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Do Hormones Cause Gestational Diabetes?

Abeer Ataallah Ayyed Al-Hadidy[1], Mowafak Khalil Hassan[2], Shaimaa Obaid Mostafa[3]

[1,2,3]Department of Biology/College of Science/ Mosul University

abesbio53@uomosul.edu.iq

1. INTRODUCTION

Diabetes mellitus is considered one of the most important health challenges in the world in the twenty-first century, as it has become an epidemic that drains human and material resources alike, threatening developing and developed countries alike. Its complications such as diabetic neuropathy, cardiovascular disease, kidney failure, amputation and blindness all lead to varying grades of inability, reduced quality of life, and increased economic burdens on the individual, the family, and then society as a whole (National Reference for Diabetes Education, 2016).

Depending on the statistical projections of the International Diabetes Federation and WHO, the number of people with diabetes in the world will reach approximately 438 million in 2030, with an increase in the age affected by the disease, i.e. 7.8% of the estimated total world population with a population of 8.4 billion, compared to a prevalence rate of 6.6% of the total world population of 7 billion in 2010 (Standards of Medical Care in Diabetes, 2015); (Ahamed and Banji, 2012), and its distribution across the world is controlled by several factors, including: heredity, age, food, geographical area, and climate (Baquer et al., 2011).

India is the country with the highest incidence of infection, as the number of infection was estimated at 50 million patients in 2010 AD, and China came in second place with the number of people with diabetes estimated at 43 million patients, while the United States of America came in third place with 27 million patients (Shrivastava *et al*., 2013); (Ahamed and Banji, 2012), and according to the World Health Organization, the Kingdom of Saudi Arabia is the highest among the countries in the Middle East in the incidence of diabetes, while indicating that the proportion of people with diabetes is more than 13.9% of adults in Iraq (WHO, 2020).

Gestational diabetes is a type of diabetes that occurs during pregnancy (usually in the fifth or sixth month of pregnancy) between week 24 to week 28 of pregnancy (as a result of the resistance of the hormones secreted by the placenta to the action of insulin, and thus the body is unable to burn sugars in the blood as it should, so the level of sugar in the blood rises and cells cannot use it as energy (Saleh and Qaliwan, 2019), it usually affects pregnant women at average 3-10% during pregnancy, and therefore it is considered one of the most common health disorders in women during pregnancy. In most cases, gestational diabetes disappears after child birth, but the possibility of it returning with next pregnancy in the future is great, and women with gestational diabetes are more at risk of complications during pregnancy and childbirth, and they, and perhaps their children as well, are in the future more likely to developing type 2 diabetes (Al-Tuni *et al*., 2017).

Definition of pregnancy

Pregnancy is the period that begins with the fertilization of an ovum and implantation of the fetus is in the mother's uterus and ends with fetus born and the expel of the fetus and placenta outside the uterus (Guyton and Hall, 2006). Pregnancy is a normal functional phenomenon accompanied by an elevate in vital mechanisms ,the anabolic processes and

changes in the values of variety hormones within the mother's body in a way it aims to create an optimal environment for the fetus inside the uterus and to sustain pregnancy as efficiently as possible and its duration ranges ,women have 260-280 days and an average of 38 weeks. During which pregnant women undergo many internal metabolic and hormonal changes that affect the efficiency of the body, as it directs the metabolic processes in the woman body in a way that meets the physiological needs of pregnancy for the needs of the fetus for the purpose of growth and development until born (Al-Qaisi, 2009).

Diabetes mellitus is defined as a chronic disease resulting from genetic and environmental factors characterized by a high value of glucose in the blood due to an absolute or partial insufficient amount of insulin or the presence of a specific disorder that prevents insulin from giving its desired effect, this deficiency of insulin affects, relative or absolutely, the metabolism of carbohydrates, proteins, fats, water and electrolytes (WHO, 2011). This disease usually leads after a long period of infection to complications and changes in the capillary vessels of the renal glomeruli, the retina of the eye, the retina and the digestive system, damages the peripheral nerves, and causes arteriosclerosis and coronary heart disease in the long term (Ahamed and Banji, 2012).

