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Effect of Some Bio Variables on Gestational Diabetes Progression: (Review)

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Received: 2 January 2023 **Accepted: 12 February 2023**

DOI: https://dx.doi.org/10.24237/ASJ.01.02.747D

Abstract

Gestational diabetes mellitus (GDM) is the most common metabolic disorder and is also defined as: impairment of glucose tolerance. This article aims to clarify the role of the changes in some hormones that may cause the development gestational of diabetes, as an attempt to understand and reduce the mechanism of this disorder. Disturbance Hormonal insulin levels, which are characterized by a reducing blood glucose reduced utilization of by muscle and body tissues. Many factors will promote the development of GDM, such as: BMI ≥ 30 Kg/m2, pre-existing gestational diabetes, family history and HbA1C ≤ 7 mmol/l. Gestational diabetes can be seen as a transient pattern of type 2 Diabetes, Symptoms appear with hormonal changes related to pregnancy. Etiology of GDM related to type 2 diabetes and insulin resistant which also may attack beta cells in pancreas. It can be concluded that the change in the level of each of these hormones (significant differences) had a role in promoting the development of diabetic pregnant more than control pregnant women.

Keywords: Gestational diabetes mellitus, insulin resistance, adiponectin, resistin, leptin, retinol, Body Mass Index.

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تأثير بعض المتغيرات الحيوية على تتطور سكر الحمل: (مقالة)

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الخلاصة

سكر الحمل هو من أكثر الاضطرابات الايضية شيوعا التي تتعرض لها الحامل، حيث يعرف سكر الحمل هو ضعف في تحمل الكلوكوز. تهدف هذه المقالة الى توضيح دور التغيرات في مستويات بعض الهرمونات التي تسبب في تطور سكر الحمل. الاضطرابات الهرمونية التي يسببها مقاومة الانسولين يمتاز بتقليل السكر المستخدم من قبل العضلات وانسجة الجسم الاخرى. عدة عوامل تساعد على تعزيز الاصابة بسكر الحمل منها: تزايد مؤشر كتلة الجسم اكثر من 30 كغم/م^2, الاصابة بسكر الحمل بفترات الحمل السابقة, وجود تاريخ مرضي للعائلة, او ازدياد معدل السكر التراكمي اقل من 7 ملم/لتر. الاصابة بسكر الحمل قد تكون من النوع الساكن الذي ليس له اعراض ظاهرة اضطرابا الهرمونية التي تتطور بفترة الحمل سبب رئيس للإظهار الاصابة به. تتشابه مسببات الاصابة بسكر الحمل مع السكر من النوع الثاني التي تتضمن مهاجمه خلايا بيتا في البنكرياس. يمكن الاستنتاج ان التغير الحاصل في مستوى كل من هذه الهرمونات الواقعة ضمن الفروقات المعنوية كان له دور في تعزيز تطور سكر الحامل أكثر من النساء الحوامل ضمن مجموعة السيطرة

الكلمات المفتاحية: سكر الحمل، مقاومة الانسولين، اديبونكتين، ريزيزتين، لبتين، ريتينول، مؤشر كتلة الجسم.

Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic disorder occur to women during their pregnancy. In other word, it is defined as impairment of glucose tolerance, it is diagnosed during pregnancy, and it does not take long to recover from it after birth. [1], [2] [3]. This term includes any level of glucose intolerance, from mild to overt diabetes. The distinction between undiagnosed type 2 diabetes or (GDM) must be taken into account [4]. Hormonal changes that cause insulin resistance, which is characterized by a decrease in muscle and body tissues receiving blood glucose [5].

The importance of this phenomenon lies in describing the evolutionary point of view, as in the effect of glucose supply of fetal growth and development. Healthy pregnant women in their third trimester have the ability to increase their insulin secretion by 2- 4 times to keep their

blood glucose within normal level. But the pregnant women with glucose intolerance are unable to promote insulin production to compensate for the increased insulin resistance [6].

