabetes (<15 years old) for the last 20 years.
- Symptom and findings pertaining to hyperglycemia (such as desert mouth, polydipsia, feeling of hunger, polyuria, weight loss and fatigue) suddenly appear.
- Patients are frequently weak or normal weight. At the same time, type 1 diabetes form which resembles type 2 diabetes where insulin resistance is dominant in terms of phenotype, is seen in overweight/obese individuals and called as

"Double diabetes", "Hybrid diabetes", "Dual diabetes" or "Type 3 diabetes" has also been defined in recent years.

- It is inclined to diabetic ketoacidosis (DKA)[9].

2.1.2 TYPE 2 DIABETES MELLITUS

This form, previously referred to as “noninsulin- dependent diabetes” or “adult-onset diabetes,” accounts for ;90–95% of all diabetes. Type 2 diabetes encompasses individuals who have insulin resistance and usually relative (rather than absolute) insulin deficiency. At least initially, and often throughout their lifetime, these individuals may not need insulin treatment to survive.

PROPERTIES

- It mainly develops after the age of 30, however, type 2 diabetes cases appeared in childhood or adolescent ages have started to increase particularly in the last 10-15 years as a result of obesity increase.
- There is a strong genetic predisposition. As long as genetic intensity increases in the family, diabetes risk increases and disease starts to be seen in earlier ages in the next generations.
- Patients are frequently obese or overweight [Body mass index (BMI) >25 kg/m_2].
- Initially, it is not inclined to DKA. However, DKA may be seen in the long-term hyperglycemic course or in the late phases when b-cell reserve decreased.
- Generally, disease has an insidious onset. Many patients do not display any symptom at the beginning.
- Some patients may apply due to blurred vision, numbness and tingling in hands and feet, foot pains, recurrent fungal infections or delay in wound healing.

2.1.3 SPECIFIC TYPES OF DIABETES

Other specific types are currently less common cause of diabetes mellitus, but are those in which the underlying defect or disease process can be identified in a relatively specific manner. (Table 2)[12].

2.1.4 GESTASTIONAL DIABETES MELLITUS (GDM)

Diabetes mellitus is divided into two parts in the pregnancy;

a) Pregestational Diabetes Mellitus(PGDM); Type I, Type II

b) Gestational diabetes mellitus (GDM)

Gestational Diabetes Mellitus (GDM) is defined as glucose intolerance disorder which develops in the pregnancy for the first time[1]. Diabetes which is detected prior to pregnancy or in the first three months of pregnancy is defined as Pregestational Diabetes Mellitus(PGDM). In a research conducted by Sheffield et al., on the diabetic women, it makes us think that pregnancy courses in women whom fasting hyperglycemia is detected prior to 24th week develop depending on apparent diabetes rather than GDM. 90% of DM observed in the pregnancy is GDM and the remaining 10% is PGDM. Type II DM accounts for 8% of which and Type I DM accounts for 2%[13].

For apparent diabetes mellitus diagnosis in workshop of IADPSG in Pregestational Diabetes Mellitus diagnosis; the following values have been suggested FPG ≥126 mg/dl, HbA1c ≥%6.5 and random blood glucose ≥200 mg/dl (in such case, FPG and HbA1c should be certainly confirmed). Results of IADPSG workshop are summarized in Table 3.

Table 3: Threshold values for IADPSG workshop apparent diabetes mellitus (mg/dl)[5]

	FPG	HbA1c	Random PG*
Apparent diabetes	≥126 *	≥%6.5	≥200

FBG: Fasting plasma glucose.*In such case, test should be confirmed with FPG and/or HbA1c.

Gestational Diabetes Mellitus prevalence is gradually increasing. This is related with obesity increase and decrease in threshold values in diagnostic tests[2]. The actual incidence is not clear since data in literature vary by the community where studies are conducted and criteria. American Diabetes Association reported that GDM is found in about 135.000 women yearly that is 4% of pregnant women[3]. While prevalence is less than 2% in low-risk populations like Sweden, it varies between 4,9% and 12,8% in high-risk populations like Native American, North Californian Hispanic and North Californian Asia. Another factor affecting the prevalence of GDM is the age of mother. While incidence in women below the age of 25 is 0,4–0,8%, this rate has been found as 4,3–5,5% in the group above 25 years old in the studies conducted[14].

There are many diagnostic and screening criteria in diagnosis of Gestational Diabetes Mellitus. Screening tests are applied for presenting the group for whom diagnostic test will be applied. Easy applicability, cost-effectivity, existence of an effective diagnostic test for those whose screening test result is positive, public acceptability and most importantly, screened disease being an important health problem in that society are the required properties in screening tests[15] .

Many tests are used for GDM screening in all over the world. One of those which have been used for long time among these tests is screening by risk factors. For this purpose, risk factors are determined in the beginning of pregnancy and diagnostic tests are performed for required patients in next period[3].

As is seen Table 4, risk factors for gestational diabetes include age, ethnic group, a history of deliveries with complications, and a history of glucose intolerance. Women at high risk for developing GDM are those who are obese, have a history of diabetes in a first-degree relative, have glycosuria, have a history of GDM or glucose intolerance in previous pregnancies, and have previously delivered a macrosomic (birth weight >4,000 g) infant. A patient is considered to be at low risk of developing gestational diabetes if she is <25 years old, is part of a low-risk ethnic group, has no family history of diabetes among first-degree relatives, has no prior history of complicated pregnancy, is of normal weight pre-pregnancy and throughout the course of the pregnancy, and has no prior history of glucose intolerance. Ethnic groups with the highest risk of developing gestational diabetes include persons of Native American, Hispanic, and Asian descent.

African American women are considered of medium risk, and non-Hispanic white women are at the lowest risk[16].

Table 4: Screening strategy in gestational diabetes diagnosis by risk factor assessment[16]

Risk assessment first visit should be realized for gestational diabetes.
Low risk : If definition of the following properties is available, blood glucose test is routinely assessed.
• If it is included into an ethnic group whose gestational diabetes prevalence is low. • No known-diabetes in first degree relatives. • < 25 years old • Normal weight prior to pregnancy • Normal weight at birth • Absence of abnormal glucose metabolism history. • Absence of poor obstetric outcome history.
Moderate risk: Perform a blood glucose test in 24-28th weeks by using one of the following.
• Two-stage procedure: Applying 100g oral glucose tolerance test on those who are at threshold value following 50 g oral loading. • Single stage procedure75 g oral glucose tolerance test, as applied in each individual.
High risk: If one or several of the following properties is/are available, perform a blood glucose test as soon as possible by using the foregoing methods.
• Severe obesity • Strong type 2 diabetes family history • Gestational diabetes, impaired glucose metabolism or glucosuria history.
If gestational diabetes mellitus has not been found, blood glucose test should be repeated in 24-28th weeks or when patient has symptoms or there are findings pointing out hyperglycemia.

Existence of numerous screening tests and different cut-off values of these tests lead to problems regarding which one will be used in recommendations and applications. The reason for reaching a consensus concerning which test is the optimal test for GDM screening and diagnosis results from this. As is seen in Table 5, there are different screening/diagnostic tests for GDM, different values are used and recommended as both screening positivity and diagnostic criteria[17].

Table 5: Comparison of tests and threshold values used for gestational diabetes mellitus [17]

APPROACH	AMOUNT OF GLUCOSE (GRAM)	DIAGNOSTIC CRITERIA	GLUCOSE THRESHOLD, mmol/L (mg/dl)				ABNORMAL VALUES (n)
			FASTING	1-H	2-H	3-H	
2 STEP	100	NDDG	5.8 (105)	10.5 (190)	9.1 (165)	8.0 (145)	2
2 STEP	100	CC	5.3 (95)	10.0 (180)	8.6 (155)	7.8 (140)	2
2 STEP	75	ADA(2000-2010)	5.3 (95)	10.0 (180)	8.6 (155)	-	2
2 STEP	75	CDA(2008)	5.3 (95)	10.6 (191)	8.9 (160)	-	2
1 STEP	75	IADPSG	5.1 (92)	10.0 (180)	8.5 (153)	-	1
1 STEP	75	WHO	6.1 (110)	-	7.8 (140)	-	1