Mechanism of sugar work in the body

Blood sugar is regulated by Negative Feed Back to maintain the body in a state of homeostasis. The pancreas is secret insulin which is the main hormone that organize the transfer glucose from the bloodstream to all body cells, especially muscle cells and adipose cells, the food carbohydrates are converted into mono-glucose within an hours, and this mono-glucose is one of the important carbohydrates in the blood that is used as fuel for cells. β-cells in the islets of Langerhans of the pancreas produced insulin in response to high level of sugar (glucose) after meal. Insulin uses about 2/3 of the body's cells to take glucose from the blood or to use it as fuel to carry out transformational processes that the cell needs to produce other molecules or for storage. The decrease in glucose levels leads to a decrease in the secretion of insulin from the β-cells and a reverse conversion to the glucagon hormone, which its effects in the opposite function to insulin, so returning glucose from the liver to the bloodstream, while muscle cells lose the mechanism of converting the stored glycogen into glucose.

Elevated insulin values increase the body's building processes such as growth and number of cells, the synthesis of protein and adipose storage. Insulin is the main indicator in converting the direction of many bidirectional metabolic mechanisms from catabolism to building and vice versa. When the blood glucose level is low, it stimulates the burning of body fat. If the amount of available insulin is insufficient, or if the cells have poor response to the effect of insulin (insulin resistance or immunity), glucose will not be properly absorbed from the body cells that need it and glucose will not be properly stored in the liver and muscles (Siddiqui *et al*., 2013).

Types of the diabetes:

First: Diabetes mellitus: is divided into two main types:
I: Insulin dependent diabetes mellitus (IDDM)
II: Non-insulin dependent diabetes mellitus (NIDDM)
Second: GDM Gestational diabetes mellitus
Third: Other types of diabetes have different causes, such as (monogenic diabetes syndromes, such diabetes that affects newborns, diseases of the outside of the pancreas such cystic fibrosis, and some pharmaceutical that cause diabetes, such as drugs used to treat AIDS (ADA, 2015).

Insulin Dependent Diabetes Mellitus (IDDM)

Juvenile diabetes is an autoimmune disease that begins in childhood or adulthood and is called juvenile diabetes. It affects people under the age of thirty years and accounts for 5-10% of diagnosed cases of diabetes (Menon *et al*., 2012). The presence of autoantibodies in the blood of people with this type of diabetes has been diagnosed, which indicates that the disease is not hereditary, although genetic factors are important in the development of the disease (Harris *et al*., 2011). Type 1 diabetes develops when pancreatic beta cells are destroyed. As a result of the autoimmune reaction in the body through the creation of antibodies Anti-glutamate acid decarboxylase (Anti-GAD) and (Anti-IA2) Anti-tyrosine phosphatase, as a result, the insulin which secreting by pancreas is stopped or secretes it in insufficient quantities (David *et al*. , 2010). It is also believed that the disease appears as a result of accidents, environmental factors, or infection with viral infections such as mumps or measles (Riaz *et al*., 2009). Free radicals and reactive oxygen species that destroy and destroy body cells, including pancreatic beta cells (Erejuwa *et al*., 2010). This type of diabetes is accompanied by the transformation of stored fats in the body into free fatty acids, leading to a high level in the blood and thus may turn into ketone bodies (acetoacetate, acetone and beta-hydroxybutyrate) It is one of the important factors in the occurrence of coma as a result of high blood acidity (Harvey and Ferrier, 2011), and its symptoms include extreme thirst, the presence of sugar in the urine, frequent urination, the body smells like acetone, fatigue, sluggishness and lethargy, significant weight loss within a short period (Singh, 2011), and patients of this type in their treatment completely depend on the hormone insulin to adjust their sugar level, as there is a complete inability to secrete insulin and to avoid complications of the disease and the occurrence of a coma caused by ketoacidosis and then death (Murray *et al*., 2009).

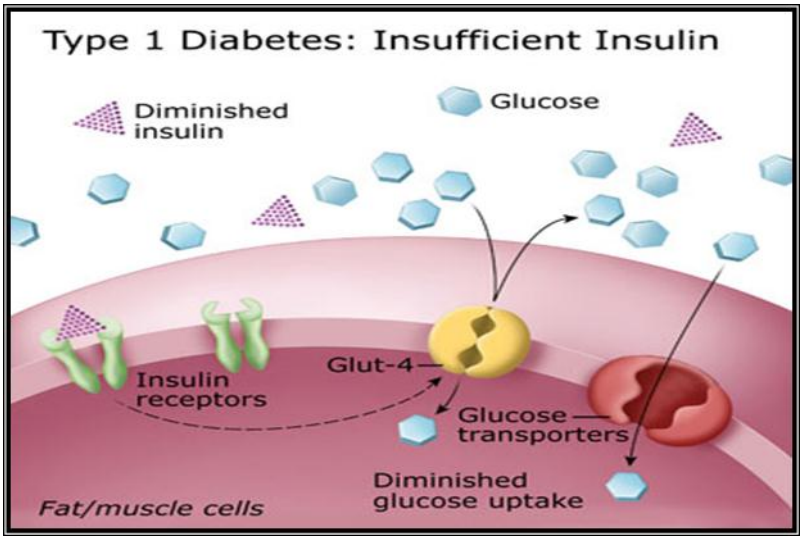

Figure (1): Type 1 diabetes (WHO, 1999)