Many of risk factors will promote GDM such as: BMI ≥ 30 Kg/m2, pre-existing gestational diabetes, family history. Pregnant women with risk factors should monitor their HbA1C and blood fasting sugar starting from the early stages of pregnancy, to take the required measures to reduce the aggravation of the injury [7]. If HbA_1C = 6.5 mmol/l, that's indicate to have overt diabetes, and performed all requirement to make the metabolism within normal range. Inversely, women with moderate HbA_1C (5.1 - 6.9) mmol/l, home fasting glucose monitoring should be followed up [8] [9].

Gestational Diabetes Mellitus with obesity

Gestational diabetes prevalence ranges widely, from 1.2% to 4.2%. A Getahun et al. investigation conducted between 1989 and 2004 [10]. High rates of gestational diabetes in the United States, which affect 14% of all pregnant women, pose a yearly danger of over 200000 GDM cases [11].

In any case, the prevalence of it varies from 1.7% and 11.6% globally [12] depending on racial and ethnic origin. The International Diabetes Association has suggested new guidelines for monitoring gestational diabetes based on the HAPO trial. When these parameters are taken into account, the prevalence of gestational diabetes rises to more than 18% [13].

Studies on gestational diabetes have revealed that the risk is roughly 2.14, 3.56, and 8.56 times higher in overweight and obese women. respectively, excessive obesity [14],[15]. It is usual practice to diagnose gestational diabetes by using the body mass index (BMI) (pre-pregnancy). Each unit of BMI increase indicates a 0.93% increase in the risk of gestational diabetes [16]. According to figure 1 [17],

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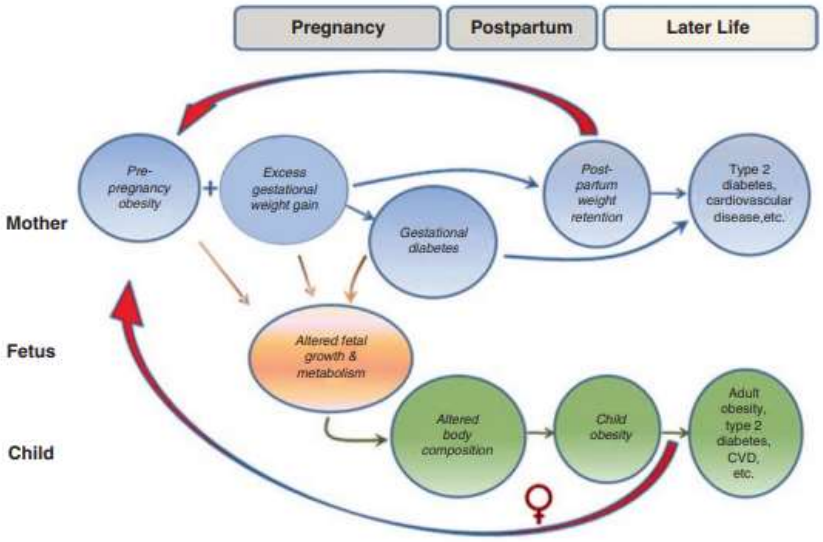

Figure 1: Intergenerational transmission of obesity and gestational diabetes mellitus [17]

Gestational Diabetes with insulin resistance

In normal pregnancies, insulin secretion will be increased by around 200% to 250% in the second trimester of pregnancy and continues until delivery in order to counteract the pathophysiology of GDM, which causes insulin resistance to rise. It is possible to think of gestational diabetes as a temporary pattern of type 2 diabetes, with symptoms that emerge quickly due to the metabolic and hormonal changes that occur during pregnancy. Insulin resistance and an immune response that targets pancreatic beta cells are two factors that are shared by the etiologies of type 2 diabetes and gestational diabetes, respectively. Gestational diabetes is considered by some to be an advanced form of type 2 diabetes, likely chronic insulin resistance that already exist in most (not all) undiagnosed diabetes to promote to be GD in pregnancy [18Beta cell defects are caused by pregnant women who secrete too much insulin and who have long-term insulin resistance. It is unclear how pregnancy and insulin resistance are related, but hormonal changes—whether brought on by steroids or lactogenic pregnancy—lead to the development of gestational diabetes. Growth hormone and other hormones produced by the human placenta, as well as cortisol, prolactin, and progesterone, are known to have an anti-insulin effect. A variety of theories, including: Insulin resistance increases in tandem with