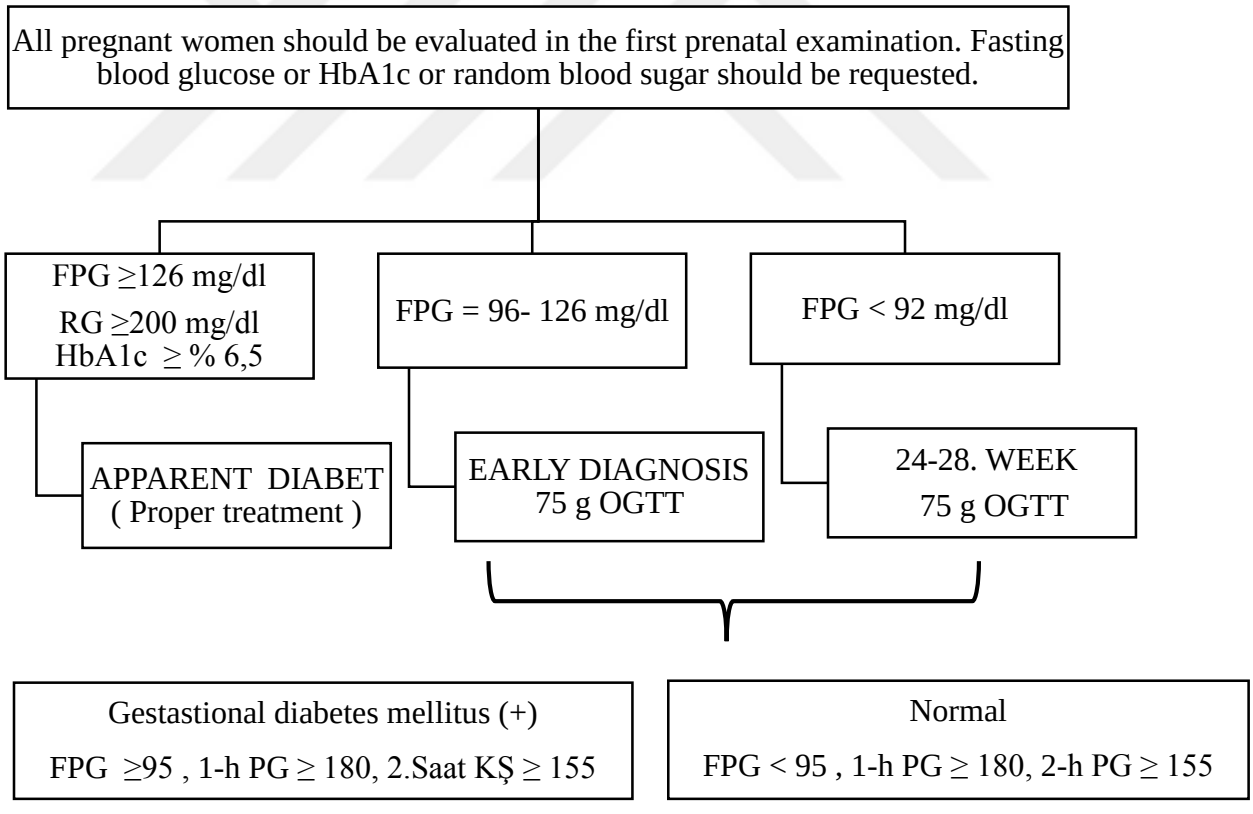
ADA: *American Diabetes Association;* CC: *Carpenter-Coustan;* CDA: *Canadian Diabetes Association;* WHO: World Health Organization; IADPSG: *International Association of the Diabetes and Pregnacy Study Groups;* NDDG: *National Diabetes Data Group.*

Gestational diabetes was firstly defined by O'Sullivan and Mahan in 1964 by establishing oral glucose tolerance test criteria[18]. These criteria have been revised by Carpenter and Coustan, American Diabetes Association and national diabetes societies over the years. A study called as HAPO (Hyperglycemia and Adverse Pregnancy Outcome) was planned under the leadership of IADPSG (International Association of Diabetes and Pregnancy Study Group) for the purpose of clarifying the current situation. This study which caused new threshold values to be suggested was published in 2008. The study was conducted in 9 countries simultaneously by designing as an observational study, data of 23.316 of 25.505 pregnants whom 75 g OGTT was

delivered were examined. According to HAPO outcomes; while a specific threshold value could not be calculated for risk increase, predominance of fasting and postprandial blood glucose was not found in perinatal risk increase prediction[19].

IADPSG organized a workshop in 2010 in order to assess outcomes of HAPO study and determine a screening/diagnostic test and optimal threshold values that can be used at international level [20]. In this workshop, it was suggested to apply single-stage 75 g OGGT, to take test threshold values as FPG ≥92 mg/dl, PG for 1st hour ≥180 mg/dl and PG for 2nd hour ≥153 mg/dl and if one of the foregoing is impaired, to establish GDM diagnosis.

In conclusion, it is deemed suitable to screen all pregnancies with FPG or HbA1c or random PG in the first trimester and to screen all pregnancies whom apparent diabetes or GDM is not detected with 75 g OGTT in 24-28th pregnancy weeks. This situation is summarized in Figure 1.



FPG: Fasting plasma glucose , **RG:** Random plasma glucose. * The diagnosis should be confirmed by FPG or HbA1c.

Figure 1: Screning for gestastional diabetes mellitus[5]

While IADPSG and WHO recommend single-stage diagnostic test, some associations deem diagnostic test for those whose screening test outcome is positive. We confront this as single-stage approach and two-stage approach. (Table 5)[6].

Table 6: Screening for and diagnosis of GDM [6]

One-step strategy			
Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes. The OGTT should be performed in the morning after an overnight fast of at least 8 h. The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded: Fasting: 92 mg/dL(5.1mmol/L) 1 h: 180 mg/dL (10.0 mmol/L) 2 h: 153 mg/dL (8.5 mmol/L)			
Two-step strategy			
Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.If the plasma glucose level measured 1 h after the load is ≥140 mg/dL* (7.8 mmol/L), proceed to a 100-g OGTT.			
Step 2: The 100-g OGTT should be performed when the patient is fasting.The diagnosis of GDM is made if at least two of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h after the OGTT) are met or exceeded:			
	Carpenter/Coustan (56)	*or*	*NDDG (57)*
Fasting	95 mg/dL (5.3 mmol/L)		105 mg/dL (5.8 mmol/L)
1 h	180 mg/dL (10.0 mmol/L)		190 mg/dL (10.6 mmol/L)
2 h	155 mg/dL (8.6 mmol/L)		165 mg/dL (9.2 mmol/L)
3 h	140 mg/dL (7.8 mmol/L)		145 mg/dL (8.0 mmol/L)
NDDG, National Diabetes Data Group. **The ACOG recommends a lower threshold of 135 mg/dL (7.5 mmol/L) in high-risk ethnic populations with higher prevalence of GDM; some experts also recommend 130 mg/dL (7.2 mmol/L).*			

2.2 DIABETES IN PREGNANCY

2.2.1 CARBOHYDRATE METABOLISM IN PREGNANCY

Pregnancy is a metabolic condition which contains dramatic increase of hormonal levels and increasing use of fuel by fetus. The aim of metabolic changes in the mother in pregnancy period is to supply adequate energy for the growing fetus. Energy stored in the first half of pregnancy is consumed for covering the needs of fetus afterwards[21].

Fasting plasma glucose level is lower due to increase of peripheral use of glucose in the first trimester. This decrease is about 15 mg/dL. Postprandial glucose levels remain high for longer time. This is because peripheral resistance to insulin increases. The first trimester is the stage when gluconeogenesis increases and the anabolic stage when maternal protein, glycogen and fat storages increase.

Catabolic phase develops in the second half of the pregnancy. HPL (human placental lactogen) which is a hormone having polypeptide structure secreted by syncytiotrophoblast increases in direct proportion to placenta mass. Lipolysis increases with the increase in this hormone; thus, glucose and amino-acids are kept for the need of fetus. HPL, progesterone, cortisol and prolactin being responsible for insulin resistance react by impairing the glucose intake of insulin-resistant cells. These hormones are the main hormones that are responsible for making pregnancy a diabetogenic state. There is no reduction in insulin receptors in the pregnancy. Insulin resistance is probably based on a disorder at post-receptor level[22]. A reduction of 44% has been found in insulin sensitivity in the third trimester in a normal pregnancy[23]. In non-diabetic pregnant, this increase in insulin resistance is easily covered by increase in insulin production.

Increased insulin resistance in diabetic patients having limited or no insulin reserve leads to hyperglycemia as the pregnancy progresses. Gestational diabetes develops in women who can secrete adequate insulin under the normal conditions however cannot cover the increasing insulin resistance of pregnancy. In addition to increasing HPL and cortisol levels, an increase is seen in triglyceride, free fatty acids, HDL and VLDL levels in the blood[24 25].

Transition of necessary substances by way of placenta accelerates once the fetus enters into fast growth period particularly in the last trimester. While mother provides the required energy for her in fasting cases over the destruction of fat mass stored previously; glucose, amino-acids, lactic acid and ketone bodies are transferred to the fetus[26]. Increase in glucose distribution volume along with transfer of either glucose or gluconeogenic amino-acids notably alanine and increase in maternal blood volume causes maternal glucose to decrease up to 45-50 mg/dL level in the fasting. This clear hypoglycemia suppresses insulin release and ketosis easily occurs in fasting case. It was found that β-hydroxybutyrate and aceto-acetate levels increased about 2-4 times following nightlong fasting. Hypoglycemia, hypoinsulinemia and hyperketonemia become apparent as the fasting is prolonged, plasma free fatty acids and glycerol levels also increase as a result of increasing lipolysis.