Non-Insulin Dependent Diabetes Mellitus (IDDM)

This type is the most prevalent, as 90-95% of diagnosed cases of diabetes are type II, and in the United States, more than 25.8 million people have been found with this type of diabetes, and it usually occurs after the age of forty and has several labels, which is adult diabetes, Maturity Onset diabetes or non-insulin-dependent diabetes (Qaseem *et al*., 2012). The cause of diabetes of this type is due to the poor response of target tissue cells to insulin, which is called insulin resistance, and this happens as a result of changes in insulin receptors or a decrease in

their number on the surface of these cells of the target tissue (Rawi *et al*., 2011). There are several factors that have a key role in the development of this type, the most important of which is genetics. Recent studies indicate that there are 36 genes responsible for 10% of the current diseases, including diabetes mellitus. Environmental conditions also have a distinctive role in the development of this type (Herder and Roden, 2011). Inactivity and lack of movement have a significant impact on increasing the risk of exposure to this disease (Maheria *et al*., 2011). In addition, the obesity factor is one of the main factors that increase the likelihood of developing this disease. As 80-85% of patients are obese (Qaseem *et al*., 2012); (Prisant, 2004). As the worker Psychological factor and oxidative stress are important factors in the development of this type of diabetes (Sheth *et al*., 2011). Patients of this type depend for their treatment on oral medications that lower the level of sugar, and sometimes patients may need the insulin hormone to adjust their sugar level (Inzucchi, 2011).

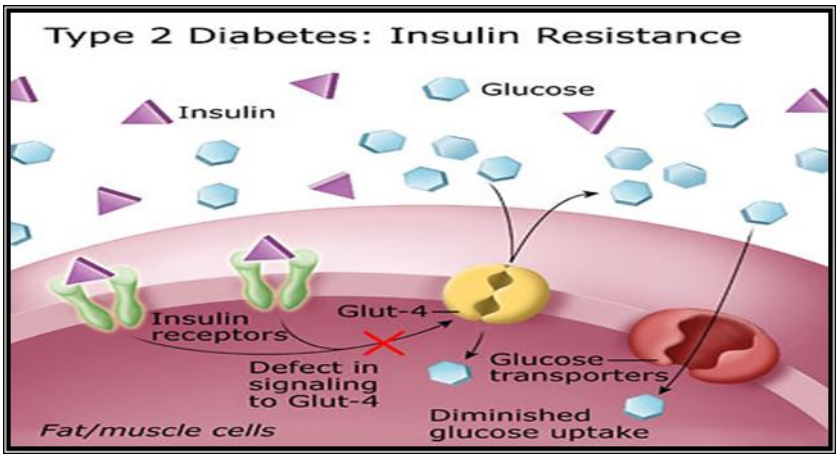

Figure (2): Type 2 Diabetes (WHO, 1999)

Gestational diabetes mellitus (GDM)

Gestational diabetes is a common type of diabetes and is a temporary condition that occurs during pregnancy, and it is estimated that about 3-10% of pregnant women suffer from gestational diabetes (Landon and Gabbe, 2011). Every seven pregnant women develop gestational diabetes. The complications of this type of diabetes affect the mother and the fetus, including hypoglycemia of the newborn fetus, neonatal death, congenital malformations, hyperbilirubinemia, hypocalcemia, shortness of breath, as well as the occurrence of gigantism, among the complications that occur to the mother during pregnancy are preeclampsia for the mother, increased risk of cesarean delivery, and high blood pressure (Al-Sawaf, 2012).and an increased chance of eye complications (Al-Hamid, 2007). Gestational diabetes often goes away after childbirth, in addition, gestational diabetes is one of the factors that enhance the risk of the mother developing type 2 diabetes later on, and gestational diabetes occurs between the 24th and 28th week of pregnancy (Al-Jubouri, 2011). The emergence and severity of complications depends on the extent to which the mother's blood sugar level is controlled, as harmful effects appear on the fetus of mothers who lack accurate blood sugar control, while the mother's follow-up of the necessary procedures and accurate control of blood sugar enables her to give birth to a healthy fetus (Ahmed, 2011).Women with impaired glucose tolerance are at risk of there is a significant risk of developing diabetes in the future compared to those who have a normal glucose tolerance during pregnancy (ADA, 2012). Also, the glucose in the blood plasma increases during the normal period of pregnancy as a result of the increase in the level of the progesterone hormone, which leads to the stimulation of the growth hormone, the anti-