fetal growth, which is accompanied by an increase in these hormones' release. ii/ The metabolic changes brought on by these hormone injections in non-pregnant subjects are comparable to those brought on by gestational diabetes, iii/ exposure of cells to insulin sensitivity leads to an impaired in uptake of glucose, such as adipocytes, due to pregnancy hormones [19].

In other word, hormonal change concentration not only main reason for insulin resistance, recent studies show the relation GDM with adipose tissue-derived mediators like as: adiponectin, leptin, resistin, visfatin, apelin [20]. As shown in figure 2.

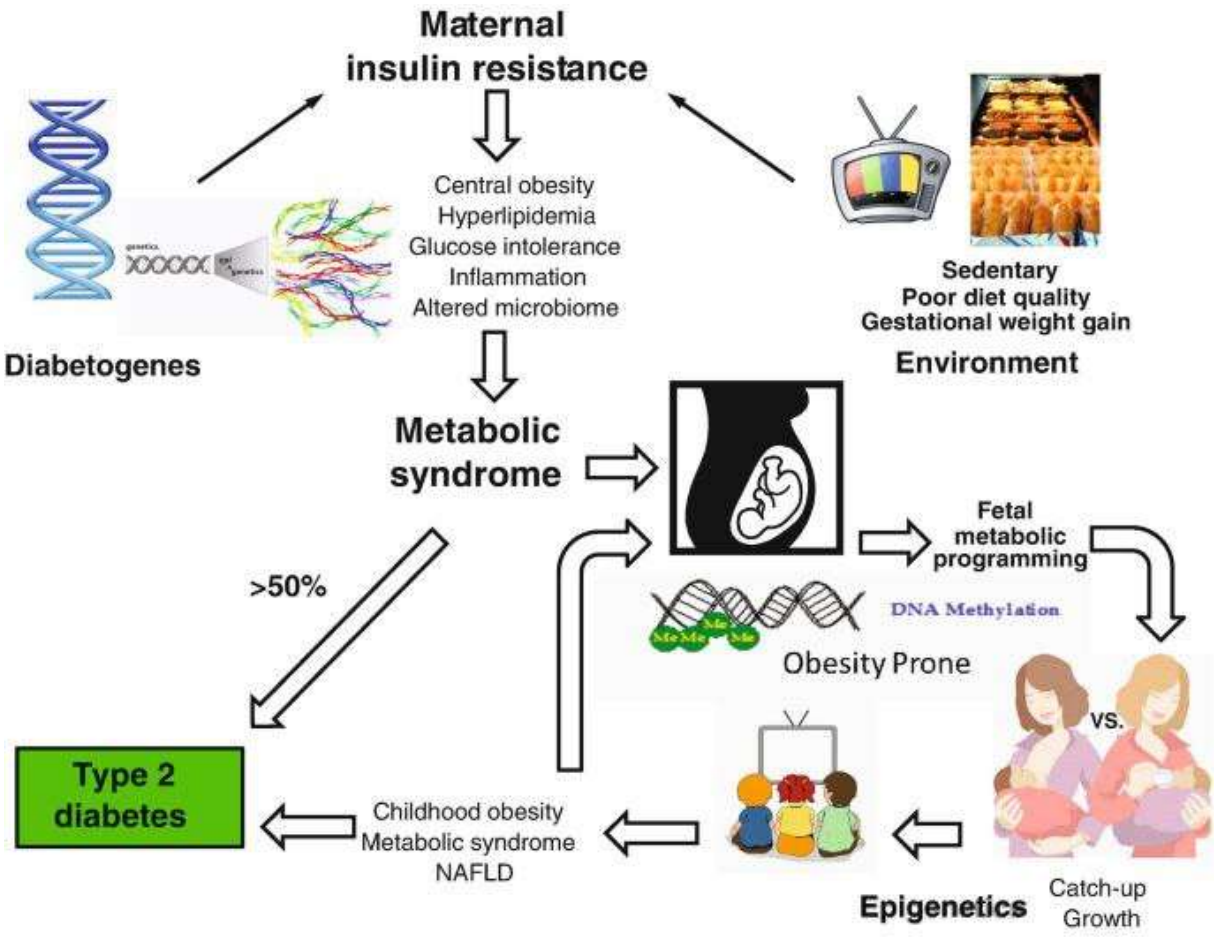

Figure 2: Insulin resistance during gestational diabetes [21]

Gestational Diabetes Mellitus with adiponectin

Adiponectin is a 244 amino acid long protein hormone that has a distinct structural domain. It is secreted by adipocytes and is produced in relatively modest amounts in various organs, including the liver, pituitary gland, and slave gland. Skeletal muscle and the colon. Trimer, Hexamer, and Mortimer's (low molecular weight LMW, medium molecular weight MMW, and height molecular weight HMW, respectively) are excreted into the blood in three homogenous forms, with the last one being the most predominate in controlling glucose homeostasis. By controlling blood glucose levels and limiting the development of insulin resistance, adiponectin has been shown to lower the risk of developing diabetes, according to numerous studies. The majority of individuals with coronary artery disease share a common adiponectinemia deficit. But other research shows: the correlation HMV with cardiovascular disease Although effective in reducing insulin resistance as total adiponectin. Plasma adiponectin level in female more than male although, has a sexual dimorphism. Although adiponectin secreted from adipose cells, it reversed it in its relationship with body mass index BMI, abdominal Fat accumulation and insulin resistant, where adiponectin plasma level will decrease with weight gain