Glucose is transferred from placenta in facilitated diffusion until it reaches to full saturation with blood glucose level. Insulin which is a major polypeptide cannot pass from placenta to fetus. Although placenta is an organ playing a very important role in transfer of foods from the mother to the fetus, lipolytic steroid that is insulin antagonist and hormones play role in regulation of maternal metabolic fuels by synthesising. Human chorionic somatomamotropin (HCS) is an essential polypeptide released by placenta. It regulates the glucose intake by fetus by causing insulin release in the mother during the pregnancy.

HCS stimulates lipolysis providing adequate glucose and amino-acid transfer during the accelerated fetal growth in the second half of pregnancy[27]. To summarize;

1. Functional state of endocrine pancreas changes in the pregnancy.
2. Pancreas Langerhans islet hormones Glucagon / insulin rate changes.
3. Placental hormones prevent the insulin impact.
4. Insulin sensitivity of peripheral tissues decreases.
5. Insulin secretion decreases with the impacts of anti-insulin hormones.
6. There is a reduction in insulin receptors of target organs.
7. Proinsulin secretion increases.

Two properties with respect to the carbohydrate metabolism are very important in GDM. The first of which is insulin resistance which reaches to the highest point in the last trimester by starting from the mid-phase of pregnancy in a normal pregnancy and resembles the insulin resistance in patients with type 2 DM. The second of which is the increase in insulin secretion from pancreas β cells against the ever-increasing insulin resistance in the pregnancy. In conclusion, change of glucose level in circulating blood in the pregnancy is too small when compared with a big change in insulin sensitivity. This is resulted from the compliance ability of β cell explaining the glucose regulation in a normal pregnancy[28 29 30].

2.2.2 METABOLIC EFFECTS OF HORMONES DURING PREGNANCY

2.2.2.1 PLACENTAL HORMONES

Human Placental lactogen (hPL or chorionic somatomammotropin)

Level of this hormone released by placenta and showing a continuous increase till the birth is directly related with placenta mass. hPL which is shown to having lipolytic effects in in-vitro studies decreases the insulin sensitivity. hPL is held responsible for the activity increase in hormone-sensitive lipases observed in the last three months. In this period, decrease of free fatty acids increasing together with hPL level just after the birth again in relation with hPL confirms the relation between lipolysis and hPL[31].

Estrogen and Progesteron

Progesteron which is required for continuation of pregnancy is essentially released by placenta, by corpus luteum in less amounts. While placenta level remains stable in 4-13th weeks, it shows a continuous increase as from the second three months to the birth[32]. In a similar way, estrogen is released by placenta at increasing amounts as from the 9th week to the birth. Estriol constitutes 80-95% of estrogen released particularly in the late periods of pregnancy. Effects of these two hormones on the

carbohydrate metabolism develop in contrary directions. Estrogen increases the effect of insulin in muscle tissue and plays a corrective role for carbohydrate tolerance. Interaction of insulin in fat cells with its receptors is also increased by estrogen. Progesterone decreases insulin sensitivity and may lead to glucose intolerance.

Ketonemia, triglyceridemia, free fatty acids increase and hypoalaninemia observed when both hormones are given together do not appear when each of them is given one by one. It was determined that pancreas has estrogen and progesterone-specific pancreas receptors and it is considered that their effects probably realize over these receptors[33].

Human Chorionic gonadotropin (hCG)

hCG which increases 300 times of beginning level in the first three months reaches to the peak in 10th week and its increase continues more slowly till the birth. Whereas its metabolic effects are not fully known, it is known that it increases progesterone secretion from corpus luteum and accelerates the formation of pregnolonon and progesterone of steroid precursors, it should be considered that its effect leading to carbohydrate intolerance occurs over progesterone at the forefront[31].

2.2.2.2 OTHER HORMONES

Glucagon

In a normal pregnancy, an increase in fasting plasma glucagon is observed particularly towards the last trimester. In gestational diabetic pregnant women, either glucagon levels do not change or they display a slight increase in the last trimester. Insulin glucagon rate increases due to high fasting insulin level in both groups. There is an increased sensitivity in suppression of glucagon secretion with hyperglycemia during the pregnancy. It is considered that all these changes do not play a role which will create a tendency for diabetes but develop as a result of increase in anabolism and insulin secretion[34].

Prolactin and Growth Hormone (GH)

Prolactin released by lactotrop cells in anterior pituitary is continuously increasing until the birth. Observing glucose intolerance, hyperinsulinemia and hypoglucagnemia in non-pregnant women with hyperprolactinemia led this hormone to be regarded among hormones creating tendency to diabetes in the pregnancy[35]. There is no increase in GH levels in a relation with pregnancy and it progresses at lower levels compared with non-pregnant women as from the first trimester. Thus, it makes us think that this hormone does not affect glucose metabolism too much.

Glucocortiocids

Maternal cortisol shows a continuous increase during the pregnancy but its rhythm within the day does not change significantly. Pharmacokinetic researches show that cortisol half-life extends and its excretion slows down and these factors are held responsible for free cortisol increase. Also, high transcortine (cortisol binding protein) levels observed particularly in the last trimester as a result of estrogen increase also increase the bound cortisol level in the plasma. Cortisol decreasing the insulin receptor interaction in fat cells is an anti-insulin hormone and leads to glucose intolerance[36]. All these placental and non-placental hormones released show different effects in varying periods of the pregnancy. While effects of progesterone and HCG are dominant in the first trimester, HPL activity is gradually increasing. Ultimately, an insulin resistance reached to peak level in the last trimester occurs[25].

2.2.3 COMPLICATIONS OF DIABETES PREGNANCY

2.2.3.1 METABOLIC COMPLICATIONS

2.2.3.1.1 Acute Complications

Hypoglycemia

This complication is a problem frequently seen in diabetics who are treated particularly with insulin. Decrease in calorie intake based on hyperemesis seen particularly in the first trimester may increase the risk of hypoglycemia[37].

Hyperglycemia

Pregnancy accelerates the hunger and increases the ketogenesis. For this reason, diabetic ketoacidosis may develop in lower glucose levels in diabetic ketoacidosis pregnant women and faster compared with non-pregnant women. When blood glucose is above 200 mg/dl in a diabetic pregnant, patient should be hospitalized if ketonuria is seen in urine and blood gas, glucose, keto and electrolyte should be monitored. Also, since fetal loss is about 20% in diabetic ketoasidosis, fetal state should be continuously monitored. Ketoacidosis and severe hyperglycemia in pregnancy are treated as in the pre-pregnancy period. While fast and adequately high amount of fluid replacement is made, insulin treatment and potassium level are regulated[38 39 40 41].

2.2.3.1.2 Chronic Complications

Retinopathy

Diabetic retinopathy is the most important reason of blindness seen between the ages of 24-64[42]. Retinopathy prevalence is associated with the term of diabetes. When diabetes term is 5 years, it reaches to 20-25%, to 50-70% in the 10th year and 95% after 15th year[43 44].

It is divided into two main groups by the degree of capillary damage in the retina. Micro aneurisms and exudation are seen in pre-proliferative stage. Neovascularization and ischemia are typical in the proliferative stage[38]. Although its mechanism is not fully understood, pregnancy is a condition aggravating the diabetic retinopathy. For this reason, eye examination should be performed in diabetic pregnant women prior to pregnancy and in the first trimester. If retinopathy has been detected prior to pregnancy, if pregnant has been diabetic for long time and there is additional vascular disease like hypertension, pregnant should be followed closely during the pregnancy. Since it is treated with laser-photocoagulation effectively and it regresses substantially after the birth, terminating the pregnancy due to diabetic retinopathy is not generally recommended[38 39 42 44].

Nephropathy

Diabetes is the main reason of last trimester renal failure. Nephropathy develops in about 20-40% of diabetic patients. Glomerulosclerosis which appears with capillary damage underlies. Nephropathy is the most important complication having effect on the course of pregnancy in diabetic persons. Once HBA1c level exceeds 10%, diabetic nephropathy risk increases. If nephropathy is accompanied by chronic hypertension in pregnant women, preeclampsia risk increased to 60%[38]. Nephropathy is defined as proteinuria value at and above 300mg/day. Values ranging between 30-300 mg/g point microalbuminuria and it is the early finding of nephropathy and cardio-vascular diseases[45 46] . Despite negative effects of nephropathy on the pregnancy, pregnancy has no effect accelerating the nephropathy[47].

Neuropathy

Neuropathy risk increases with term of diabetes, as is in other complications. It has three types as mononeuropathy, symmetrical polyneuropathy and autonomous neuropathy. Even though it is a rare complication, peripheral symmetric sensorimotor neuropathy based on diabetes may develop in some pregnant women. Diabetic gastropathy that is another form leads to nausea, vomiting, nutritional problems and difficulty in glycemic control in the pregnancy[38 43].