insulin, which in turn leads to an increase in the level blood glucose level. The pancreas may not be able to meet this increase in women who are genetically susceptible to both types of diabetes (Al-Lahibi, 2006); (Grestein, 2001). The incidence of diabetes is greater among older and obese women, as well as among those with repeated pregnancies (ADA, 2012).

White's Classification of Gestational diabetes mellitus

To facilitate dealing with diabetic patients during pregnancy, many classifications have been developed, the most famous of which is White's Classification, as shown in Table 1:

White's Classification of Gestational diabetes mellitus
A1: The mother's fasting blood sugar level is within the normal limits of less than 120 mg/dl
A2: The fasting blood sugar level is more than the normal limit during pregnancy, more than 120 mg/dl
B: A pregnant woman whose diabetes started after the age of 20 and has persisted for less than 10 years.
C: A pregnant woman whose diabetes started before the age of twenty and has persisted for more than 10 years.
D: A pregnant woman whose diabetes started between 10-19 years and continued between 10-19 years.
F: A pregnant woman has diabetic nephropathy.
E: A pregnant woman with diabetic retinopathy.
H: A pregnant woman has atherosclerosis and cardiopathy.

Table 1: White's classification of gestational diabetes (Heppard and Garite, 2010).

Causes of Gestational diabetes

Most pregnant women suffer from impaired glucose tolerance due to hormonal alteration during pregnancy, and this means that their glucose value is higher than the normal range, but not in a way that causes sugar, and in the last three months of pregnancy, these hormonal alteration display pregnant women risk of gestational diabetes.

Placenta during pregnancy secretes hormones which help the mother maintain a normal blood glucose value and protect her from hypoglycemia, as these hormones reduce the response to the insulin hormone. As pregnancy progresses, these hormones impair the pregnant woman's ability to tolerate glucose, which leads to high blood sugar. The pregnant pancreas secretes insulin in large quantities, up to three times the amount of the normal human, to overcome the effect of pregnancy hormones on the sugar level. If the pancreas cannot overcome this hormonal effect, the blood sugar level rises, and this results in gestational diabetes (Rayburn and Carey, 2008).

Gestational diabetes complications

A- Effect of gestational diabetes on the fetus

There are many effects and complications of gestational diabetes on the fetus while in the womb, after birth or at a later age in life.

I- The effect of gestational diabetes on the fetus inside the uterus

1- Intrauterine death of the fetus

Fetal death often occurs in the 36th week of pregnancy in mothers with gestational diabetes, who have poor blood sugar control. Several studies that explain this

phenomenon indicate that high blood sugar leads to an abnormality in the placenta, which reduces the mechanism of oxygen transport and the occurrence of acidity in the fetus's blood, which leads to death (Al-Qawasmah, 2006).

2- Congenital malformations

The incidence of malformations increases in mothers who lack good sugar control, and these malformations occur at a rate of 5-10% in the fetuses of mothers with gestational diabetes, which increases at a rate of two to four times than the normal conditions and abnormalities that may occur in the fetuses of mothers with gestational diabetes, sorted according to the incidence.

a. Heart abnormalities: hole in the wall of the atria and ventricles, inversion in the position of the arteries and veins of the heart, and narrowing of the aorta.
b. Atrophy of the coccygeal vertebrae as in Figure (3).
c. Congenital malformation of the extremities, as in Figure (4), and these malformations are responsible for half of all intrauterine deaths (Baker, 2006).