Conversely, will increase with weight loss, as well as its inverse relationship with insulin resistance, as mentioned previously [22]. Adiponectin levels keep the same level or tend to decrease in early stage of pregnancy and adverse relation with maternal BMI change or insulin sensitivity.

The level of adiponectin was observed is decreasing in 30 women with GDM compared with 40 healthy pregnant women by (cesh et al). Furthermore, adiponectin concentration had a linear negative correlation with leptin, fasting C peptide, tumor necrosis factor- α TNF(α), insulin resistance (can use fasting C peptide/ blood glucose ratio, as indirect parameter). In any case, the pregnant women who suffer from decreasing in adiponectin level in first trimester, it indicates the development of gestational diabetes, furthermore, when adiponectin concentration in women were less than (4.6 µµ/ml) are at risk of gestational diabetes (by 4.6 fold) compared with higher concentration. Previous study indicated the measurement of adiponectin

concentration at three different times (3 months, 1, and 1.5 yeas) after childbirth. Gestational diabetes persists with the mother until about 1.6 after delivery.

Low Adiponectin concentration is also associated with decrease in insulin sensitively, low HDL, negative correlation with inflammation markers such as (CRP), plasminogen activator inhibitor-1 (PAI-1), Despite the decline in BMI after birth. Until now, the basis for adiponectin deficiency with gestational diabetes remains unclear. Several mechanisms are proposed to improve insulin sensitivity to adiponectin, included a/ Enhancing the role of receptors for insulin signaling b/ reduction of glucose synthesis c/ i improvement lipid oxidation, d/ Inhibition of TNF-that relative to adipose tissue [23]. Adiponectin can also promote hepatocytes to action of insulin and inhibitor for some enzyme like: phosphoenolpyruvate carboxykinase and glucose-6-phosphatas which plays a role in the gluconeogenesis, and also effect on lipid situation like fatty acid metabolism plasma triglyceride and non-aster fatty acid circulation. Adiponectin regulates and Promotes insulin secretion even vitro or vivo, despite the existence of insulin resistance [24].