2.2.3.2 GESTATIONAL COMPLICATIONS

Preeclampsia

It is seen in diabetic persons having vascular complications particularly like proteinuria and perinatal mortality increases 20 times in preeclamptic diabetic women when compared with normotensive ones[48]. Preeclampsia incidence in pregestational diabetic women increases 2-3 times compared with non-diabetic ones. The basic factors increasing the risk are term of diabetes, nephropathy and vascular complications like chronic hypertension. While class B diabetics in While classification have similar risk with non-diabetics, hypertensive complications increased in classes D, F, R[49 50]. If diagnosis has been established particularly prior to 24th pregnancy week in gestational diabetic women, preeclampsia incidence is quite more compared with ones having normal glucose tolerance[51].

Polyhydramnios

If particularly glycemia control is not good in diabetes, excessive amniotic fluid forms. Values exceeding 2000 ml are defined as polyhydramnios. It is seen in 10-20% of diabetic pregnant women. When compared with non-diabetic controls, it is seen that incidence of polyhydroamnios increases 30 times in diabetic pregnant women. It is considered that fetal hyperglycemia being secondary to maternal hyperglycemia develops and fetal glycosuria leads to this condition[37 41]. It was found that amniotic fluid index progresses in parallel with amniotic fluid glucose level in diabetic women[52]. Preterm action, early membrane rupture, cord hanging or ablation increase the placental risk.

Urinary Infections

About 300mg/day glycosuria is normal depending on the increasing glomerulus filtration rate in the pregnancy. This rate further increases in diabetic pregnant women. Dilatation in urinary tracts with hormonal effects leads to retention of urine whose glucose content is high. This condition creates predisposition for bacteria colonization.

Asymptomatic bacteriuria develops in rate of 20% in diabetic pregnant women and pyelonephritis appears in one forth of whom[37].

Preterm Labaur

While there were no tests for fetal well-being and maturity, preterm labaur was being applied consciously in diabetic pregnant women in order to prevent fetal deaths. Although this practice is abandoned today, preterm labaur incidence is still frequent in diabetic pregnant women and accordingly, neonatal morbidity is a serious problem. Diabetes existing prior to pregnancy is a risk factor in terms of preterm labaur and complications developed based on diabetes may require early termination of the pregnancy. Since beta-mimetic agents used for preterm action stimulate hyperglycemia and hyperinsulinemia, magnesium sulphate or calcium channel blockers should be used for tocolysis in diabetic pregnant women. If steroid will be given for pulmonary maturation, plasma glucose should be controlled more frequently[39].

2.2.3.3 FETAL COMPLICATIONS

Discovery of insulin in 1922, obstetrics and developments in newborn intensive care decreased the perinatal mortality about 30 times in pregnancies. Diabetic pregnant women were able to be followed until the birth through the developments in providing maternal euglycemia and thus, iatrogenic respiratory distress syndrome rates decreased. Despite all these developments, perinatal mortality rates in diabetic women are about two times more than non-diabetic women[39].

Abortus

If glycemia control is inadequate particularly in periconceptional period in diabetic women, it has been found that spontaneous abortion rate is more. Also, as it is climbed to classes C, D, F, abortus incidence is increasing. In periconceptional period,

abortus risk falls to the rates in normal population with a good glycemia control. In this period, HbA1c values should be controlled and if these values are high, patient should be monitored closely[38 39 53].

Congenital Abnormalities

Congenital abnormalities seen in 1-2% incidence in general population are 4-8 times more in those who have apparent pregestational diabetes and it is the most important death reason in diabetic pregnancies [38 39 54 55]. Even though abnormalities may be seen in every system, mainly cardiac and central nervous system abnormalities are seen in infants of diabetic mothers. Caudal regression syndrome is an anomaly rarely seen but being specific to the diabetes [56 57] . Paternal diabetes, normoglycemic mother or not detecting increase in anomaly rate in existence of gestational diabetes developed following the first trimester show that glycemic control in embryogenesis stage plays the major role. In pregnancies whom HbA1c level is found high in the first trimester, it is encountered with congenital abnormalities more frequently. As HbA1c level increases, anomaly rate is also increasing[39 57 58] .

Which mechanism hyperglycemia uses for abnormalities is not clear. It is considered that inositol, prostaglandins and free oxygen radicals affects metabolisms. In fact, vitamins E and C that are antioxidants have been shown to decrease abnormalities based on hyperglycemia in animal experiments. In similar way, the same result was seen in prostaglandins[59]. 3-6th weeks of the pregnancy are the weeks when embriyo is the most sensitive to teratogens. If proper glycemic control is provided in this period, anomaly rates may fall to general population level. Particularly diabetic women who consider to be pregnant should be informed of this issue[40].

Macrosomia and LGA (Large for Gestastional Age)

Macrosomia defines a fetus weighting more than 4000 g being independent from gestational age. (Some accept this value as 4500 g and above) LGA is a condition in which birth weight is above 90 percentile by the pregnancy week[39 60 61] . Macrosomia is

three times more in diabetic women when compared with normoglycemic women and this condition is related with many morbidities in infants of diabetic mother[62 63] . While fetal skeletal system is not affected from excessive growth in such infants typically, fat deposits are seen particularly in shoulder and bodies. When compared with macrosomic infants of normoglycemic mothers, head/shoulder rate decreases and shoulder width and upper extremity subcutaneous thickness increases in such infants. This abnormal antropometry in infants of diabetic mothers further increases the shoulder dystocia risk compared with other infants weighting same[64 65]. The main element in macrosomia development appears as fetal hyperinsulinemia developed as a response to maternal hyperglycemia. About 80% of maternal glucose levels are seen in the fetus. Thus, fetus of hyperglycemis mothers synthesizes more insulin. Tissues of fetus like liver, fatty tissue, muscle tissue, heart, adrenal glands, pancreas which are tissues being sensitive to insulin undergo hypertrophy and hyperplasia. The same change is not seen in brain, kidneys and femur length. In similar way, insulin resistance and maternal amino-acid use as a result of hypoinsulinemic condition decrease in diabetic women and fetal development accelerates as a result of stimulating insulin secretion by transferring amino-acids increased in the circulation to the fetus[38 66]. In addition to diabetes, overweight infant history, pre-pregnancy weight, weight gained during the pregnancy, multiparity, male fetus, pregnancies exceeding 40th week, maternal height and negative result in 100g OGTT but positive result in 50g loading are the other risk factors for macrosomia[65].

Fetal Growth Restriction

It is more seen in pregestational diabetic women. It develops based on uteroplacental failure in pregnant women whom diabetes-related micro and macrovascular complication developed[40].

In Utero Mort Fetalis

Unexplained stillbirth is a condition encountered in pregnancies complicated with apparent diabetes. These infants are typically big by their ages and generally they die in 35th week or later prior to the birth. Incidence is about 1%[48 67]. While mechanism

here is not completely known, hypoxy or glucose motions developed as a result of binding glucose to fetal erytrocytes and sudden substitutions in water and electrolytes are suspected[37]. It may be provided to encounter this state more rarely with optimum glycemic control and close follow-up.

Birth Injuries

Birth injuries including shoulder dystocia and brachial plexus injuries are more frequently seen in diabetic maternal infants and macrosomic infants. While shoulder dystocia develops in normal pregnant women in rate of 0.3% - 0.5%, this rate is 2-4 times more in diabetic women. While half of shoulder dystocia occurs during the birth of normal weighted infants, incidence above 4000g increases 10 times and if maternal diabetes is available, risk for every 250g above 4000g increases 5 times[39].

Neonatal Problems

Despite developments in modern maternal and neonatal care, abnormalities in glucose metabolism in diabetic mothers cause a set of neonatal problems to be seen more frequently.

Respiratory Distress Syndrome

Respiratory distress syndrome was the most commonly seen disease in infants of diabetic mothers until recently. Today, its incidence fell from 31% to 3% however it is 5-6 times more frequent in infants of diabetic mothers[39]. Fetal pulmonary maturation is completed until 37th pregnancy week in 99% of normal pregnancies. In diabetic pregnancies, it cannot be ensured that pulmonary maturation is completed prior to 38.5th week[68]. It is considered that hyperglycemia and hyperinsulinemia are responsible for the delay in pulmonary maturation. Insulin affects surfactant production negatively by inhibiting enzymes playing role in phospholipid synthesis or by blocking glycocorticoid receptors. Sensitivity of L/S (lecithin/sphingomyelin) rate used for detecting fetal pulmonary maturation is low in diabetic women. For this reason,

determination of phosphoglycerid in amniotic fluid is more reliable rather than L/S rate[68 69].

Hypoglycemia

Hypoglycemia is seen in about 25-40% of infants of diabetic mothers the first hours of life. Poor maternal glycemia control during the pregnancy, and particularly high maternal glucose levels during the birth increase the risk of neonatal hypoglycemia risk. Stimulation of intrauterin fetal pancreas due to apparent maternal hyperglycemia leads to fetal beta cell hyperplasia and thus, hyperinsulinemia. When trasplacental glucose source is ceased after the birth, hypoglycemia develops[70 71]. Since prolonged hypoglycemia convulsion may lead to coma and brain damage, these infants should be closely monitored.

Polycythemia

It is a condition in which hematocrit is higher than 65%. It is seen in 10-40% of infants of diabetic mothers. It is assumed that hyperglycemia leads to chronic hypoxy and as a result of this, increased erythropoietin secretion causes polycythemia. Alternatively, hyperglycemia is accused to have caused early destruction of erythrocytes[38 70].