Figure 3

Figure 4

Figure 3: Coccygeal atrophy of a child whose mother suffers from gestational diabetes. Figure 4: Leg deformity of a child whose mother suffers from gestational diabetes (Al-Muhaishi, 2014)

3- Macrosomia

The size of the fetus increases with elevate in the value of sugar in the blood of mother's than 130 mg / dl. This inflation becomes more pronounced after the 24th week of pregnancy, and the weight after birth exceeds 4000 g and more. Studies indicate that the increase in insulin secretion as a result of high blood sugar in the mother results to an elevate in the thickness of the layers of the skin , increase in muscle mass, enlargement of organs, and an inappropriate distribution of fat in the trunk and shoulders area compared to the head, which leads to difficult labor and dislocation of the shoulders as in Figure (5) (Daftary and Chakravarti, 2005).

Figure (5): Shoulders dislocated in a large newborn 5.5 kg as a result of gestational diabetes in its mother

II- Postpartum effects of gestational diabetes

1-Hypoglycemia

Low blood sugar occurs after birth immediately after cutting the umbilical cord, and exposure to high levels of glucose from the mother stops, while the pancreas of the newborn still secretes large amounts of insulin, which leads to a sharp drop in blood sugar. Therefore, the blood sugar of the newborn should be measured immediately after birth. Sugar level 60 mg/dl or less a sugar solution should be given intravenously to control the glucose level because hypoglycemia may lead to coma and death if not treated quickly (Daftary and Chakravarti, 2005).

2-Preterm Operative Delivery

Previous infection with gestational diabetes and poor control of sugar level is one of the most important causes of premature birth, and if the pregnancy lasts more than 38 weeks, it gives an opportunity for the fetus to grow up and thus requires the delivery of the fetus by cesarean delivery (Heppard and Garite, 2010).

3-Hypocalcemia and hypomagnesemia

Magnesium deficiency in the blood reduces the secretion of parathyroid hormones, and thus leads to an increase in the loss of calcium and magnesium salts with urine, which in turn leads Glucosuria. Clinical symptoms of calcium deficiency include anxiety and tension, mouth tremors, muscle cramps, and changes in heart rate (Inzucchi, 2005).

4-Respiratory distress syndrome (RDS)

This syndrome occurs when premature birth occurs, and the development and maturity of the lungs are incomplete, resulting in shortness of breath. The newborn may need to be placed under a ventilator until the lungs are fully developed and breathing is normal (Baker, 2006).

5-Polycythemia

Newborns of mothers with gestational diabetes are more likely to develop coagulation syndrome due to an increase in the mass of red blood cells. The symptoms

of blood clotting include cramps and digestive disorders. Treatment is by blood transfusion to reduce the mass of red blood cells (Inzucchi, 2005).

6-Hyperbilirubinemia

It appears in the form of yellowing in the eyes and skin, and the occurrence of jaundice is associated with premature birth, and what may result in liver failure, blood viscosity and increased red blood cell breakdown (Rayburn and Carey, 2008).

Long-term effects of gestational diabetes

1-Obesity

High blood sugar in the second half of pregnancy during the development of fat cells, muscle cells, pancreatic cells and endocrine glands of the fetus makes it more vulnerable to obesity during childhood and adulthood (Al-Anzi, 2010).

2-Type 2 diabetes mellitus

Any defect in the growth and function of the islets of Langerhans in the fetal pancreas during pregnancy or after birth leads to a decrease in insulin concentration and loss of glucose tolerance, which in turn leads to type 2 diabetes in the post-pubertal stage (Al-Anazi, 2010).

B- Effect of gestational diabetes on the mother

1- Gestational hypertension

Pregnancy-induced hypertension, which is more than or equal to 140/190 mm Hg, starting from the 20th week of menopause (Rohowyj, 2012), and several studies have shown a significant decrease in pressure in the case of intensive treatment of gestational diabetes. Among the factors causing high blood glucose and high blood pressure (pregnant age, obesity, chronic stress, family history) (Yuan *et al.*, 2016).

2- Preeclamp

Preeclampsia is a pregnant woman with high blood pressure with the appearance of a percentage of proteins in her urine more or equal to 0.3 g / 24 h. This condition may lead to insufficient amounts of blood reaching the placenta, causing the fetus to die inside the uterus. There is a close relationship between preeclampsia and gestational diabetes, and among the causes of preeclampsia are kidney disease, chronic blood pressure, pregnant age, overweight and obesity (Lee *et al*., 2017).

3- Inflammatory complications

In the case of pregnancy without diabetes, urinary infections increase with high glycosuria, but in the case of gestational diabetes, these symptoms are accompanied by urinary tract infection (Rohowyj, 2012).