Gestational Diabetes with resistin

Resistin, also known as adipose tissue-specific secretory factor (ADSF), is a cysteine-rich peptide hormone that was discovered in 2001. Insulin resistance was seen in mice after resistin injections; for this reason, resistin was named. Resistin has two metameric form structures in blood circulation, a hexamer and a trimer, whether in human or mouse bodies. Pre-peptide for resistin in humans has a 108 amino acid residue chain. more frequently in women's serum than in men's. Since resistin is secreted by adipose tissue, it has been linked to diseases other than cardiovascular disease that are related to heart disease. Adipose tissue is an endocrine active member that releases many inflammatory factors and adipokines and also insulin resistance. Therefore, the idea that serum resistin is increased in obese individuals was supported, several studies referring to expression of resiten in abdominal tissue in fat individual's is correlate with DM_2 and insulin resistance. Although, the others failed to establish this relationship. Hence physiological role for resistin with obesity and insulin resistance is a controversial issue. Many

studied refer to the resistin is derived from macrophagocyte , The incidence of inflammation with metabolic disorder is a two-way correlation ,This is why resistin can be considered a biomarker for inflammation and metabolic disease in human . In the first and second trimesters of non-diabetic pregnancy it observed that the resistin serum was similar in relation to its levels in non-pregnant women, but, its levels will be significantly raise in third trimester. Furthermore, resistin gene expression in placenta tissue is much higher than that in chorionic villous tissue in beginning stage of pregnancy. The rise in resisten levels in the third trimester of pregnancy coincides with the placenta derived hormone secretion might contribute to insulin resistance and hyperglycemia when consumption a main meal in late pregnancy. Lappas et al, points out that insulin is a biphasal action hormone, decreased insulin levels promote release of resistin, while it can be returned to basal level during the placenta is exposed to much higher concentrations of insulin leading to Resin levels were higher in GDM pregnant women than nondiabetics pregnant [25] [26] [27]

Leptin is a It was revealed in 1994 that a poly-peptide hormone generated from adipose tissue plays a key role in maintaining energy hemostasis (intake and expender) as well as maintaining equilibrium between hunger and metabolism.It is regarded as one of the greatest biomarkers of obesity and is a human gene located on chromosome 7. According to how leptin interacts with the receptor, six different types of leptin receptors have been identified to date. Ob Raf represents the primary leptin binding activity and has been secreted into the bloodstream. When compared to leptin levels in healthy women of the same age as non-pregnant women, pregnant women have higher amounts of the hormone. It is still unclear if pregnancy increases leptin levels. Although many studies indicated that the hormonal change during pregnancy like cortisol and estrogen levels can act as a catalyst for the release of leptin from the placenta to circulation. furthermore, metabolic disorder and fat accumulation in pregnancy can release a leptin from adipose tissue [28].

Leptin during pregnancy is produced by placental cell and adipose tissue for both maternal and fetus Leptin plasma level will increase in second and third trimester that related to placenta secretion in comparison with that level at first trimester [29]. it has many physiological roles

related to endocrine and metabolic system, such as: to maintain a balance between food consumption and energy hemostasis by hypothalamus, reproductive system feature (gonadotrophin releasing hormone (GnRH) related to hypothalamus and LH, FSH, related to pituitary gland), insulin secretion inhibiter from the beta cells of the pancreas that help to simulate transporting of glucose and utilize, glycogenesis, fatty metabolism. High levels of leptin in recent stage of pregnancy, which is secreted from placental cells, works to reduce insulin secretion by affecting on ATP sensitive potassium channel.

Several studies have indicated that leptin prevents beta cell secretion by blocking the CAMP signal. Moreover, leptin also can hinder secretion of insulins by cAMP-dependent protein kinase A, C (PKA) (PKC), respectively. Leptin has essential role for regulating endocrine function, e of inflammation progressive, immune response, and angiogenesis. Decline in leptin concentration is associated with weight loss, starvation. While Leptin levels will rise when weight gain Subsequently increase adipose tissue, which is main source for leptin production. Pregnant women suffer from high levels of leptin around 2 to 3 fold more than non-pregnant women. Resulting dysregulating in adipose tissue connected with insulin resistance. Leptin level returns directly to normal range after delivery. More than 90% of placental leptin is excreted into the circulation. Leptin play an important role in embryo formation such as: developmental growth, and organogenesis, furthermore, has a critical role for fetal skeletal growth and lung development [30].