Hyperbilirubinemia

Newborn hyperbilirubinemia is seen in about 25% of infants of diabetic mothers, but it is seen in a twofold incidence of normal population. It is more frequently seen due to increases preterm birth rates and polycythemia. It has generally mild-moderate degree. It is treated with hydration and phototherapy[38 39].

Hypocalcemia

It is a condition in which serum calcium level is <7 mg/dl. It is frequently seen in diabetic mothers' infants. It leads to irritability and tetany. It is less frequently seen in

those whose maternal glycemia control is good. Hypocalcemia is generally accompanied by hypomagnesemia[38 70].

Hypertrophic Cardiomyopathy

It is particularly seen in macrosomic infants of mothers whose diabetes control is unsatisfactory. It is a benign condition and it disappears within six months after the birth. It is considered that high fetal insulin levels cause fat and glycogen to be stored in myocardium and septal hypertrophy develops[70 72].

2.2.4 TREATMANT OF GESTASTIONAL DIABETES

2.2.4.1 NUTRITIONAL TREATMENT

The first stage in treatment of gestational diabetes is to revise diet of patient.

Daily calorie requirement

Calorie is calculated for ideal body weight.

- 24 kcal/kg in obese diabetic
- In non-obese diabetic, 30 kcal/kg in the first trimester and 35 kcal/kg as from the second trimester

Nutrient components

Nutrient components in daily total calorie requirement should be calculated as follows:

- Carbohydrate: 45-50% (≥200 g/day)
- Protein: 18-20% (1-1.5 g/day)
- Fat: 30-35% (40-60 g/day)

Number of meal

Total 7 meals as 3 main meals and 4 snacks. Daily calorie requirement's:

- In main meals; 3/18 in the mornings, 4/18 at noon, 4/18 in evenings
- 2/18 in each one of 3 snacks
- 1/18 in the snack prior to bedding.

Weight gain speed

- 1-2 kg in a week in the first trimester
- 250-500g in a week as from the 2nd trimester
- Weight gain should not exceed 10-12 kg during the pregnancy.

Blood glucose in 75-80% of diabetic patients improves[9].Also, exercise should be recommended for the patient. Exercise contributes to regulation of blood glucose by increasing insulin sensitivity. Generally, it is recommended to exercise for 15-30 minutes 3 times in a week.

2.2.4.2 MEDICAL TREATMENT

Insulin Therapy

Insulin therapy is started in patients whom diet and exercise fail behind in regulation of blood glucose. American Diabetes Association determined insulin inception threshold values as 105mg/dL for fasting blood glucose, 155mg/dL for postprandial 1st hour blood glucose and 130mg/dL for postprandial 2nd hour blood glucose[73]. Targeted blood glucose values are 95 mg/dL in fasting, 140 mg/dL in postprandial 1st hour and 120 mg/dL in the postprandial 2nd hour [74]. However, there are conservative approaches suggesting that these values should be required as 90 mg/dL for FBG and 120 mg/dL for postprandial 1st hour blood glucose [75]. In a study conducted

by Langer et al., it is recommended to keep blood glucose between 87-104 mg/dl in patients receiving insulin therapy [76]. Crystallized insulin and NPH insulin are used in therapy of pregnant women. Use of insulin lispro and insulin aspart has been increased to category B by FDA. Studies regarding the use of long-acting analogs (glargine and detemir) are being continued and they are still not recommended. It should be revised to include from proteins. Blood glucose improves in 75-80% of diabetic patients[74].

Oral Anti-diabetics

Since many oral anti-diabetics pass through the placenta, the use of them is not recommended in the pregnancy. However, it has been shown that gliburidin does not pass through the placenta and studies regarding its use in the pregnant women are continued[77]. In studies conducted concerning treatment of gestational diabetes recently, a significant difference was not found between insulin and gliburid treatments in terms of maternal glycemic control, infant birth weight and c-section rates. Any difference was not found between groups treated with oral anti-diabetics (gliburid and metformin) and with insulin in terms of congenital malformation[78]. In a similar way, there are studies regarding the use of acarbose in GDM treatment[79]. However, large-scaled studies are needed for the use of oral anti-diabetics in the pregnancy. Final treatment of gestational diabetes is birth. In some studies, while it is shown that shoulder dystocia may be regressed from 10% to 1,4% with induction of birth in 38-39th weeks, it has been reported that birth induction in a term infant may be useful in reduction of complications[80 81]. Extensive studies are required in this regard. Type 2 diabetes should be searched with 75 g OGTT in the mother at the 6th postpartum week. In conclusion, although gestational diabetes has been defined long years ago, recent studies regarding use of various oral anti-diabetics and insulin in treatment are being conducted. Complication rates have decreased significantly with early diagnosis and close follow-up today. These patients should be informed of Type 2 diabetes and followed in the postpartum period.

3 METHODS and PROCEDURES

147 pregnant women who were monitored in Yeditepe University Hospital Gynecology Policlinic between January 2012 and January 2014, had no previously known diabetes and glucose intolerance and were firstly diagnosed with GDM during the pregnancy, completed therapy in Yeditepe University Endocrinology and Nutrition and Dietetics Departments after GDM diagnosis was established and gave birth in Yeditepe University Hospital, were recruited into this study.

List of all pregnant women who were diagnosed with GDM on HOS (Hospital Operating System) between January 2012 and January 2014 was provided by Hospital's Information Processing Directorate. In the study, while pregnant women' age, height, pre-pregnancy weight, weight gained during the pregnancy, pregnancy number, family diabetes history, whether GDM diagnosis has been established in previous pregnancies or not, smoking, preeclampsia, birth week, birth complications were questioned, newborn's weight, APGAR score, post-partum complications were examined. It was targeted to obtain these data from patient's medical records. Incomplete data in patients' medical records were completed by contacting by phone. Pregnant women whose data were not completed were excluded from the study.

75 g OGTT (oral glucose tolerance test) was applied in each pregnant women who was monitored in Gynecology Policlinic between 24-28th weeks. The following values were used for 75 g OGTT; 92mg/dl for fasting, 180 mg/dl for 1st hour and 153 mg/dl for 2nd hour that are the threshold values of IADPSG (International Association of the Diabetes and Pregnancy Study Groups). Those whose only one value exceeded threshold value were assessed as having GDM. These pregnant women were directed to Endocrinology Policlinic for diet and/or insulin therapy. They were directed from Endocrinology policlinic to Nutrition and Diet Policlinic for diet therapy.

In all pregnant women, 24kcal/kg diet was applied in obese diabetics, 30kcal/kg in non-obese diabetics in the 1st trimester, 35kcal/kg in the 2nd trimester as from the establishment of diagnosis. Daily total calorie requirement was calculated in such way; 45-50% of which (≥200 g/day) from carbohydrates, 18-20% (1-1.5 g/day) from protein, 30-35% (40-60 g/day) from fats. There were total 7 meals in a day; 3 main meals and 4

refreshments. Daily calorie requirement was regulated in such way; in main meals; 3/18 in the mornings, 4/18 at noon, 4/18 in evenings, 2/18 in each one of 3 refreshments, 1/18 in the refreshment prior to bedding.

Two-weeks SMBG (capillary blood glucose profile) results were examined by Endocrinology physician, insulin was started in presence of uncontrolled glycemia which physician detected. Targeted fasting blood glucose was determined as < 95 mg /dl and 1st hour post-prandial blood glucose as <140mg/dl during the pregnancy. All pregnant women were asked to measure 7 point blood glucose at least for 2 days in a week. Data collected at the end of pregnancy were compared.

STATISTICAL METHOD: Data were analyzed by using SPSS 23.0 (Statistical Packages of Social Sciences) program in the computer. Conformity of data to normal distribution was assessed with Kolmogorov-Smirnov test. Descriptive statistics were shown in form of mean ± standard deviation for continuous variables and in form of frequency and percentage for categorical variables. In comparison of data complying with normal distribution of independent two groups, two independent sampling t test was used. Chi-square test and conditionally Fisher definite probability test were performed for the analysis of difference between categorical variables. In case of $p<0,05$, difference was accepted as significant.

4 FINDINGS

Total 147 pregnant women were included into the study and pregnant women were examined in two groups by therapy forms they received as those who receive medical nutrition therapy (MNT group, n=105) and those who receive insulin therapy in conjunction with medical nutrition therapy (MNT+ insulin group, n=42).

Blood glucose levels of all pregnant women measured in the first trimester were in the reference range, they were not using any drug out of vitamin and mineral supplement. When pregnant women were examined in terms of demographic properties (Table 7).

While average age of pregnant women in MNT group was 32.46, average age of pregnant women in MNT+ insulin group was found higher and statistically significant with the age of 34,1 ($p<0.05$).When BMI values were compared, average BMI value of MNT group was 24.29 kg/m^2 and 26,34 kg/m^2 in MNT+ insulin group. It was determined that these values were not statistically significant ($p>0.05$).