4- Complications of childbirth

In addition to cesarean delivery, gestational diabetes increases complications during childbirth (dystocia, neonatal injury, postpartum hemorrhage) and this is all linked to macrosomia in the fetus (Al-Tuni *et al.*, 2017).

4- Incidence of diabetes, whether type II or gestational diabetes in the future (Al-Tuni *et al*., 2017).

Hormonal changes during Pregnancy

The placenta secretes many anti-insulin hormones, by reducing the sensitivity of insulin receptors, thus insulin resistance, and this explains the possibility of diabetes in some pregnant

women (Inzucchi *et al*., 2005). One of the hormones that stimulate the rise in blood sugar of the pregnant mother:

A- Placental hormones

1- Human Chorionic Gonadotropin hormone

2- Human Placental Lactogen

3-Human Somatomammotropin hormone

4-Placental Insulinase

5-Estrogen and Progesteron Hormones

The proportion of estrogens secreted from the placenta in a pregnant woman increases from day 35 of pregnancy, and the concentration of progesterone increases from day 65 of pregnancy, as progesterone has a direct effect on carbohydrate metabolism (Inzucchi *et al*., 2005); (Li *et al*., 2020).

B - Other hormones

1-Cortisol Hormone

It is secreted by the adrenal cortex. An increase in the Cortisol hormone was observed during pregnancy, as its concentration doubled in late pregnancy (Feng *et al*., 2020).

2-Leptin and Adiponectin hormones

The hormones secreted from fat cells play an important role in metabolism, including the hormones adiponectin and leptin, as they have an important role in the continuity of the natural pregnancy and have a role in pregnancy complications, including gestational diabetes, leptin is a hormone produced by fatty tissue outside or during pregnancy. Several studies have shown an increase in leptin concentration by 30% in the first trimester of pregnancy and with an increase in leptin levels in the plasma as this hormone increases food consumption, and the association of leptin hormone with its receptor contributes to insulin resistance (Pérez-Pérez *et al*., 2020).

Insulin sensitivity increases by leptin due to affecting the producing of insulin secretion, glucose utilization, lipid, glycogen synthesis, gonadotropins regulate the production of hormones from the hypothalamus and activates the sympathetic nervous system, along with its effect on GnRH regulation, leptin plays a functional role in the nesting process of the fetus and induces production of human chorionic gonadotrophin in trophoblast cells, as well as regulating placental development, increases leptinemia in early pregnancy appears to predict an increased risk of developing gestational diabetes at a later time (Chen *et al*., 2010).

The concentration of adiponectin decreases in women with gestational diabetes and inversely with blood sugar if compared with its concentration in women with normal pregnancies. The first trimester of pregnancy is an indicator of gestational diabetes. Finally, both leptin and adiponectin hormones are related to insulin resistance during pregnancy and give an expectation to follow the therapeutic model to bring insulin to its normal state (Georgiou *et al*., 2008).

3-Prolactin Hormone

Some experiments showed that high concentration of prolactin in the blood leads to insulin resistance or hyperinsulinemia (Li et al., 2020).

4-Cytokines

Some studies have proven that Tumor Necrosis factor-α (TNF-α) has an effective role in insulin resistance, as it is secreted during pregnancy from fat cells and the placenta (Atègbo *et al*., 2006); (D'Anna *et al*., 2007).

2. REFERENCES

Ahmed, Al-Moataz (2011). Diabetes and Pregnancy, International Diabetes Federation, King Faisal Hospital, Kingdom of Saudi Arabia, p. 382.

Ahamed, M. and Banji, O. (2012)." A review on diabetic neuropathy and nephropathy. *IJPSR*, 3(2): 300- 304.

Al-Anazi, Musa (2010). Diabetes, first edition. Electronic library. Riyadh.

Al-Hamid, M. (2007). Diabetes: its causes, complications and treatment, first edition, Riyadh, pp. 22-26.

Al-Jubouri, R. H. (2011). The effect of some herbs on the level of some biochemical variables in the blood of patients with type II diabetes. Master Thesis. Faculty of Education. University of Al Mosul. Iraq.

Al-Lahibi, N. I. (2006). Effect of the separated base amino acid fraction of bovine colostrum on blood glucose level and other biochemical parameters. Master Thesis. Faculty of Education. University of Al Mosul. Iraq.

Al-Muhaishi, Muhammad (2014). Women's Health, First Edition, Dar Al-Manar for Printing and Publishing, Misurata, pp. 305-331.