Gestational Diabetes with retinol

Pregnant women undergo several changes during pregnancy, such as hormonal disturbances, a metabolic syndrome and also glucose intolerance is not the only cause of obesity or insulin resistant, it might be because: retinol binding protein -4 (RBP-4) which is created mainly from hepatocytes and adipocytes, act as carrier for retinol in blood circulation, discovered at 2005.RBP -4 has appropriate role Postpartum in glucose metabolic regulation and insulin sensitive.

many studies have also indicated that high levels of retinol are associated with those who suffering from the glucose intolerance, such as (obesity, PCOS, insulin resistance, and cardiovascular diseases). Furthermore, RBP-4/ retinol ratio can be considered a good marker for metabolic syndrome than RBP-4 only. Pregnant women with insulin resistance lead to dysregulating GLUT4 (which in turn acts as a trigger for insulin) It leads to an impaired the absorption of glucose by the adipose tissue, it will help to increasing secretion of adipokine and RBP in adipose tissue. [31],[32].

In healthy pregnant women, RBP reports as a significant increase between first and third trimester, associated with decreasing in insulin sensitivity, while, some reports, showed low levels of this hormone after the initial period of pregnancy. This hormone is controversial in terms of its effect on gestational diabetes, whether it rises, falls, or even this hormone remains at the same level. In Pgdm, many reports showed a raise in level of this hormone even after 18 months and more postpartum in normal women or with impaired glucose tolerance compared with women without GDM, Xiyu Du.et al (2019). An experimental study was conducted on 60 women with gestational diabetes. The hormone was measured and found appositive correlation with level of insulin fasting, as well as 6 months after delivery, additionally, hormone significantly declining in control group Unlike pregnant women with GDM, where this hormone begins to decline, but in a non-significant rate. ($P<0.OO5$) was observed between two groups [33].

Gestational Diabetes with visfatin

visfatin is adipocyte hormone discovered at 2004, has a direct relationship with T_2DM. visfatin bind with insulin receptor by site different from that site which insulin binding with it. It causes hypoglycemia thought reduced glucose realizing from liver and stimulate adipocyte to utilized glucose and uptake. This hormone was found in cytoplasm and nucleus of cell and many organs identified like kidney, brain, spleen, lung but secreted mainly from visceral fat more than subcutaneous fat, and also visfatin can help to cell prolifrication enhancement and biosynthesis

of nicotinamide mono. It is similar to PREB cell colony enbarecing factor PBEF which describe at 1994 play role of lymphocyte maturation and make of inflammation control. Conversely,

the effect of this hormone on pregnant women and the extent of their gestational diabetes development, [34]. Visfatin level will higher concentration with obesity and metabolic syndrome such as T_2DM and insulin resistant. but other studied show that no relation of visfatin with visceral fat mass in obesity. In pregnancy, some authors reported on change in vesfatin serum concentration in third trimester as in non-pregnant women. while, other studies show peak of vesfatin concentration between 19 and 26 weeks during pregnancy, but it has lower concentration between 27 and 34weeks of gestation. Morgan et al show visfatin have paracrine or may have autocrine since it is expressed by omental fat without any raises of concentration in plasma during pregnancy. Furthermore, some reports have shown significant increase of visfatin level as well as glucose concentration in women with GDM [35].