Figure 2: Assessment of groups by age averages (p=0,018)

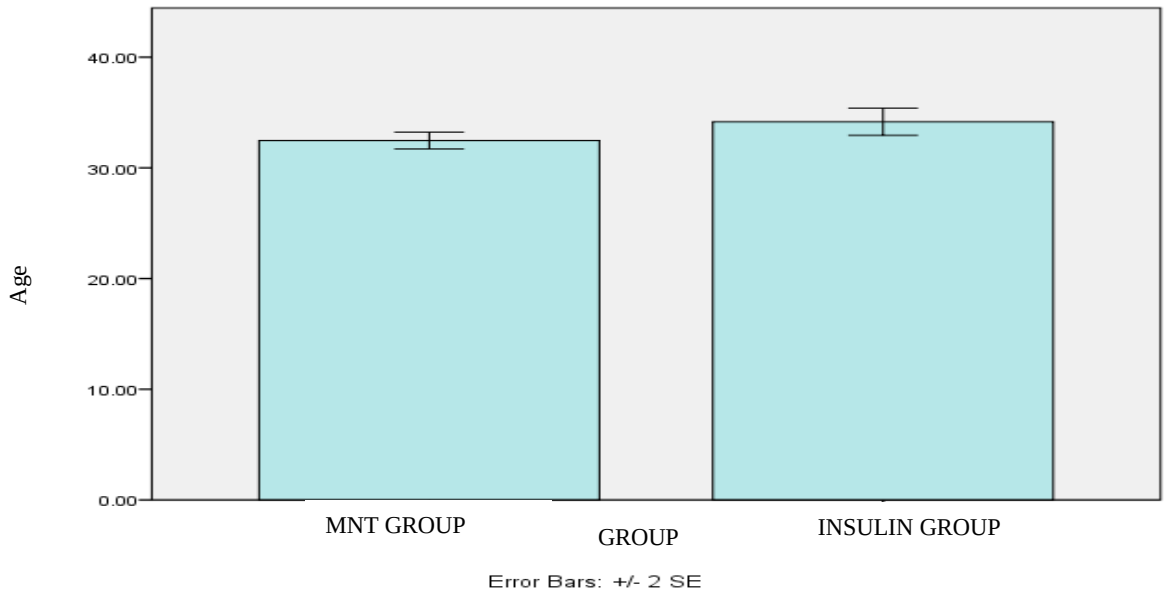


Table 7 : Maternal demographic properties in the pregnancy

	MNT GROUP (n=105)	MNT+ INSULIN GROUP (n=42)	P
Age (years)*	32,46 +/-3,87	34,1+/-3,97	0,018*
Height (cm)	1,63+/-0,08	1,62+/-0,04	0,76
Pre-pregnancy weight (kg)*	63,98+/-10,45	69,75+/-11,87	0,04*
BMI (kg/m^2)	24,29+/-6,21	26,34+/-4,62	0,05
The number of pregnancies (%)			
first	58,1	45,2	0,15
+1	41,9	54,8	
Family history of DM (%)	36,2	42,9	0,45
GDM history (%)	2,9	-	0,55
Cigarette (%)	1,9	7,1	0,11
Weight gain in pregnancy (kg)	12,12+/-5,32	14,43+/-12,49	0,11

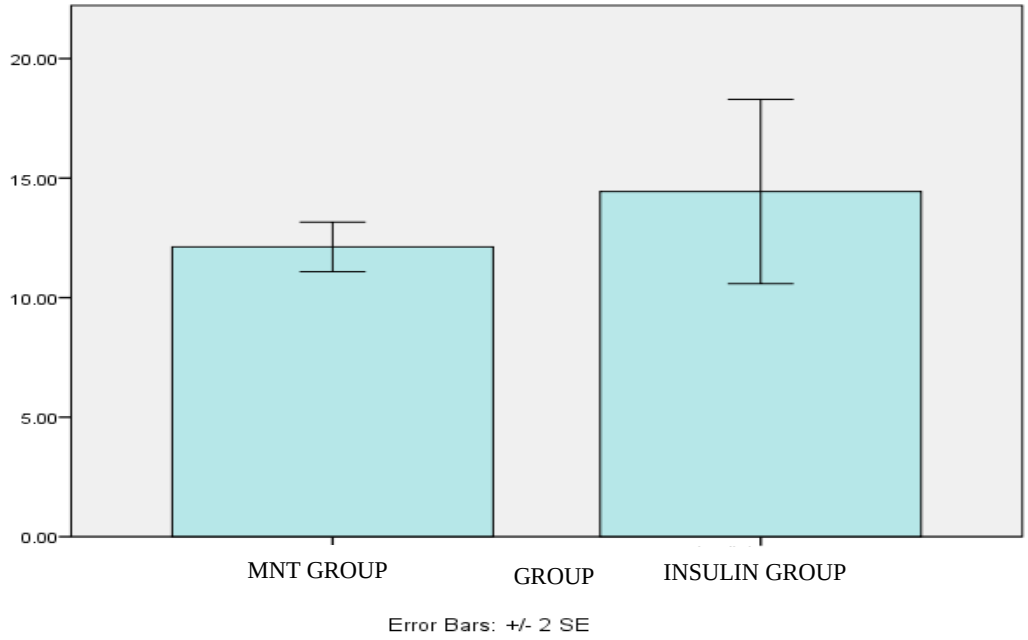
χ^2*: Chi-square Test * p <0.05 significant*

t test

While DM history was detected in 36,2%, smoking in 1,9% and GDM history in 2,9% of pregnant women who received MNT, DM history was detected in 42,9%, smoking in 7,1% of pregnant women who received MNT+insulin therapy and GDM history was not detected in these pregnant women, unlike the other group. A statistical difference was not observed in the groups ($p>0.05$).

Weight gained during the pregnancy was higher in pregnant women who received MNT (12,12+/-5,32 kg) than pregnant women who received MNT+insulin therapy (14,43+/-12,49 kg), however this was not statistically significant ($p<0.05$).

Figure 3: Assessment of groups by the weight gained during the pregnancy



Newborn data were examined under the headings of infant weight, birth week and APGAR score and results were shown in Table 3.

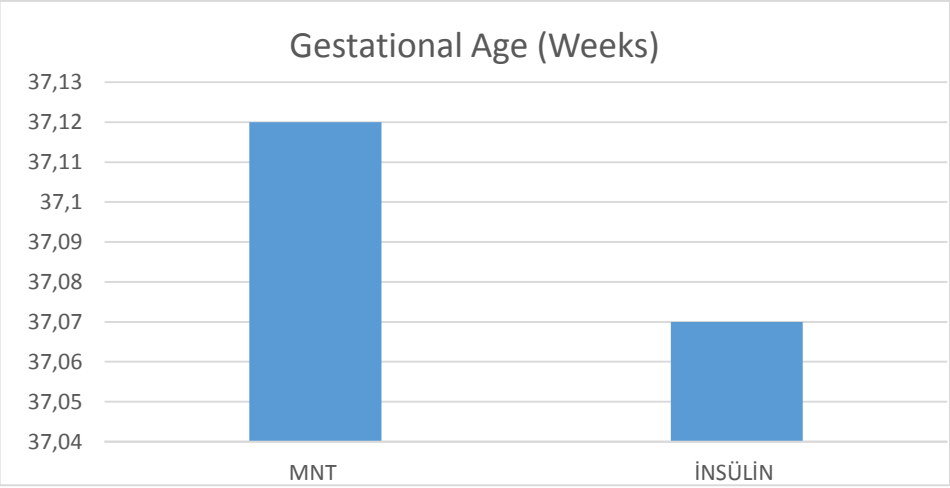
While average infant weight was 3070 grams, average birth week was 37, average APGAR scores were 8 in the first minute, 9 in the second minute, 9 in the third minute, respectively, in the group who received only MNT therapy; infant weight was 3099 grams, average birth week was 37, average APGAR scores were 8 in the first minute, 9 in the third minute, 9 in the fifth minute, respectively, in the group who received MNT+insulin group. Results were found highly similar, it was determined that they were not statistically significant ($p<0.05$).

Table 8 : Newborn data

	MNT GROUP (n=105)	MNT+ INSULIN GROUP (n=42)	P
Birth Weight (grams)	3070+/-505,88	3099+/-564,22	0,76
Gestational Age (Weeks)	37,12+/-2,12	37,07+/-2,21	0,89
APGAR scores			
First minute	8,21+/-1,19	8,19+/-0,99	0,90
Second minute	9,28+/-0,97	9,26+/-0,76	0,90
Fifth minute	9,76+/-0,58	9,71+/-0,50	0,60

*t test * p <0.05 significant*

Figure 4: Assessment of groups by the birth week



Complication was observed in total 57 pregnant women (38,8%) during the study. Gestational complication was detected in 46 mothers (31,3%), fetal complication in 37 infants (25,2%) and both fetal and gestational complication in 26 pregnant women (17,7%).