Al-Qaisi, M. D. (2008). Follow-up of oxidative stress and physiological and biochemical changes in pregnant women. Master Thesis. College of Science. Tikrit University. Iraq.

Al-Qawasma, A. (2006). Encyclopedia of pregnancy and childbirth. Dar Osama for Publishing and Distribution. Amman. Jordan

Al-Sawaf, R. N. (2012). Effect of a herbal mixture on some biochemical variables and some fatty components in the blood of patients with type diabetes. Master Thesis. Faculty of Education. University of Al Mosul. Iraq.

Al-Tuni, L. F.; Khalifa, W. A. and Bakrmut, H. M. (2017). Gestational Diabetes. One of the educational publications for a project to care for gestational diabetes patients in Upper Egypt. Assiut University. The Egyptian Arabic Republic.

American Diabetes Association. (2012). Standards of Medical Care in Diabetesd-2012. *Diabetes Care*, 35(1):11-63.

American Diabetes Association. (2015). Diagnosis and classification of diabetes mellitus. *Diabetes Care,* 38(1): 8- 16.

Atègbo, J.-M.; Grissa, O.; Yessoufou, A. *et al*. (2006). Modulation of adipokines and cytokines in gestational diabetes and macrosomia. *J. Clin. Endocrinol. Met*, 9: 4137-4143.

Baker, P.N. (2006)**.** Obestetrics by Ten teacher. Hodder Arnold. Eighteenth edition. India. Pp: 186- 189.

Baquer, N.; Taha, A.; Kumar, P. *et al*. (2011). Metabolic and molecular action of Trigonella foenum-raecum (fenugreek) and trace metals in experimental diabetic tissues. *J Bio Sci*, 36 (2):383-396.

Chen, D.; Xia, G.; Xu, P. and Dong, M. (2010). Peripartum serum leptin and soluble leptin receptor levels in women with gestational diabetes. *Acta Obstet Gynecol Scand*, 89(12):1595-1599.

Daftary, S. N. and Chakravarti, **L.** (2005): Manual of obstetrics. Elsevier publisher. Second edition. India. Pp:136- 137.

D'Anna, R.; Baviera, G.; Cannata, M. *et al*. (2007). Mid-trimester amniotic fluid leptin and insulin levels and subsequent gestational diabetes. *Gynecol Obstet Invest*, 64 (2): 65-68.

David, A.; John, F. and Stephen C. (2010). Eye care of the patient with Diabetes Mellitus. American Optometric Association: 2- 83.

Erejuwa, O.; Sulaiman, S.; Abdul Wahab, M. *et al*. (2010). Antioxidant Protective Effect of Glibenclamide and Metformin in Combination with Honey in Pancreas of Streptozotocin-Induced Diabetic Rats. *Int. J. Mol. Sci*, 11: 2056-2066.

Feng, Y.; Feng, Q.; Qu, H. *et al*. (2020). Stress adaptation is associated with insulin resistance in women with gestational diabetes mellitus. *Nutrition & Diabetes,* 10: 1- 4.

Georgiou, H.; Lappas, M.; Georgiou, G.; Marita, A. *et al.* (2008). Screening for biomarkers predictive of gestational diabetes mellitus. *Acta Diabetol*, 45(3):157-65.

Gerstein, H.C. (2001). Cow's milk exposure and type I diabetes mellitus acritical over view of the clinical literature. *DaibCare,* 24(1): 180-182.

Guyton, A. and Hall, J. (2010). "Text Book of Medical Physiology". W.B. Saunders Company.

Harris, P.; Mann, L.; Phillips, P. *et al.* (2011). Diabetes management in general practice. Seventh edition. Novartis Australia. Pp12.

Harvey, R. and Ferrier D. R. (2011). Lippincott's Illustrated reviews: Biochemistry. Fifth edition. Wolters Kluwer. New York. Pp337-348.

Herder, C. and Roden, M. (2011). Genetics of type 2 diabetes: athophysiologic and clinical relevance. *European journal of clinical investigation*, 41 (6): 679-92.

Heppard, M. C. and Garite T. J. (2010). Acute Obstetrics, Mosby publisher. Second edition. New York. Pp: 41- 54.

Inzucchi, S. E. (2011). "Diabetes facts and guidelines" .Takeda Pharmaceuticals North America. Inc. Pp: 1-55.

Inzucchi, S.; Porte, D.; Sherwin, R. S. and Baron A. (2005): The diabetes mellitus manual. The Mc Graw Hill Companies. Sixth edition. Singapore. Pp: 202- 228.