Gestational Diabetes with C reactive protein CRP

C- reactive protein is an inflammatory sensitive marker, circulating CRP levels highly correlated with human physical measurement such as BMI, waist circumferences, waist to hip ratio. Its level tends to increase in individuals with T_2DM, insulin resistance, central fat and cardiovascular disease. Unpredictable and negative pregnancy outcomes can be predicted by high level of CRP. Furthermore, many reports show that high level of CRP in first trimester is accompanied with reducing fetus size inside uterus. An experimental study was conducted on a cohort of women who measured the criteria for gestational diabetes has been founded the level of CRP increasing during 10 weeks of first trimester of pregnancy [36]. High levels of CRP in the first trimester of pregnancy exposure pregnant women at risk of developing gestational diabetes by 3- times more than those who have a decreasing CRP level. Adiponectin and inflammatory proteins play pathologic role in impairment function of Beta cell, that causing high level of insulin resistant – resulting dysregulating of glucose uptake association with maternal for month or even year postpartum. recent studies support the concern of significant increase in CRP level in 3 months after delivery with Pgdm compared with control. Other

authors reported negative correlation between adiponectin level with CRP but this correlation is not within the significantly limits. There is a cross sectional study found significantly correlation not with GDM while significantly with obesity. many studied pointed to increase of CRP level with development of GDM is questionable, while There is an independent relationship between obesity and CRP. Metabolic disorder and insulin resistant related to obesity not to CRP concentration [37].

Gestational Diabetes with Apelin and Chemerin

Apelin is an endogenous peptide related to adipokines family, secreted by adipose tissue, discovered by 1983, The importance of Apelin role has not been diagnosed yet. This bioactive peptide has physiological process, where Apelin participates in angiogenesis even normal or pathologic, which is important in development and growth adipose tissue. Apelin prevalence in most of tissue enhance its role such as hemostasis body flood, angiogenesis and regulating blood pressure by expansion of the endothelial blood vessels *apelin*. Additionally, a contribute to numerous pathological processes like heart failure, obesity, and insulin resistance. Many tissues, including the human placenta, which is necessary for endothelial cell proliferation and the formation of blood vessels, can express apelin.. Baris et al pointed to decreasing of apelin serum concentration in women with GDM than normal pregnant women, while, Emel et al found increase of Apelin concentration GDM in women. However, more studies should be conducted to clarify of Apelin role in normal pregnant women and compare it with complicated [38] [39].

Another protein secreted known as Chermerin which is expressed deeply by adipose tissue, liver, lungs and the tissue is related to skeletal muscle, has a complex role metabolic function but also has independent target to support immunity system. Chermerin level are raising with obesity individual's and exhibit positive correlation with plasma lipid different features of metabolic syndrome such as obese, insulin resistant and glucose dysregulating uptake [40].

Recommended

Exercise has an essential role that help body to enhance insulin sensitivity, and reducing the risk of GDM development, The Canadian Diabetes Association (CDA) has a mainly role to promoting about physical activity from where (kind, frequency and duration) for women with metabolic disorder to reduce GDM development [41]. Some facts that must be followed for pregnant women to reduce the incidence of gestational diabetes:

*Keeping aerobic exercise to maintain physical fitness not for competition purpose. * Providing a suitable environment for pregnancy, in terms of temperature highly, humidity environment should be avoided.* Preventing stressful sports for pregnant women that expose them to trauma such as skiing and skipping robe.*/ Gradual initiation of exercise for pregnant women who are not accustomed to exercising [42].

Conclusion

Pregnant women undergo many changes during pregnancy, Metabolic disorders with hormonal imbalance lead to many complications for the pregnant woman and the fetus. The most common of these disorders in women is gestational diabetes, Increasing insulin resistance with the failure to control the cause of the development of gestational diabetes gives negative results for pregnancy such as fetus abnormal growth, premature birth, or threatened miscarriage.

Each pregnant woman must monitor the HbA1c during pregnancy to prevent the development of disorders occurring and infection during pregnancy, in addition to monitoring the hormones that are related to metabolic disorders such as: adiponecton, resisten, lipten.

Acknowledgements

The authors wish to thank Department of Chemistry, College of Science, University of Diyala, Iraq, the support provided to conduct this work.

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