When complications were examined between two groups separately;

Complication was observed in 38 (36,2%) of 105 pregnant women who received only MNT therapy. Gestational complication was observed in 32 of these pregnant women (30,5%), fetal complication in 25 (23,8%) and both gestational and fetal complication in 19 (18,1%).

Complication was observed in 19 of 42 pregnant women who received MNT+insulin therapy (45,2%). Gestational complication was detected in 14 of these pregnant women (33,3%), fetal complication in 12 (28,6%) and both gestational and fetal complication in 7 (16,7%).

When these two groups were compared by taking total, gestational, fetal, both gestational ad fetal complication rates into account, a statistically significant difference was not found ($p<0.05$). Fetal and gestational complication rates are shown in Table 4.

Figure 5: Fetal and gestational complication rate

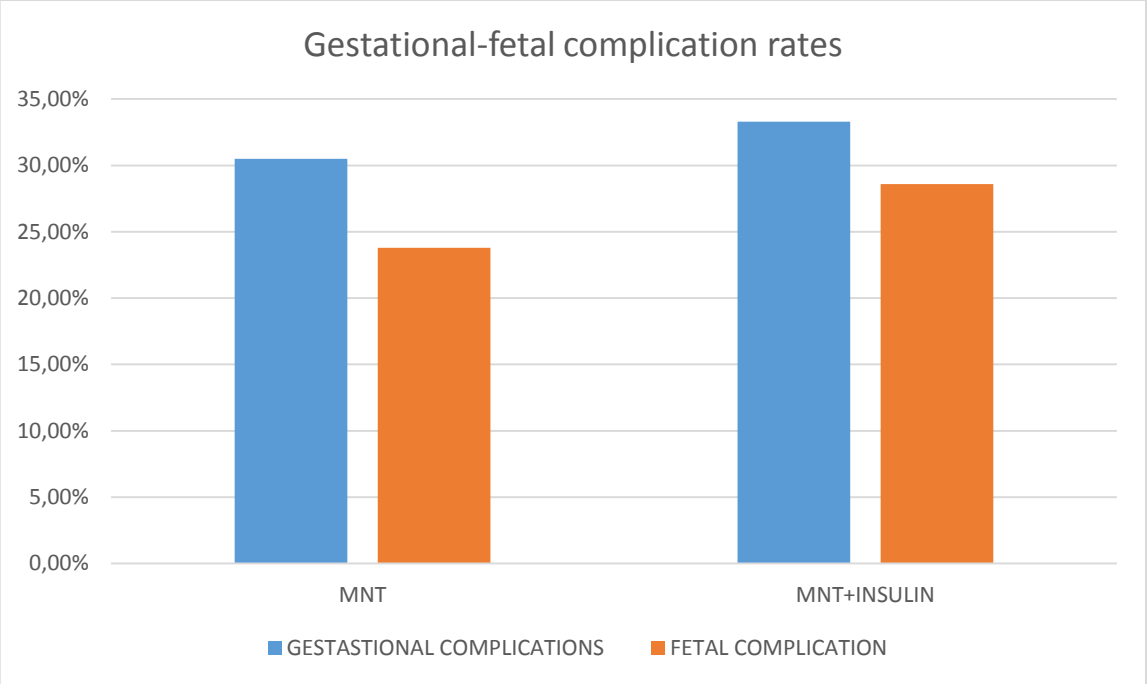


Table 9 : Newborn complications

	MNT GROUP	MNT+ INSULIN GROUP	P
	n(%)	n(%)	
	105 (%71,4)	42 (%28,6)	
Total complications 57 (%38,8)	**38 (%36,2)**	**19 (%45,2)**	**0,3**
Gestational + fetal complications 26 (%17,7)	**19(%18,1)**	**7 (%16,7)**	**0,83**
Gestational complications 46 (%31,3)	***32 (%30,5)***	***14 (%33,3)***	***0,1***
Preeclemsia 6 (%4,1)	3 (%2,9)	3 (%7,1)	0,35
Polyhydroamnios 1 (%0,7)	-	1 (% 2,4)	0,28
Oligohydroamnios1 (%0,7)	-	1 (% 2,4)	0,28
Preterm 42 (%28,6)	29 (%27,6)	13 (%31)	0,68
Premature rupture of membranes (PROM) 6 (%4,1)	4 (%3,8)	2 (%4,8)	1
Presenta percreta 1 (%0,7)	-	1 (% 2,4)	0,28
Fetal complications (n=37)	***25 (%23,8)***	***12 (%28,6)***	***0,54***
In Utero Mort Fetalis 3 (%2)	3 (%2,9)	-	0,55
Respiratory Distress Syndrome (RDS) 18 (%12,2)	12 (%11,4)	6 (%14,3)	0,63
Hypoglycemia 6 (%4,1)	3 (%2,9)	3 (%7,1)	0,35
Intrauterine Growth Retardation (IUGR) 2 (%1,4)	1 (%1)	1 (% 2,4)	0,49
Premature 16 (%10,9)	10 (%9,5)	6 (%14,3)	0,39
Fetal Distres 1 (%0,7)	1 (%1)	-	1
Neonatal problems (%1,4)	1 (%1)	1 (% 2,4)	0,49

*χ^2: Chi-square Test * p <0.05 significant*

Fisher's Exact Test

At the end of the study, gestational and fetal complications were examined separately;

Gestational complication was detected in total 47 pregnant women; 32 of whom in MNT group and 14 in MNT+insulin group. 3 pregnant women have preeclampsia, 29 pregnant women have preterm and 4 pregnant women have emr in MNT group. Polyhydramnios, oligohydramnios and presentapercreta complication were not found in this group, unlike MNT+insulin group. There are 3 preeclampsia, 1 polyhydramnios, 1 oligohydramnios, 13 preterm, 2 emr and 1 presentapercreta complications in MNT+insulin group, these rates are the same as the other group. When examined separately, a statistical difference was not observed among gestational complications ($p > 0.05$).

Totally, 37 infants have fetal complications; 25 of whom in MNT group, 12 in MNT+insulin group. 3 infants have inuteromorte and all of them are in MNT group. Apart from this, RDS was found in 12 infants, hypoglycemia in 3 infants, IUGR in 1 infant, prematurity in 10 infants, fetal distress in 1 infant and newborn problem in 1 infant in MNT group. Zionist color in infant and being bradycardiac were described as newborn problem. Unlike the other group, inuteromorte and fetal distress findings were not found in MNT+insulin group. RDS was found in 6 infants, hypoglycemia in 3 infants, IUGR in 1 infant, prematurity in 6 infants, newborn problem in 1 infant. When two groups were examined by taking complications as basis one by one, a statistical difference was not observed between two groups ($p > 0.05$).

5 DISCUSSION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance disorder occurred in the pregnancy for the first time[1]. Pregnancies complicated with diabetes contain a set of maternal and fetal risks compared with normal pregnant group. In the early of the last century, maternal mortality and perinatal mortality were progressing in too high rates as 45% and 60% respectively in the pregnancies complicated with diabetes. In 1920's, these rates highly decreased when insulin was started to be used in treatment. Nevertheless, it is still encountered with some complications more frequently in pregnant women diagnosed as GDM[38].

Primary aim of the gestational diabetes treatment is to keep plasma glucose levels in reference ranges and to reduce or minimize maternal-perinatal mortality and morbidity risks. Sometimes insulin requirement is needed in addition to medical nutrition therapy in order to keep plasma glucose levels in reference ranges. Recent studies indicate that approximately 15% of women with GDM require insulin therapy[82]. In another study carried out, Lahore[83] reported that 40% of patients with gestational diabetes require insulin. In our study, percentage of pregnant women who needed insulin requirement for glycemic control was found as 28,6%, consistant with literature data.

The aim of this study is to compare those who receive only MNT (MNT group, n=106,71,4%) with those who receive insulin in addition to MNT therapy (MNT+ insulin group, n=44,28,6%) in pregnant women who are diagnosed with GDM in terms of complication growth.

In our study, it was found when demographic characteristics were examined that age and pre-pregnancy weight were found significantly higher in insulin group. Altough pre-pregnancy weight were found higher in insulin group, there is no significant difference in term of VKİ. That is, we can say that as age increases, the requirement of using insulin in addition to diet regulation also increases. In a research conducted by Ouzounian et al., it was found that the need of insulin therapy along with diet increases for glucose regulation in overweight (BMI=25-29,9 kg/m2) and obese (BMI >29,9)

GDM patients but we found there is no significant differences in terms of VKİ in this study.

Several obstetric problems occur in diabetic pregnancy, their frequency being directly related with the quality of the diabetic control achieved[84]. Although well glycemic control was provided, 38,8% of all GDM patients had complication in this study. Of those group who had complications 36,2% of whom were in MNT group, MNT+ insulin group had higher rate with 45,2%, however a statistical difference was not found between two groups.