Landon, M. B. and Gabbe, S.G. (2011). Gestational diabetes mellitus. *Obstet Gynecol*, 118:1379-1393.

Lee, J.; Ouh, Y.; Ahn, K. *et al*. (2017). Preeclampsia: A risk factor for gestational diabetes mellitus in subsequent pregnancy. *PLoS ONE* 12(5): 1- 8.

Li, M.; Song, Y.; Rawal, SH. *et al*. (2020). Plasma Prolactin and Progesterone Levels and the Risk of Gestational Diabetes: A Prospective and Longitudinal Study in a Multiracial Cohort. *Frontiers in Endocrinology*, 11:83.

Maheria1, P.; Parchwani, D.; Upadhyay, A. and Sharma, M. (2011). Analysis of insulin resistace in various components of metabolic syndrome. *National journal of medical research*, 1(2): 2249-4995.

Menon, P. (2012). Adiponectin and Type 1 Diabetes Mellitus in Children. *Indian Pediarics*, 49(16): 267.

Murray, R.; Bender, D.; Botham, K. *et al*. (2009). Harpers' illustrated biochemistry. 28th. edition. Mc Graw Hill Company. NewYork.

National reference for diabetes education. (2016). Auxiliary Agency for Preventive Medicine General Administration of Non-communicable Diseases. First edition. Ministry of Health. Kingdom Saudi Arabia.

Pérez-Pérez, A., Vilariño-García, T.; Guadix, P. *et al*. (2020). Leptin and Nutrition in Gestational Diabetes**.** *Nutrients*, 12: 2- 18.

Prisant, L. M. (2004). Preventing type II diabetes mellitus. *Clin. Pharm. J*, 44 (4): 406-413.

Qaseem, A.; Linda, L.; Sweet, D. *et al.* (2012). Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline from the American College of Physicians. *Ann Intern Med*, 156:218-231

Rawi, S.; Mourad, I. and Sayed, D. (2011). "Biochemical changes in experimental diabetes before and after treatment with *mangifera indica* and *psidium guava* extracts". *Int J Pharm Biomed Sci*, 2(2): 29-41.

Rayburn, W. F. and Carey, J. C. (2008). Obstetrics and gynecology. Williams and Wilkins Publisher, Middle East edition. Egypt. Pp: 24- 44.

Riaz, S. (2009). "Diabetes mellitus" *Scientific Research and Essay*, 4 (5): 367-373.

Rohowyj, A. (2012). Hyperglycémie provoquée par voie orale : étude d'interprétabilité des courbes plates au cours de la grossesse. A propos de 83 patientes suivies à la maternité régionale de Nancy. Doctoral thesis. Médecine de Nancy. France.

Saleh, T. M. and Qaliwan, F. A. (2019). Study of the effect of gestational diabetes on human fetuses. The second annual conference on theories and applications of basic and biological sciences. Misurata University.

Sheth, J.; Shah, U.; Sheth, F. *et al*. (2011). "Genoprotective Effect of Indian Gentian in Type 2 Diabetes Mellitus (T2DM): Comet Assay, Sister Chromatid Exchange and Protein Oxidation Studies". *Int J Hum Genet*, 11(2): 83-88.

Shrivastava, S.; Shrivastava, P. and Ramasamy, J. (2013). Role of self-care in management of diabetes mellitus. *Journal of Diabetes & Metabolic Disorders*, 12:14.

Siddiqui, A.; Siddiqui, Sh.; Ahmad, S. *et al*. (2013). Diabetes: Mechanism, Pathophysiology and Management-A Review. *international Journal of Drug Development and research*. 5(2): 1- 23.

Singh, L.W. (2011). "Traditional medicinal plants of Manipur as anti-diabetics". Journal of Medicinal Plants Research, 5(5): 677-687.

Standards of Medical Care in Diabetes. (2015). *Diabetes Care*, 38(1): 593.

World Health Organization. (1999). Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of WHO. Department of Non-communicable Disease Surveillance. Geneva.

World Health Organization (2011). Use of Glycated Haemoglobin HbA1c in the Diagnosis of Diabetes Mellitus .Geneva.

World Health Organization (2020). Diabetes .Geneva.

Yuan, X.; Liu, H.; Wang, L. *et al*. (2016). Gestational Hypertension and Chronic Hypertension on the Risk of Diabetes among Gestational Diabetes Women. *Journal of Diabetes and its Complications,* 30(7): 1269- 1274.