Pregnancy induced hypertension was the commonest maternal complication (44.4%) followed by polyhydramnions (23.6%) which has got an incidence of 3 to 32% [85 82] . In our study, 4,1% of pregnant women had preeclampsia, 2,9% of whom were in the group monitored with MNT and 7,1% were in the group monitored with insulin, there is no significant difference between two groups. Sibai et al., reported that preeclampsia is encountered 2-3 times more frequently in pregnant women with gestational diabetes mellitus [49]. Also, in the study conducted by Lindsay et al. (27), average arterial blood pressures were found higher in patients whose gestational diabetes appeared in the early period of pregnancy and for whom insulin therapy was needed compared with patients who were regulated with diet and had normal glucose tolerance. In our study, percentage of patients for whom insulin therapy was needed was higher than the other group[86]. Polyhydramnios is a common complication, with a reported incidence of 3- 32%[85] in diabetic pregnancies. Perveen[82]in her study also found that polyhydramnios is the most common maternal complication of GDM. In our study, polyhydramnios has the lowest percentage with a reported incidence of 0,7%. Only 1 pregnant woman had polyhydramnios in the group and this pregnant was in the pregnant group who was followed with insulin. Also 1 pregnant woman had oligohydramnios and this pregnant was in the pregnant group who was followed with insulin. When these were compared statistically, there was no significant difference. It was determined in the study which was conducted by Dashe et al. in the literature that amniotic fluid index progresses in parallel with amniotic fluid glucose level in diabetic women[52].

Since macrosomia and unexplained fetal losses (in-utero mort fetus) incidence gradually increases in pregnancies complicated with diabetes in the advancing pregnancy weeks, many of physicians do not expect spontaneous trauma and they generally terminate the pregnancy with induction or caserean section[39 49 87]. These mentioned reasons explain the increased caserean and preterm birth rates in pregnancies accompanied with diabetes. Preterm labour occurs in about 20% of the diabetic pregnancies[84]. A study which was conducted in Lahore has shown that 15 (38%) of diabetic women delivered preterm[88]. In our study, preterm labor was observed in 28,6% of all pregnant women as complication. 27,6% of whom were in MNT group and 31% were in MNT+ insulin group. We found average birth week of pregnancies as 37,12+/-2,12 in the group who was monitored with MNT and 37,07+/-2,21 in the MNT+ insulin group in our study and a significant difference was not found when compared with the other group.There were 3 in-utero mort fetuses in the group and all of them were in the group receiving only medical nutrition therapy but there was no need for using insulin. When these 3 cases were checked, it was seen that fetal loss were not related to GDM or its complications and when compared with the other group, it does not make a statictical sense.

One of the most important complications in diabetic pregnancies is fetal macrosomia. The reported incidence of macrosomia is 25-40%[85], but more in another developing world study, i.e 46.6%[89]. In our study, we accepted infants who were born with a weight of 4500g and above as macrosomic regardless of the birth week. Any macrosomic infant was not observed in our study. In a study conducted by Coustan, in three groups of gestational diabetic case which were never treated, on which only diet was applied and prophylactic insulin was applied along with diet, macrosomia was reported in the following rates; 50% in the untreated group, 36% in the group on which diet was applied and 7% in the group which received insulin plus diet[90]. In a study, 1800-2000 kcal of diet was applied in 153 patients with gestational diabetes which was detected with screening tests in 24-28th week pregnancies and blood glucose was measured with frequent controls. Insulin therapy was started in cases whose blood glucose was not regulated and ultimately, there was no difference in fetal macrosomia incidence between both groups. From this point of view, those who conducted the study emphasized that prophylactic insulin practice is unnecessary[91]. However, patient

population in this study is mild and moderate gestational diabetic cases and it is a fact that insulin therapy may be effective in severe cases.

Hypoglycaemia during the first few hours of life occurred in 25 – 40% [85] of infants of diabetic mother which is much higher than that of our study (4,1 %). Good maternal glycemic control during pregnancy and labor decrease the risk of neonatal hypoglycaemia as shown in the current study. We found the newborn hypoglycemia as 2,9% in the group who was monitored with MNT and 7,1% in the MNT+ insulin group in our study. Although hypoglycemia percentage was found higher in the group having insulin requirement, we did not find a significant difference.

JM. Brudenel et al., reported in the study they conducted fetal distress rates as 21-33% and perinatal mortality as around 5% in pregnancies complicated with diabetes[92]. When we compared the study groups by the fact that first minute's apgar score is below seven, we found normal values with the rates of 8,21+/-1,19 in the group monitored with MNT and 8,19+/-0,99 in the group monitored with insulin and there was no statistically significant difference.

Until recently, respiratory distress syndrome has been the most common disease in infants of diabetic mothers. Today, its incidence decreased from 31% to 3%, however, it is 5-6 time more frequent in infants of diabetic mothers[39]. Fetal pulmonary maturation is completed until 37th pregnancy week in 99% of normal pregnancies. In diabetic pregnancies, it cannot be sure that pulmonary maturation is completed prior to week 38.5[68]. It is considered that hyperglycemia and hyperinsulinemia are responsible for delay in pulmonary maturation. In our study, the most frequently seen complication (n=18) which supports data of our study is respiratory distress syndrome. 12 of whom were seen in the group monitored with MNT and 6 were in the group monitored with insulin. When these were compared, a significant difference was not observed.

6 CONCLUSIONS AND RECOMMENDATIONS

In conclusion;

In this retrospective research, since the case number is limited, discussing the comments in basis of case number will be appropriate.

As a result we can say that, age and BMI levels are significant signs for insülin treatment at GDM patients. GDM is recognised to be associated with increased rates of adverse maternal and neonatal outcomes, which are supported by the findings of our study.

It should be kept in mind that various complications such as congenital anomaly, preeclampsia, newborn hypoglycemia are encountered more frequently in pregnant women with gestational diabetes and risky pregnant women should be followed and treated by screening in the early pregnancy weeks. Antenatal controls should be performed more frequently and maintained by a fixed team consisting of endocrinologist, dietician and gynecologist, if possible. Since some metabolic problems are frequently seen in infants of diabetic mothers notably hypoglycemia after the birth, such infants should be closely followed.

Glycemic control is essential in women who are monitored with GDM. If blood glucose regulation can not be obtained, insülin treatment should be considered.

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8 APPENDICES

8.1 Ethical Approval

T.C. YEDİTEPE ÜNİVERSİTESİ

Sayı : 37068608-6100-15-1116 12/11/2015
Konu: Klinik Araştırmalar Etik Kurulu Başvurusu hk.

İlgili Makama (Sayın Dyt Nazlı Şişik)

Yeditepe Üniversitesi Hastanesi Biyokimya AD' da görevli, Prof.Dr.Serdar Öztezcan'in sorumlu olduğu "**Gestasyonel Diyabette Tedavi Etkinliklerinin Karşılaştırılması**" isimli araştırma projesine ait Klinik Araştırmalar Etik Kurulu (KAEK) Başvuru Dosyası (**1107** Kayıt Numaralı KAEK Başvuru Dosyası), Yeditepe Üniversitesi Klinik Araştırmalar Etik Kurulu'nun **11.11.2015** tarihli toplantısında incelenmiştir.

Kurul tarafından yapılan inceleme sonucu, yukarıdaki isimi belirtilen çalışmanın yapılmasının etik ve bilimsel açıdan uygun olduğuna karar verilmiştir (**KAEK Karar No: 533**).

Bilginizi ve gereğini saygılarımla arz ederim.

Prof. Dr. Turgay ÇELİK
Yeditepe Üniversitesi
Klinik Araştırmalar Etik Kurulu Başkanı

Yeditepe Üniversitesi 26 Ağustos Yerleşimi, İnönü Mahallesi Kayışdağı Caddesi 34755 Ataşehir / İstanbul
T. 0216 578 00 00 www.yeditepe.edu.tr F. 0216 578 02 99

9 CURRICULUM VITAE

Kişisel Bilgiler

Adı	Nazlı	**Soyadı**	ŞİŞİK
Doğum Yeri	SAMSUB/Bafra	**Doğum Tarihi**	17.09.1987
Uyruğu	T.C.	**Tel**	05063737117
E-mail	nazlisisik@gmail.com		

Öğrenim Durumu

Derece	**Alan**	**Mezun olduğu Kurumun Adı**	**Mezuniyet yılı**
Doktora	-	-	-
Yüksek Lisans	Beslenme ve Diyetetik	Yeditepe Üniversitesi	2016
Lisans	Beslenme ve Diyetetik	Başkent Üniversitesi	2011
Ön lisans	Sağlık Kurumları İşletmeciliği	Anadolu Üniversitesi-Açık Öğretim Fakültesi-	2010
Lise	Fen	Bafra Anadolu Lisesi	2006

Bildiği Yabancı Dilleri	**Yabancı Dil Sınav Notu**
İngilizce	

İş Deneyimi

Görevi	**Kurum**	**Süre (Yıl-Yıl)**
Diyetisyen	Yeditepe Üniversitesi Hastanesi	**09/2011-Halen**

Bilgisayar Bilgisi

Program	**Kullanma Becerisi**
Microsoft Office Word-excel-power point-outlook	Çok iyi
BEBİS- Beslenme Bilgi Sistemi	Orta
SPSS	Orta